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Manuscript Types

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Letters to the editor should pertain to articles published within the Journal of Pediatric Academy or highlight important new clinical or laboratory insights. The text should contain 1000 words or fewer.

Table 1.
Limitations for each manuscript type

Manuscript Type	Word Limit	Abstract Word	Limit Reference	Limit Table Limit	Figure Limit
Editorial comment	1500	No abstract	15	2	5
Original Article	3500	300	50	6	6
Invited Review	5000	350	100	6	10
Case Report	1500	200	15	2	5
Image corner	500	No abstract	5	-	3
Letter to the Editor	100	No abstract	5	1	1

References:

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Cite unpublished data—such as papers submitted but not yet accepted for publication and personal communications, including e-mail communications—in parentheses in the text. If there are more than three authors, name only the first three authors and then use et al. Refer to the List of Journals Indexed in Index Medicus for abbreviations of journal names, or access the list at http://www.nlm.nih.gov/tsd/serials/lji.html. Sample references are given below:

Journal Article:

1. Ang KK, Price RE, Stephens LC, et al. The tolerance of primate spinal cord to re-irradiation. *Int J Radiat Oncol Biol Phys*. 1993;25:459–464.

Journal Article published in non-English Languages:

2. Altuntaş N, Çelebi DT, Koçak M, Andıran N. Yenidoğan bebeklerde direkt coombs testi taraması ve pozitifliğinin morbidite üzerine, etkisi; tek merkezd eneyimi. *Pam Tıp Derg* 2015;8:39-44. (in Turkish)

Book Chapter:

3. Dimery IW. Chemotherapy in head and neck cancer. In: Myerhoff WI, Rice DH, eds. Otolaryngology: head and neck surgery, 2nd ed. Philadelphia: WB Saunders, 1992:1027–1045.

Entire Book:

4. Virchow R. Cellular Pathology. Philadelphia: JB Lippincott, 1863.

Software:

5. Epi Info [computer program]. Version 6. Atlanta, GA: Centers for Disease Control and Prevention; 1994.

Online Journals:

6. Friedman SA. Preeclampsia: a review of the role of prostaglandins. Obstet Gynecol [serial online]. January 1988;71:22–37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

Database:

7. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute; 1996. Updated March 29, 1996.

World Wide Web:

8. Gostin LO. Drug use and HIV/AIDS [JAMA HIV/AIDS Web site]. June 1, 1996. Available at: http://www.ama-assn.org/special/hiv/ethics. Accessed June 26, 1997.

URL (Uniform Resource Locator)

9. (J. M. Kramer, K. Kramer [jmkramer@umich.edu], e-mail, March 6, 1996).

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A Narrative Review: Transforming Pediatric Oncology Care Through Virtual Reality - Pain Management and Enhanced Patient Experience

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Abstract

Virtual reality (VR) technology has received considerable interest in the healthcare field, particularly in pediatric oncology. The purpose of this study was to examine the existing and future applications of VR in reducing the discomfort associated with pediatric oncology procedures such as bone marrow biopsy, bone marrow aspirate, and lumbar puncture. A comprehensive search was conducted across numerous databases from 2005 to 2023, embracing several study designs to provide a strong evidence foundation. Using diversion and relaxation strategies, VR can help pediatric cancer patients cope with the emotional issues they confront during operations. VR has shown significant potential for lowering pain and anxiety during several pediatric medical procedures. Patient feedback focused on VR's empowering and anxiety-reducing benefits, while healthcare staff reported increased patient participation and procedural efficiency. VR implementation challenges include the cost of specialized technology, the need for specific virtual settings, and the need for training healthcare workers. VR shows promise in improving the pediatric cancer experience, but more study and cooperation are required to realize its full potential.

Keywords: Virtual reality, pediatric oncology, bone marrow biopsy, bone marrow aspiration, lumbar puncture

Introduction

Virtual reality (VR) is an advanced technology that immerses users in computer-generated environments, simulating visual, auditory, and even haptic sensory experiences. Its prospective healthcare applications are extensive. VR can restructure medical training and education by providing medical students and professionals with realistic and risk-free simulations that can improve their skills and decision-making abilities.[1] VR can also be used for pain management and therapeutic interventions. The use of VR as a distraction technique for patients undergoing painful procedures effectively reduced their perception of pain and anxiety.[2] These applications illustrate the prospective role of VR in transforming the healthcare landscape and

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enhancing patient outcomes, particularly in specific patient populations, such as the pediatric oncology population.

Bone marrow aspiration, bone marrow biopsy, and lumbar puncture (LP) are essential for the diagnosis and management of hematologic malignancies in children.[3] Fear and anxiety associated with the anticipation of pain render these procedures challenging to perform. Hence, the importance of identifying additional methods to alleviate patients' suffering above and beyond the use of analgesics and sedation.

VR has shown considerable promise in reducing pain and anxiety during pediatric medical procedures.[4] By providing an immersive and engaging environment, VR can serve as a potent distraction tool, diverting the patient's attention away from the discomfort of the procedure. In a randomized controlled trial by Gold et al.[2], the use of–VR during painful medical procedures such as intravenous line placement reduced pediatric patients' pain perception and distress: when VR was applied, children, parents, and nurses reported no significant differences in affective pain in the Faces Pain Scale with intravenous line placement, compared with a four-fold increase in affective pain with topical anesthetic with no distraction.

The purpose of this literature review was to examine the current and potential applications of VR technology in bone marrow aspiration, bone marrow biopsy, and LP procedures in pediatric oncology.

Methodology

Search Strategy and Inclusion Criteria

This original review was conducted in August 2023. The authors performed a search through PubMed, Scielo, Cinahl, Web of Science, and ScienceDirect using the following keywords: "Virtual Reality" "Pediatric Oncology" "Bone Marrow Biopsy" "Bone Marrow Aspiration" "Lumbar Puncture".

The inclusion criteria for the articles considered in this review were as follows:

1. Publication Language: Articles published in English were included.

2. Publication Date: Articles published between 2005 and 2023 were considered to ensure coverage of the recent research and developments.

3. Study Design: Various types of studies were included, such as case-control studies, cross-sectional studies, cohort studies, and review articles. These diverse study designs were chosen to capture several evidence on the topic.

Selection Process

Two authors independently conducted the literature searches, ensuring a comprehensive search across the specified databases. Duplicate articles were automatically detected and removed using Zotero. After eliminating duplicates, the remaining articles underwent further screening by Rayyan. During this screening process, the authors independently evaluated the titles and abstracts of these articles, excluding any literature that did not meet the inclusion criteria. The reasons for exclusion at this stage included studies not related to the topic, non-English articles, and those published before 2005.

Following the title and abstract screening, the full text of the accepted articles was reviewed to determine their eligibility for inclusion in the study.

Data Analysis

Two authors independently extracted data from the included studies. Data extraction encompassed key information such as medical procedures, applications, limitations, main findings, and any information pertinent to the review objectives. This approach ensured that a comprehensive and thorough assessment of the literature was performed.

Following this methodological process, we aimed to identify and select articles that were most relevant to the objectives of this review, thereby providing a robust foundation for our analysis.

Results and Discussion

Medical Procedures in Pediatric Oncology

Bone marrow biopsy and bone marrow aspiration are essential procedures for diagnosing and treating various pediatric hematologic malignancies. However, these procedures often evoke significant anxiety and fear, especially because of concerns about potential pain. Zernikow et al.[5] conducted interviews with pediatric oncology patients (n=265), revealing that one-third of them identified bone marrow aspiration and biopsy as the most painful procedures. Notably, the use of general anesthesia was associated with reduced pain during these procedures.[5]

LP is another common procedure in pediatric oncology used for evaluating cerebrospinal fluid for various conditions, including infection, hemorrhage, or cancer cell presence.[3] LP is particularly crucial for diagnosing and treating central nervous system involvement in leukemia and lymphoma. Pediatric patients undergoing LP often experience anxiety and apprehension due to fear of pain, which is exacerbated by the requirement to remain still during the procedure. Fein et al.[6] conducted a comparative study, which revealed that less than a quarter of the 353 children involved in the study had received any form of pain management before LP. This highlights the challenge of inadequate pain management in pediatric patients, primarily because of the difficulty in assessing their pain. Healthcare providers employ various pain management techniques, including local anesthesia and psychological support, to alleviate anxiety.[6] Additionally, sedation or distraction techniques, such as VR, may be used to mitigate emotional distress and improve the patient experience during LP.[7] Findings of the articles are summarized in the **Table 1**.

Virtual Reality Applications in Healthcare

VR has demonstrated potential across various medical contexts, including surgical training and education, where it simulates complex procedures for medical

professionals' practice and skill refinement in a safe environment.[8] VR has also shown promise in treating anxiety disorders and phobias through virtual exposure therapy scenarios, aiding in desensitization and therapeutic interventions.[9]

Virtual Reality in Pediatric Care

VR has been applied in pediatric settings, including medical procedures, to provide distraction and relaxation, thus reducing the need for sedation.[10] A meta-analysis by Eijlers et al.[8] showed that VR significantly reduced procedural pain and emotional distress in pediatric patients. VR was particularly effective in reducing pain and anxiety associated with various procedures, such as intravenous line placement, blood draw, port access for chemotherapy, and burn dressing.[8] It demonstrated greater effectiveness in younger children, possibly because of their heightened engagement in imaginative thinking.[11]

Moreover, the use of VR prior to, during, and after influenza vaccination in 244 children aged 2-16 years resulted in significant reductions in pain (ranging from 48% to 75%) and fear (ranging from 52% to 71%) compared with standard care.[12] In eleven burn patients aged 9-40 years, VR, along with standard pharmacologic treatment, led to a substantial reduction from 35% to 50% in perceived pain.[13] Similarly, among the 25 patients aged 10-25 years experiencing sickle cell crises, VR contributed to a decrease in pain intensity and descriptors.[14]

Highlights

- Therapeutic interventions using virtual reality (VR) technology are revolutionizing medical care, especially regarding procedures involving painful experiences in vulnerable populations, such as the pediatric population.
- This study conducted a thorough systematic search of various databases for English-language articles published between 2005 and 2023 discussing the use of VR in pediatric oncology procedures.
- VR reduces pain and anxiety during pediatric medical procedures, improving patient and family cooperation and efficiency. Challenges include specialized hardware costs, tailored scenarios, and professional training.

Virtual Reality in Pediatric Oncology

In pediatric oncology, VR is a valuable distraction tool during procedures. Hoag et al.[15] conducted a randomized controlled trial, demonstrating that VR significantly reduced procedural pain and distress during subcutaneous port access in 25 children and adolescents with cancer compared with guided imagery. VR mitigated the impact of pain catastrophizing on the pain experience by alleviating feelings of helplessness and reducing rumination about pain.

In addition, VR simulations play a significant role in educating pediatric oncology patients and their families about procedures. Tennant et al.[16] reported that immersive VR improved procedural knowledge and satisfaction among thirty pediatric oncology patients undergoing computed tomography simulation for radiotherapy.

Virtual Reality Implementation in Pediatric Oncology Procedures

VR implementation in pediatric oncology procedures, such as bone marrow biopsy and aspiration and LP, requires VR headsets and interactive tools.[11] High-quality VR headsets offer a completely immersive experience that transports the patient to a virtual world while obstructing the outside world.

Table 1.
Table summarizing the articles' findings

Author	Findings
Comparcini et al.,[10] 2023	VR has been applied in various pediatric medical procedures because it provides distraction and relaxation, reducing the need for sedation.
Eijlers et al.,[8] 2019	VR was found to be effective in reducing patient-reported pain and anxiety associated with intravenous line replacement, placement, blood draw, port access for chemotherapy, and burn dressing. VR had a better effect on distraction ability than other distraction tools such as music and movie distractions. VR was more effective in younger children than in older children.
Derek et al.,[12] 2002	Younger children are more engaged in magical and creative thinking than older children.
Mack, 2017	The use of VR for a duration of 30 s prior to, during, and after influenza vaccination in children aged 2-16 years has been linked to a significant reduction in pain (ranging from 48% to 75%) and fear (ranging from 52% to 71%) compared with standard care.
Hoffman et al.,[13] 2008	Out of eleven burn patients aged 9-40 years, the use of VR along with standard pharmacologic treatment resulted in a 35-50% reduction in perceived pain compared with pharmacologic treatment alone.
Agrawal et al.,[14] 2019	Out of 25 patients aged 10-25 years experiencing sickle cell crises, the use of VR among children resulted in a 16% decrease in pain intensity and a 33% decrease in pain descriptors.
Hoag et al.,[15] 2022	VR was found to significantly reduce procedural pain and distress during subcutaneous port access in children and adolescents with cancer compared with guided imagery. VR reduced the influence of pain catastrophizing on pain experience by twofold by alleviating feelings of helplessness and reducing rumination about pain.
Tennant et al.,[16] 2021	The use of VR on thirty pediatric oncology patients undergoing computed tomography simulation for radiotherapy showed prompt enhancement in procedural knowledge and retention at the 2-week follow-up. Immersive VR also increased patient satisfaction due to increased procedural knowledge and reduction of anticipatory and procedural anxiety.

VR; Virtual reality

Depending on the type of technology utilized, these headsets may be cordless or attached to a computer.[17] To enhance the VR experience, patients can use tools such as hand controllers or haptic feedback gloves to interact with and manipulate elements of the virtual environment. The design and selection of the virtual scenarios must be adapted to the procedure to maximize distraction and relaxation for young patients.[18]

Substantial training of healthcare professionals performing pediatric oncology procedures is required before integrating VR into the workflow. Healthcare professionals must be familiar with the capabilities and restrictions of VR systems as well as the correct use and maintenance of the equipment. Moreover, it is essential to create virtual situations tailored to a particular procedure to assure their applicability and efficiency. Teaching medical professionals how to introduce VR to their patients, explain its advantages and drawbacks, and respond to any queries or concerns is also needed. Importantly, medical professionals should monitor patients in real time during the procedure to gage their comfort level and modify the VR experience accordingly.[19]

Healthcare centers planning to incorporate VR technology into their pediatric oncology practices should work with VR developers to produce specialized applications that agree with pediatric oncology requirements, including scenarios suitable for patients' age and preferences. These centers should establish dedicated VR spaces equipped with the required technology and offering a relaxing atmosphere. Accessibility and availability should also be taken into consideration.[19]

Importantly, ethical issues regarding the appropriate integration of VR in pediatric oncology procedures need to be addressed. It is necessary to ensure that clients, parents, and legal guardians understand the advantages and drawbacks of using VR before giving informed patient consent. Respecting patients' and families' cultural diversity and viewpoints is essential. Finally, when using VR technology, privacy and security issues pertaining to the preservation of patient data must be addressed.[20]

Patients and Healthcare Providers' Perspectives

Numerous patients have reported positive experiences using VR, citing VR as a potent distraction tool that helped minimize their anxiety and perceived discomfort during bone marrow biopsy, bone marrow aspiration, and LP.[21]

Patients frequently appreciate the option to choose from custom VR experiences tailored to their preferences, including interactive games, tranquil nature vistas, or instructional information. In addition, patients feel empowered by VR, as it gives them a sense of control during otherwise unpleasant medical procedures.[22]

Parents and caregivers have emphasized the value of having a range of VR scenarios to cater to the child's individual tastes in line with their interests and age group. Healthcare professionals have reported notable decreases in patients' anxiety levels and better patient cooperation, which improves procedural efficiency.[20] They also observed that VR has simplified the process of patient preparation, requiring less sedation or immobilization before procedures.[23]

Some healthcare practitioners have expressed skepticism or reluctance to use VR in pediatric oncology procedures.[23] However, as the advantages of VR in terms of patient experiences and procedural outcomes become increasingly clear, there has been a noticeable change in the attitudes of healthcare professionals toward VR, and they are more likely to accept VR technology.[23] Thanks to training programs and workshops, the level of confidence and competence of healthcare workers in using VR during procedures has significantly increased. More healthcare professionals are now adopting and promoting VR as a secure and useful supplemental tool in pediatric oncology.[24]

Limitations of Virtual Reality Use in Healthcare

The technical requirements for specialized hardware and software can be expensive and thus impede the widespread adoption of VR. Moreover, VR simulations may not accurately replicate the complexities of real-world scenarios, resulting in potential disparities between virtual experiences and actual patient situations. Safety concerns and the potential for motion sickness and disorientation must also be addressed. Nonetheless, ongoing technological advancements and expanding research in the field hold promise for solving these issues and further optimizing the use of VR in patient care.

Future Directions and Potential Developments

VR technology is developing rapidly. Future research should focus on advancements in VR hardware, such as higher resolution displays, lighter, more comfortable headgear, and improved haptic feedback systems, which will provide patients with even more engaging and realistic experiences.[25] The incorporation of augmented reality (AR) into VR settings may provide medical professionals with real-time overlays of patient data and procedure-related information during interventions, enhancing procedural accuracy and efficacy. Furthermore, the integration of biofeedback and biometric monitoring into VR settings may enable medical professionals to further customize the experience and enhance its efficacy based on distinct patient reactions.[26]

Although the use of VR in pediatric oncology is promising, there are still many open questions requiring additional research. The implications of using VR during procedures, including its impact on patients' emotional health, coping mechanisms, and general attitude toward medical care, need to be studied over a longer period.[25] Protocols for integrating VR into pediatric oncology procedures are required. It will be important to determine the optimal timing and length of exposure to VR and to adapt VR experiences to patient preferences and age group.[4] Randomized studies will be required to assess VR's efficacy, clinical usefulness, and affordability compared with conventional sedative methods or other distraction strategies.

Collaborations between VR developers and healthcare professionals are essential to advance the development and applications of VR technology in pediatric oncology.

Developers will need input from healthcare practitioners to build realistic and procedure-specific virtual scenarios that accommodate clinical demands and patient requirements.[26] Through collaboration, patient-centered and clinically successful VR platforms can be developed, with the potential to transform pediatric oncology care and improve patient experiences across a range of medical specialties.[27]

Study Limitations

The above results of our study are subject to the inherent limitations of a narrative review. Also, it is important to note that articles from other databases or in languages other than English were not included. Finally, all articles containing animal models were disregarded, which might have affected the results.

Conclusion

Bone marrow biopsy, bone marrow aspiration, and LP are essential procedures for the accurate diagnosis and management of pediatric malignancies. However, these procedures often cause anxiety and pain. VR, as a potent diversionary tool, has demonstrated promising results in easing anxiety, reducing perceived pain, enhancing patient cooperation, and improving patient experience during these procedures. Thanks to the encouraging results in recent studies and the ongoing developments in VR technology, including the creation of immersive, interactive, and tailored experiences, VR can significantly improve pediatric oncology practice. Future studies should focus on refining VR hardware, incorporating AR and biofeedback, and establishing protocols to incorporate VR in the pediatric oncology setting.

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Validity of Erythrocyte Indices in Differentiation between Iron Deficiency Anemia and β-Thalassemia Trait in Children

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Abstract

Iron deficiency anemia (IDA) and β-thalassemia trait (BTT) are the most common causes of hypochromic microcytic anemia (HMA). Various erythrocyte indices that may help in the initial discrimination between IDA and BTT have been reported, but data evaluating their reliability in children are scarce. We aimed to evaluate the validity of 12 erythrocyte indices in the differentiation between IDA and BTT in children. These indices were red blood cell (RBC) count, Mentzer Index, England and Fraser Index, Srivastava Index, Shine and Lal Index, RBC distribution width (RDW), Ricerca Index, Green and King Index, RDW Index, Sirdah Index, Ehsani Index, and Serdar Index. Among 1,444 children with HMA, 136 (9.4%) were stratified into the IDA group and 137 (9.5%) into the BTT group. Of the 12 indices, the Green and King Index showed the highest reliability, as it had the highest Youden's index (75.1%). Its sensitivity, specificity, positive predictive value, negative predictive value and correct diagnosis rate were 92.7%, 82.4%, 84.1%, 91.8% and 87.5%, respectively. The second most reliable index was the RDW Index, having a Youden's index, sensitivity, specificity, positive predictive value, negative predictive value and correct diagnosis rate of 64%, 94.2%, 69.9%, 75.9%, 92.2% and 82%, respectively. Receiver operating characteristic analysis showed that the revised cut-off values for the Green and King Index and RDW Index had higher sensitivity and specificity levels than the cut-off values commonly used in the literature. The findings of this study suggest the superiority of the Green and King Index and the RDW Index as screening tools in the initial differentiation between IDA and BTT among children with HMA.

Keywords: Iron deficiency anemia, β-thalassemia trait, hypochromic microcytic anemia, erythrocyte indices, discrimination index

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Introduction

Iron deficiency anemia (IDA) is a prevalent problem worldwide, mainly affecting populations in underdeveloped and developing countries. It is the most common cause of hypochromic microcytic anemia (HMA). Beta-thalassemia trait (BTT), another common cause of HMA, is prevalent in certain regions of the world.[1] It has a prevalence of 2.5% in the Isparta province of Turkey. The city of Isparta is located in the Mediterranean region of Turkey, and its distance from Antalya is approximately 130 km.[2]

The correct diagnosis of a patient with HMA is important in several aspects. Identification of BTT is particularly crucial for genetic counseling, whereas IDA as the underlying cause warrants appropriate therapy. In most affected children, IDA can easily be treated with oral iron supplementation and dietary advice and may be associated with adverse neurocognitive outcomes if left untreated. On the other hand, blanket therapy with iron supplements in a BTT case may lead to excessive iron intake with possible harmful effects. A recent randomized controlled trial study including 562 children reported that adolescents who had no anemia and received iron supplements in infancy showed poorer performance on visual-motor and quantitative reasoning and displayed more errors on neurocognitive tasks than those who had no anemia and did not receive iron supplements in infancy.[3]

On competitive blood count (CBC) testing, IDA and BTT cases usually have similar hematologic findings, such as decreased mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH), and it may be quite challenging to discriminate between the two conditions correctly. The diagnosis of IDA usually relies on a low serum ferritin level and/or transferrin saturation index (TSI), whereas BTT is mostly diagnosed by an increased hemoglobin (Hb) A_2 (HbA_2) level in Hb electrophoresis. However, these laboratory investigations have significant costs and are time-consuming. In addition, they are not accessible to a large number of physicians. Since the 1970's, several indices such as the Mentzer Index calculated from simple erythrocyte parameters have been proposed for the inexpensive and simple differentiation between IDA and thalassemia carrier status.[4-15]

Most studies evaluating the efficiency of various erythrocyte indices in discriminating between IDA and BTT have been conducted in adults, and data in children are scarce.[16-26] We aimed to evaluate the reliability of 12 erythrocyte indices in the differential diagnosis between IDA and BTT in children with HMA.

Material and Method

This study included children aged 6 months-18 years who admitted to a pediatric outpatient clinic of Süleyman Demirel University, Medical Faculty Hospital between January 2018 and January 2020, and were found to have HMA using the data obtained from electronic records of the hospital. HMA was defined as follows: Hb < mean for age and sex-2 standard deviations (SD) (6 months-2 years <10.5 g/dL, 2-12 years <11.5 g/dL, boys aged 12-18 years <13 g/dL and girls aged 12-18 years <12 g/dL) and MCH < mean for age and sex-2 SD (6 months-2 years <23 pg, 2-6 years <24 pg, 6-18 years <25 pg) and MCV < mean for age and sex-2 SD (6 months-2 years <70 fL, 2-6 years <75 fL, 6-12 years <77 fL and 12-18 years <78 fL).[27] If the case had more than one CBC result consistent with HMA during the mentioned two-year period, then only the first testing was was taken into account.

Children with HMA were stratified into three groups as follows: 1) those with a serum ferritin level <12 ng/mL or those without a ferritin level measured, but with a TSI level <10% were classified in IDA group, 2) children having an HbA_2 level ≥3.5% in Hb electrophoresis were included in the BTT group; and 3) cases fulfilling the criteria of both IDA and BTT were classified in IDA + BTT group.

The efficiency of the 12 erythrocyte indices in differentiating between IDA and BTT was assessed using the data of children in the IDA and BTT groups, and cases in the IDA+BTT group were excluded from the analyses. The formulas for the erythrocyte indices and their previously proposed cut-off values are presented in **Table 1**.[4-15]

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences, version 23.0 (SPSS, Chicago, IL, USA), and for each erythrocyte index, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), correct diagnosis rate, and Youden's index (YI, sensitivity + specificity -1) were calculated. YI provides a reliable measure of the diagnostic validity of a certain technique because its formula involves both sensitivity and specificity.[28,29] Its value ranges between 0 and 1, and the minimum point for having an acceptable YI is 0.5. Receiver operating characteristic (ROC) analysis was performed to evaluate the erythrocyte indices in the differentiation between IDA and BTT. A p value <0.05 was considered statistically significant.

Süleyman Demirel University Faculty of Medicine Clinical Research Ethics Committee approval (February 2021 and 72 session number) was obtained before starting the study.

Results

During the study period, 1,444 children were found to have at least one CBC finding consistent with HMA. Among them, 136 cases (9.4%; 51 males and 85 females) were included in the IDA group and 137 cases (9.5%; 74 males and 63 females) in the BTT group. Data of nine subjects with both IDA and BTT were not included in the analyses.

Table 2 shows the laboratory findings of the subjects in the IDA and BTT groups, and **Table 3** displays the sensitivity, specificity, PPV, NPV, correct diagnosis rate, and YI of the 12 erythrocyte indices in differentiating BTT from IDA. The Green and King Index and RBC distribution width (RDW) Index had the highest YI (75.1% and 64.0%, respectively) and correct diagnosis rate (87.5% and 82.0%, respectively) (**Table 3**).

In ROC analysis, the revised cut-off values for the Green and King Index and RDW Index were found to have higher levels of sensitivity and specificity than the cut-off values commonly used in the literature. **Table 4** shows the ROC analysis results and the sensitivity and specificity levels of the indices according to the revised cut-off values. **Figure 1** presents the ROC curve.

Discussion

The findings of this study suggest that the Green and King Index and RDW Index may be superior to other erythrocyte indices in differentiation between IDA and BTT cases in our region. Many of the indices previously defined in the literature do not seem to be suitable for our study population.

Among the 1,444 children found to have HMA in the present study, only 282 (19.5%) could be included in the IDA, BTT or IDA + BTT group, and interestingly, the number of cases in the IDA and BTT groups was almost the same. We would rather expect iron deficiency to be the main cause of HMA in our patients. These findings may be explained by the lack of serum iron parameters or the presence of an accompanying infectious or inflammatory state when blood samples were taken, which may have caused an increase in serum ferritin levels in some cases with IDA. In children with HMA who do not fit into IDA diagnosis using markers such as serum ferritin at presentation, serum ferritin and other iron parameters should be examined intermittently in order not to miss IDA diagnosis.

We included only children with HMA in our study. In an individual, iron deficiency may be present without accompanying anemia. In addition, in its early stages, anemia associated with iron deficiency may be normocytic.[30] Cases of iron deficiency unaccompanied by HMA were not included in our study. In addition, we used "12 ng/mL" and "10%" as the cut-off values for low serum ferritin and TSI levels, respectively, which are both below the levels ("20 ng/mL" and "16%", respectively) in some studies in the literature.[18,20,22,23] Therefore, cases with HMA and a serum ferritin level in the range of 12-20 ng/mL or a TSI level in the range of 10-16% were not included in the IDA group in our study. However, the use of such low ferritin and TSI levels may have enabled a relatively high specificity of these variables for IDA diagnosis in our cases with HMA. Finally, as our hospital is the only tertiary care center in our province, most cases with suspected BTT may have been referred to our hospital for further analyses, resulting in a relatively high percentage of children with BTT in our study.

Highlights

- Iron deficiency anemia (IDA) and β-thalassemia trait (BTT) are the most common forms of hypochromic microcytic anemias, and differentiation between these two conditions is important as their management differs completely.
- Several indices calculated from some erythrocyte parameters on hemogram test have been proposed so far for the initial differentiation between IDA and BTT.
- None of these indices is 100% reliable in the discrimination between IDA and BTT.
- In children from Isparta province of Turkey, Green and King Index and red cell distribution width Index (RDWI) may be helpful in the initial differentiation between IDA and BTT.

Iron deficiency accompanying BTT may be thought to interfere with BTT diagnosis by decreasing HbA_2 levels. However, iron deficiency, even when very severe, is very unlikely to significantly interfere with HbA_2-based identification of BTT.[31,32] In patients with iron deficiency, HbA_2 levels have been reported to be lower, but not below the 3.5% cut-off.[33,34] Therefore, we believe that cases with IDA and an HbA_2 level <3.5% in our study are very unlikely to have additional BTT.

Among the erythrocyte indices evaluated here, we found the YI of only four (Green and King Index, RDW Index, Srivastava Index and Sirdah Index) to be acceptable (>50%) in differentiation between IDA and BTT (**Table 3**). Mentzer Index (MCV/RBC), one of the best-known erythrocyte indices in differentiation between IDA and BTT, had a sensitivity of 93.4% in the present study; however, its YI was found to be quite low (40.5%), which can be attributed to its low specificity (47.1%) (**Table 3**). Similar to our findings, some previous studies have also reported a high sensitivity and NPV but a low specificity and PPV of the Mentzer Index for BTT diagnosis.[23,24,26]

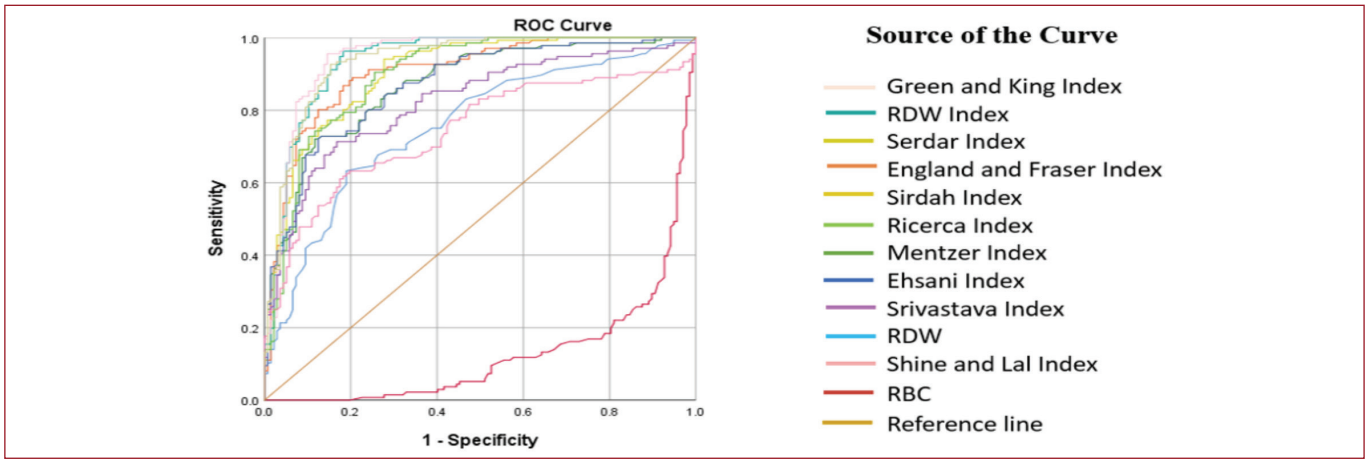

Figure 1. ROC curve of erythrocyte indices for differentiation of BTT from IDA.

ROC; Receiver operating characteristic, BTT; β-thalassemia trait, IDA; Iron deficiency anemia

However, the results of some other studies seem to contradict these observations.[16,18,20-22]

Another erythrocyte index commonly used in differentiation between IDA and BTT is the RBC count (**Table 1**). However, Aslan and Altay[35] reported that in 36 (26%) of 140 children aged 6 to 48 months who had IDA and no accompanying thalassemia trait, the RBC count was high (≥5.0 x 10^6/L) at the time of diagnosis. The authors observed the elevation in RBC count to be more pronounced in patients with mild anemia, who have the highest probability of being misdiagnosed as having a thalassemia trait, and concluded that an elevated RBC count is not reliable in differentiation between IDA and thalassemia trait in certain patient groups. We also found that the RBC count not to be reliable in differentiation between IDA and BTT. Similar to the Mentzer Index, it had low specificity and PPV levels, and its YI was below the acceptable range (**Table 3**).

In a recent study evaluating the roles of 30 erythrocyte indices in differentiation between IDA and BTT in adults, a newly proposed index (Serdar Index) was found to be superior to 29 previously reported indices.[15] However, in our study, which included only children, this new index did not reliably differentiate between IDA and BTT (**Table 3**).

The results of different studies evaluating the efficiencies of various erythrocyte indices in the differential diagnosis of IDA and BTT seem to be controversial.[15-26,35-39] In our study, the Green and King Index and RDW Index were found to be the most reliable indices. Some previous studies from different countries have also reported the Green and King Index to be among the most reliable erythrocyte indices in differentiation between IDA and BTT.[23,32-35] The YI of the Green and King Index ranged between 68% and 79.8% in those studies. In addition, the RDW Index has been found to be among the most valuable indices in the differentiation between IDA and BTT in some previous studies.[23,26,36,39] We also observed the Green and King Index and RDW Index to better differentiate BTT from IDA by using their revised cut-off values found in the ROC analysis (**Table 4**). The Green and King Index was also superior to other indices in ROC analysis (**Table 4**, **Figure 1**).

On the contrary, other studies, including one study from the East Thrace region of Turkey, have reported that the

Table 1. *Formulas and cut-off values of erythrocyte indices used for differentiating IDA and BTT*

Index	Formula cut-off value
RBC count	RBC
BTT	>5
IDA	<5
Mentzer index	MCV/RBC
BTT	<13
IDA	>13
England and Fraser index	MCV-RBC-(5 x Hb)-8.4
BTT	<0
IDA	>0
Srivastava index	MCH/RBC
BTT	<3.8
IDA	>3.8
Shine and Lal index	MCV²xMCH/100
BTT	<1530
IDA	>1530
RDW	RDW
BTT	<14
IDA	>14
Ricerca index	RDW/RBC
BTT	<4.4
IDA	>4.4
Green and King index	MCV² x RDW/(Hb x 100)
BTT	<65
IDA	>65
RDW index	MCV RDW/RBC
BTT	<220
IDA	>220
Sirdah index	MCV-RBC-(3 x Hb)
BTT	<27
IDA	>27
Ehsani index	MCV-(10 x RBC)
BTT	<15
IDA	>15
Serdar index	(MCV² × RDW)/[(10 × RBC)² × MCHC]
BTT	<0.96
IDA	>0.96

BTT; β-thalassemia trait, Hb; Hemoglobin, IDA; Iron deficiency anemia, MCH; Mean corpuscular Hb, MCHC; Mean corpuscular Hb concentration, MCV; Mean corpuscular volume, RBC; Red blood cell, RDW; Red cell distribution width

Table 2. *Hematologic data of the subjects in the IDA and BTT groups*

	IDA group (n=136) Mean ± SD (Min.-Max.)	BTT group (n=137) Mean ± SD (Min.-Max.)
Hb, g/dL	9.82±1.50 (6.2-11.6)	11.15±0.81 (9.8-13.6)
Hct, %	31.20±3.62 (23.3-35.8)	34.32±2.78 (28.3-42.0)
RBC, x10^6/mm^3	5.16±0.44 (4.33-5.89)	5.84±0.48 (4.43-6.88)
MCV, fL	60.57±5.81 (49.6-72.5)	58.54±4.06 (51.5-70.9)
MCH, pg	19.05±2.55 (13.4-23.7)	19.10±1.29 (16.3-22.6)
MCHC, g/dL	31.47±1.50 (26.9-33.6)	32.63±1.00 (30.9-36.1)
RDW, %	19.99±3.61 (13.6-30.0)	16.80±1.70 (14.5-25.1)
HbA2, %	2.37±0.44 (1.3-3.2)†	5.24±0.68 (3.7-6.9)
Ferritin, ng/mL	5.24±2.47 (0.5-11.0)	66.19±117.30 (12.6-780.0)‡
TSI, %	4.28±2.39 (0.25-19.88)	24.04±10.53 (2.27-44.92)‡

†HbA2 was examined in 37 subjects in the IDA group.
‡Serum ferritin and TSI levels were available in 123 and 72 subjects in the BTT group, respectively.
BTT; β-thalassemia trait, Hb; Hemoglobin, Hct; Hematocrit, IDA; Iron deficiency anemia, Max.; Maximum, MCH; Mean corpuscular Hb, MCHC; Mean corpuscular Hb concentration, MCV; Mean corpuscular volume, Min.; Minimum, RBC; Red blood cell, RDW; RBC distribution width, SD; Standard deviation, TSI; Transferrin saturation index

Table 3. *Predictive values of erythrocyte indices for differentiating BTT from IDA*

Index	Sen. (%)	Spe. (%)	PPV (%)	NPV (%)	Corr Dia (%)	YI
Ehsani index	94.2	47.1	64.2	88.9	70.7	41.2
England and Fraser index	98.5	36.0	60.8	96.1	67.4	34.6
Green and King index	92.7	82.4	84.1	91.8	87.5	75.1
Mentzer index	93.4	47.1	64.0	87.7	70.3	40.5
RBC	96.4	44.1	63.5	92.3	70.4	40.5
RDW	0	99.3	0	49.6	49.5	-0.7
RDW index	94.2	69.9	75.9	92.2	82.0	64.0
Ricerca index	99.3	14.0	53.8	95.0	56.8	13.2
Serdar index	97.1	42.7	63.0	93.6	70.0	39.7
Shine and Lal index	100.0	0	50.2	0	50.2	0
Sirdah index	94.2	59.6	70.1	91.0	77.0	53.7
Srivastava index	86.9	67.7	73.0	83.6	77.3	54.5

BTT; β-thalassemia trait, Corr Dia; Correct diagnosis, HMA; Hypochromic microcytic anemia, IDA; Iron deficiency anemia, NPV; Negative predictive value, PPV; Positive predictive value, RBC; Red blood cell, RDW; RBC distribution width, Sen.; Sensitivity, Spe.; Specificity, YI; Youden's index

Table 4. *ROC analysis results and sensitivity and specificity levels according to the revised cut-off values*

Index	AUC	SE	Cut-off	Sen. (%)	Spe. (%)	P value
Ehsani index	0.868	0.021	9.3	72.1	87.6	<0.001
England and Fraser index	0.905	0.018	-4.7	80.1	87.6	<0.001
Green and King index	0.944	0.015	60.7	95.6	85.4	<0.001
Mentzer index	0.869	0.021	11.8	72.1	88.3	<0.001
RBC	0.127	0.021	5.39	21.3	19.0	<0.001
RDW	0.756	0.029	18.0	63.2	81.0	<0.001
RDW index	0.937	0.015	190.2	94.9	82.5	<0.001
Ricerca index	0.897	0.019	3.1	90.4	74.5	<0.001
Serdar index	0.936	0.015	0.66	92.6	84.7	<0.001
Shine and Lal index	0.742	0.031	773.5	61.0	82.5	<0.001
Sirdah index	0.904	0.018	21.5	94.1	72.3	<0.001
Srivastava index	0.822	0.026	3.7	71.3	83.2	<0.001

AUC; Area under the curve, RBC; Red blood cell, RDW; Red cell distribution width, SE; Standard error, Sen.; Sensitivity, Spe.; Specificity

Green and King Index and RDW Index not to be valid in differentiating BTT from IDA.[19,22,40] In all these studies, the YI for both the Green and King Index and the RDW Index has been reported to be in the unacceptable range (<50%), and some other erythrocyte indices such as the England and Fraser Index have been found to be more reliable. The controversial findings in different studies may be explained by the inclusion of cases with different age ranges, by accepting different cut-off values for some variables such as serum ferritin in defining IDA, and by other differences in study designs. In addition, the IDA and BTT characteristics may change from one population to another. For example, the percentage of severely affected IDA patients may be higher in populations where nutritional anemia is more prevalent, and these cases may have more pronounced abnormalities in erythrocyte indices. On the other hand, the erythrocyte phenotype of individuals with BTT may be affected by the underlying β-globin mutations and, if present, by the type of the accompanying α-globin mutations which vary from one population to another.

In the present study, 273 children with HMA could be included either into the IDA (n=136) or the BTT group (n=137). This moderate sample size and the almost equal number of cases in the two groups are among the strengths of this study. However, our study has some limitations, mainly due to its retrospective nature. First, the most reliable indicator of IDA is an increase in reticulocyte count and Hb level following sufficient oral iron therapy; however, we could not evaluate data regarding the response to iron therapy in our patients included in the IDA group. Second, although iron parameters such as serum ferritin levels were analyzed in most subjects in the BTT group, HbA_2 was available in only 37 (27.2%) of 136 cases in the IDA group (**Table 2**). This may be because physicians examining these patients did not suspect an underlying thalassemia trait because of a reason such as the resolution of HMA in the follow-up. Finally, we did not have any data about the presence or absence of any accompanying α-globin mutations, the presence of which may affect erythrocyte indices. However, we are of the opinion that α-globin mutations may have been present in only a few individuals among our cases, which may have had no significant effect on our results.

In conclusion, none of the erythrocyte indices are 100% specific or sensitive in differentiating BTT from IDA. Hb electrophoresis, and in selected cases, genetic analysis will offer a definitive diagnosis. However, our results suggest that the Green and King Index and RDW Index are superior to other indices analyzed here and could guide physicians in the initial discrimination between

IDA and BTT among children in the Isparta province of Turkey.

Ethical Approval: Süleyman Demirel University Faculty of Medicine Clinical Research Ethics Committee approval (February 2021 and 72 session number) was obtained before starting the study.

Informed Consent: Retrospective study.

Author Contributions: Uzunoğlu E: Surgical and Medical Practices, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Yılmaz Keskin E: Surgical and Medical Practices, Concept, Design, Literature Search, Writing.

Conflict of Interest: The authors declare no conflicts of interest. The authors are responsible for the content and writing of this article.

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Hemogram Parameters Cannot Distinguish Pediatric COVID-19 from Other Respiratory Infections

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Abstract

To fight against the pandemic, which has become the most significant public health problem of modern times, the isolation of patients and early detection of the coronavirus disease-2019 (COVID-19) disease are crucial. This study aimed to show the diagnostic predictor of hemogram parameters and the rates obtained from these parameters in differentiating COVID-19 from other respiratory tract diseases. Data of patients aged between 1 month and 18 years who were admitted to the 3rd and 2nd level pediatric emergency with the pre-diagnosis of "COVID-19-like disease" between 12 January 2022 and July 12, 2022, which is one month after the Omicron (Nu) variant was accepted as an established variant in Türkiye, were retrospectively reviewed. A total of 724 children with pre-diagnosis of COVID-19-like disease whose complete blood count and severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) polymerase chain reaction (PCR) test from oropharynx/nasopharyngeal swab samples were included in the study. Two hundred children were positive for SARS-CoV-2 PCR (27.6%). Total leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, platelets, platelet distribution width, platelet crit counts, and neutrophil/lymphocyte ratio were lower, and hemoglobin values were higher in the COVID-19 group than in the other group. These differences were statistically significant ($p<0.05$). When these parameters were evaluated by receiver operating characteristic analysis, the area under the curve values of the other parameters, except the eosinophil count, were statistically significant. However, when the obtained possibility ratios were examined, significant cut-off values could not be obtained regarding diagnostic predictiveness. It was found that using complete blood count parameters in the diagnostic process is not helpful in differentiating SARS-CoV-2 from other respiratory tract diseases. It is essential to conduct studies with larger sample sizes to understand whether complete blood count parameters can predict the diagnosis of COVID-19.

Keywords: COVID-19, triage, children, laboratory indices, SARS-CoV-2

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Introduction

Since the first case reported in December 2019 in the city of Wuhan, Hubei province, China, the Coronavirus disease-2019 (COVID-19) pandemic has become the most significant modern public health emergency, with approximately 641 million infections and 6.6 million deaths worldwide as of December 2022.[1,2] COVID-19 disease is a multisystemic infection affecting the pulmonary, neurological, and gastrointestinal systems.[3] Therefore, many patients with flu-like symptoms should be tested to rule out COVID-19. Considering the duration of the SARS-CoV-2 PCR test results, there have been delays in making the diagnosis and isolation decision for clinicians.[3,4] However, differentiating COVID-19 infection from other respiratory tract infections is essential for disease control.[5] Generally, leukocyte, neutrophil, lymphocyte count, neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR) are markers of systemic inflammation.[6] In studies comparing COVID-19 and other viral infections in children, it has been reported that the lymphocyte count is lower in those with influenza infection, and the leukocyte and neutrophil counts are higher in patients with influenza and human adenovirus infections.[7-9] In studies comparing viral infections such as influenza and respiratory syncytial virus with COVID-19, the NLR was found to be lower in COVID-19.[8,10] Therefore, complete blood count parameters, which are frequently requested laboratory tests in the emergency department, can be used for diagnosis, especially in cases where serological or molecular tests cannot be performed rapidly in centers with limited resources or when demand exceeds supply due to seasonally increasing respiratory tract infections, and may be necessary for the isolation decision.[11] Although studies have generally focused on hemogram parameters and clinical severity of COVID-19, there are not enough studies on this subject in children. This study aimed to demonstrate the role of complete blood count parameters in diagnosing COVID-19 in patients admitted to the emergency department with a COVID-19-like disease.

Material and Method

Study Design

The data of the patients between the ages of 1 month and 18 years who were admitted with a pre-diagnosis of "COVID-19-like disease" for 6 months between January 12, 2022, and July 12, 2022, which is one month after the first isolation date (12 December 2021) of the SARS-CoV-2 VOC (B.1.1.529): Omicron (Nu) variant in Türkiye in terms of being an established variant, was scanned in Çanakkale Onsekiz Mart University and Çan State Hospital Pediatric Emergency Service.

Study Procedure and Data Collection

The study protocol was approved by the Çanakkale Onsekiz Mart University Local Clinical Research Ethics Committee (date: 18.01.2023, no: 2023/02-20), and the study was conducted according to the principles of the Declaration of Helsinki. On the specified dates, the patients whose SARS-CoV-2 PCR test and complete blood count were studied and who had at least one of the following symptoms: 1) the child had a history of fever or the measured temperature value is 38.0ºC or higher, 2) presence of lung auscultation findings, 3) presence of tachypnea, 4) presence of new-onset cough, 5) Oxygen saturation ≤92% in room air, as stated in the "COVID-19; Pediatric Patient Management and Treatment" guide published on 06.01.2022, were included. We classified the patients with positive SARS-CoV-2 PCR tests as the COVID-19 group and those with negative results as the other group. From complete blood count parameters, we recorded leukocyte, neutrophil, lymphocyte, monocyte (M), eosinophil (E), platelet (PLT), and erythrocyte counts; hemoglobin, mean erythrocyte and platelet volume, erythrocyte and platelet distribution width (PDW), platelet crit (PCT), and mean corpuscular hemoglobin concentration.

Outcome Measures

The primary outcome was whether there was a difference in hemogram parameters between the COVID-19 group and the other group in patients whose complete blood count was studied with the pre-diagnosis of "COVID-19-like disease". The secondary outcome was to evaluate the diagnostic predictiveness of these hemogram parameters in terms of predicting the diagnosis of COVID-19.

Statistical Analysis

Descriptive statistics such as mean ± standard deviation or median and interquartile range were used for continuous variables, and frequency (n) and percentage (%) for categorical variables, depending on whether the data was parametric or not. We analyzed the primary outcome using the t-test and the secondary outcome using receiver operating characteristic (ROC) analysis. Cases with a type 1 error level of 5% were interpreted as statistically significant. We used the SPSS program (version 23.0, IBM Company, SPSS Inc.) for statistical analysis.

Results

Participant Characteristics

A total of 724 children with a pre-diagnosis of COVID-19-like disease whose complete blood count and SARS-CoV-2 PCR test from oropharynx/nasopharyngeal swab samples were included in the study. The mean age of the participants was 80.5 (±69.5) months, and 423 (59.7%) were male. 200 (27.6%) patients with positive SARS-CoV-2 PCR were included in the COVID-19 group.

Primary Outcome Analysis

Total leukocyte, neutrophil, lymphocyte, monocyte, eosinophil, PLT, PDW, and PCT counts and NLR were lower, and hemoglobin values were higher in the COVID-19 group than in the other group. These differences were statistically significant ($p<0.05$) (**Table 1**). The NLR was lower in the COVID-19 group (2.86 vs. 3.92, $p=0.010$), but there was no statistical difference in the PLR between the two groups (148 vs. 168, $p=0.096$).

Secondary Outcome Analysis

When the parameters that differed significantly between the groups were evaluated by ROC analysis in terms of predicting the diagnosis of COVID-19, except for the eosinophil count, the "area under the ROC curve (AUC)" value of the other parameters was statistically significant. The highest AUC value (AUC=0.575) was obtained for hemoglobin (**Table 2**). However, when the possibility ratios were examined, significant cut-off values could not be obtained regarding diagnostic predictors (**Table 2**) (**Figure 1**).

Highlights

- Our study shows that it is not possible to use complete blood count parameters in the diagnosis process in centers where severe acute respiratory syndrome-coronavirus-2 and/or other respiratory viral polymerase chain reaction tests cannot be concluded quickly.
- Early detection and differentiation of cases from other respiratory diseases are important in terms of follow-up and treatment in the coronavirus disease-2019 (COVID-19) pandemic.
- In our study, we focused on demonstrating the role of complete blood count parameters in the diagnosis of COVID-19 in patients admitted to the emergency department with a COVID-19-like illness.

Discussion

This retrospective study, which included 724 patients, had two main findings. First, the rate of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, platelets, and NLR was lower in the COVID-19 group in children with COVID-19-like disease symptoms. Second, these complete blood count (CBC) parameters were not predictive of the diagnosis of COVID-19.

First, the COVID-19 group had decreased platelet counts, neutrophils, lymphocytes, monocytes, eosinophils, total leukocytes, and NLR levels.

White blood cell populations (monocytes, lymphocytes, and neutrophils) play an essential role in the systemic inflammatory response in conditions such as severe infection and trauma, whereas platelets are the primary mediators of hemostasis.[12,13] Current evidence shows that COVID-19 can cause a severe systemic inflammatory response by causing a cytokine storm and causing damage, especially to T lymphocytes, because viral spread cannot be limited to adults.[14-16] However, unlike adults, COVID-19 does not cause a significant systemic inflammatory response in children.[14] In addition, it has been reported that eosinophil counts in the peripheral circulation are low because eosinophils accumulate in infected tissues during the acute phase of viral infections.[13] Similar to our study, studies comparing hemogram parameters of patients with COVID-19-like symptoms and patients with COVID-19 reported lower leukocytes, neutrophils, and eosinophil counts in the COVID-19 group.[7-9,17] Although the virus is expected to cause lymphopenia due to damage to T-lymphocytes, there are conflicting results regarding lymphocyte counts in the literature.[8,9,18] Nonetheless, when patients with COVID-19 were compared with patients with COVID-19-like symptoms, it was shown that only lymphopenia could significantly distinguish patients in the two groups.[19] The NLR is frequently used to evaluate the inflammatory state.[20] In studies similar to our study, it has been reported that the rate of NLR in COVID-19 patients is lower than that in other respiratory tract infections.[8,10]

Second, the diagnosis of COVID-19 could not be made using these CBC parameters as a predictive diagnostic tool.

Given the global epidemiology and alarming severity of COVID-19 infection, early detection of COVID-19 remains crucial despite the introduction of vaccines.[21,22] Confirmation of infection is performed by RT-PCR,

Table 1. *Blood count characteristics of patients with a pre-diagnosis of "COVID-19-like disease"*

Parameter	General (n=724)	SARS-CoV-2 PCR		p-value
		Positive (n=200)	Negative (n=524)	
Leucocyte (/mm³)	10.100±5.100	7.600**±4.400**	11.100**±5.100**	<0.001**
Neutrophil (/mm³)	6004.4±4220.1	2862.6**±3920.2**	3925.2**±5306.3**	0.003**
Lymphocyte (/mm³)	3134±2501.6	2614.1**±2076.3**	3332.4**±2620.6**	<0.001**
Monocyte (/mm³)	818.5±505.1	725.2**±436.2**	854.12**±525.1**	0.002**
Eosinophil (/mm³)	145.8±230	105.1**±164.4**	161.4**±249.1**	<0.001**
Hgb (g/dL)	12.4±1.5	12.6**±4.1**	12.3**±1.6**	0.017**
RBC (x10⁶mm³)	4.6±0.5	4.6**±0.5**	4.6**±0.5**	0.060
MCV (fL)	80.5±7.4	80.7 4**±6.7**	80.4**±7.7**	0.630
PLT (x10³mm³)	300±104.9	280.7**±91.2**	307.3**±108.8**	0.001**
RDW (%)	14±1.4	13.9**±1.5**	14.1**±1.4**	0.872
MPV (fL)	9.2±1.2	9.4**±1.2**	9.1**±1.2**	0.073
PDW (fL)	14.3±2.4	13.6**±2.8**	14.5**±2.2**	<0.001**
PCT (%)	0.2±0.08	0.2**±0.07**	0.2**±0.08**	<0.001**
MCHC (g/dL)	33.3±1.4	33.5**±1.1**	33.2**±1.5**	0.094

*Numerical variables are shown as mean ± SD.
**p<0.05
Hgb; Hemoglobin, RBC; Red blood cells, MCV; Mean corpuscular volume, PLT; Platelet, RDW; Red blood cell distribution width, MPV; Mean platelet volume, PDW; Platelet distribution width, PCT; Platelectrit, MCHC; Mean corpuscular hemoglobin concentration, COVID-19; Coronavirus disease-2019, SARS-CoV-2; Severe acute respiratory syndrome-coronavirus-2, PCR; Polymerase chain reaction, SD; Standard deviation

Table 2. *Evaluation of the relationship between SARS-CoV-2 PCR result and complete blood count with ROC analysis*

Parameter	Area under the curve of ROC curve	Standard deviation	p-value	95% confidence interval OR		Cut off levels	Sensitivity	Specificity
				Lower limit	Upper limit			
Leucocyte	0.262	0.022	<0.001	0.220	0.304	6.485/mm^3	50	16
Neutrophil	0.288	0.021	<0.001	0.247	0.330	3.190/mm^3	50	21
Lymphocyte	0.396	0.023	<0.001	0.351	0.442	1.975/mm^3	50	33
Monocyte	0.413	0.024	<0.001	0.366	0.459	615/mm^3	51	36
Eosinophil	0.469	0.022	0.197	0.426	0.512	55/mm^3	53	44
Hgb	0.575	0.023	0.002	0.529	0.620	12.2 gr/dL	66	48
Thrombocyte	0.420	0.023	<0.001	0.375	0.462	270.500/mm^3	58	40
PDW	0.437	0.025	0.009	0.388	0.487	15 fL	50	36
PCT	0.406	0.023	<0.001	0.360	0.452	0.26%	50	39
Neutrophil/ Lymphocyte	0.428	0.023	0.003	0.382	0.470	1.6	50	40

Hgb; Hemoglobin, PDW; Platelet distribution width, PCT; Platelectrit, ROC; Receiver operating characteristic, OR; Odds ratio, SARS-CoV-2; Severe acute respiratory syndrome-coronavirus-2, PCR; Polymerase chain reaction

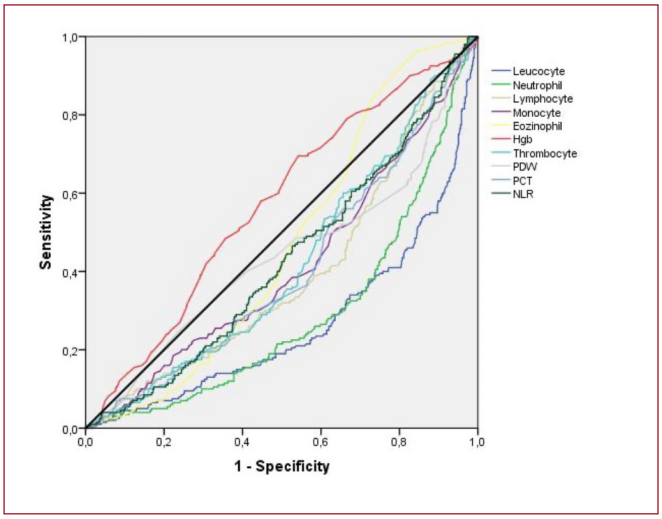

Figure 1. ROC analysis of hemogram parameters
ROC; Receiver operating characteristic

which is considered the gold standard for laboratory diagnosis.[21] However, human resources and laboratory capacities often must be improved to diagnose comprehensively and rapidly.[19] Several laboratory parameters have been proposed to distinguish SARS-CoV-2-positive patients from those with COVID-19-like symptoms.[23,24] Although the AUC values obtained for the NLR were found to be statistically significant, as in our study, in studies conducted to distinguish between patients with COVID-19 and patients with COVID-19-like symptoms, sufficient specificity and sensitivity values could not be obtained in terms of diagnostic predictiveness.[5,25] Monocytes play an essential role in maintaining the inflammatory response. A previous study found that monocytosis had the highest AUC value and specificity among hemogram parameters.[21] In another study, neutrophilia and leukopenia were interpreted as predictive findings in predicting a positive COVID-19 PCR test.[26] These results may be due to the small sample size, and further research with a larger sample size is needed to reach a firm conclusion.

Study Limitations

This study has some limitations. First, there may be case selection bias because this is a retrospective study. Second, in some patients, the SARS-CoV-2 PCR test may be falsely negative, depending on the person receiving the swab, viral load, specimen collection, and transport conditions. Finally, we could not analyze for agents because we could not confirm viral infection agents other than COVID-19 by PCR.

Conclusion

In summary, early detection and differentiation of cases from other respiratory diseases are essential for follow-up and treatment in the COVID-19 pandemic, which has become a unique health crisis. Considering all these results, laboratory findings differ significantly between studies conducted in different clinical and research centers. Our study shows that it is impossible to use complete blood count parameters in the diagnosis process in centers where SARS-CoV-2 and/or other respiratory viral PCR tests cannot be performed quickly. However, the authors suggest that studies with larger sample sizes are needed to understand whether complete blood count parameters can predict the diagnosis of COVID-19.

Ethical Approval: The study protocol was approved by the Local Clinical Research Ethics Committee (dates 18.01.2023, no: 2023/02-20 - Çanakkale Onsekiz Mart University Clinical Research Ethics Committee), and the study was conducted according to the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Author Contributions: Çelik T: Surgical and Medical Practices, Concept, Design, Analysis or Interpretation, Literature Search, Writing.; Kasap T: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Çakan B: Surgical and Medical Practices, Data Collection or Processing, Analysis or Interpretation,

Literature Search, Writing.; Aydemir Kılıç N: Surgical and Medical Practices, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.

Conflict of Interest: The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Evaluation of Etiologic Agents of Lower Respiratory Tract Infections in Children Hospitalized Just Before Normalization of COVID-19

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Abstract

Lower respiratory tract infections (LRTIs) are one of the most common causes of hospitalization among children in the early childhood period. Knowing the pathogens that cause pneumonia, its management will be more exact and effective. In this study, we aimed to investigate the frequency of pathogens causing LRTIs in children at the end of the COVID-19 pandemic by performing a real-time multiplex polymerase chain reaction (RT-MPCR) test within our hospital. We included two hundred forty-seven children, aged between 1 month and 18 years, diagnosed with LRTIs, and hospitalized between May 2021 and April 2022. Demographic characteristics and clinical and laboratory findings were retrospectively collected from patients' hospital records. Of the 247 children diagnosed with LRTIs, 153 (61.9%) were female. At least one pathogen was identified in the nasopharyngeal swap specimens of 218 (88.3%) patients, and 74.9% (n=185) of them were viruses. The most common identified pathogens were respiratory syncytial virus (24.7%), human bocavirus (21.1%), and severe acute respiratory syndrome coronavirus 2 (15.4%). 7.7% of identified pathogens were bacteria. *Haemophilus influenzae* was the most commonly detected bacteria. Despite a lengthy period of isolating the community causative agents of pneumonia, their frequency remains unchanged from before the isolation time. RT-MPCR is beneficial for the early detection of pathogens and in the prevention of unnecessary antibiotic usage.

Keywords: Children, etiologic agents, lower respiratory tract infections, real-time multiplex polymerase chain reaction test, viruses

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Introduction

Lower respiratory tract infections (LRTIs) are one of the most common causes of hospitalization in children during the early childhood period. According to the World Health Organization, pneumonia is responsible for 14% of deaths of children under five years of age, and approximately annually 740.180 child deaths occur worldwide.[1] The causative pathogens vary depending on the region and age of the children. Viruses are responsible for the majority of diseases, especially among children aged 5 years, and the incidence decreases with age increase.[2-4] The respiratory syncytial virus (RSV) is the most common virus causing LRTIs in young children; parainfluenza viruses 1, 2, and 3 (PIV 1,2,3), influenza A and B viruses (IFV A/B), adenovirus (AdV), rhinovirus (RV), human metapneumovirus (hMPV), human bocavirus (HboV), parechovirus, coronaviruses (CoV), and enterovirus are the others.[5-8] *Streptococcus pneumoniae (S. pneumonia)* is the most common bacterial cause in all age groups of children; others are non-typeable *Haemophilus influenzae (H. influenzae)* and *H. influenzae type b, Streptococcus pyogenes (S. pyogenes), Staphylococcus aureus (S. aureus), Moraxella catarrhalis (M. catarrhalis), Mycoplasma pneumonia (M. pneumonia)* and *Chlamydophila pneumonia (C. pneumonia)*.[2,7,9] Although most LTRIs are caused by viruses, there is no specific clinical finding to distinguish viral infections from bacterial infections. Therefore, early and accurate detection of etiological pathogens and the initiation of appropriate treatment will significantly reduce unnecessary antibiotic usage and enable appropriate treatment to reduce morbidity and mortality. Studies have shown that blood cultures have a low rate of pathogen detection (1-3%), and routine serologic tests have limited usage. On the other hand, recent studies have shown that real-time multiplex polymerase chain reaction (RT-MPCR) is helpful in rapidly diagnosing etiologic bacterial and viral pathogens of LRTIs.[2,10-14] Our study aims to identify pathogens of LRTIs and their frequency in children after long isolation periods in the community to prevent unnecessary antibiotic usage.

Material and Method

This was a retrospective cross-sectional study. The study population comprised children aged between 1 month and 18 years hospitalized due to LRTIs in the Pediatric Department between May 1, 2021 and April 30, 2022. Patients' demographic data, clinical and laboratory findings, treatment, and outcomes were recorded from their medical files. LRTI was defined as the presence of clinical findings of fever, cough, chest pain, tachypnea, and dyspnea with abnormal auscultatory findings and/or radiographic findings in chest X-rays. Radiographic findings were classified as bronchiolitis, bronchopneumonia, and lobar pneumonia. Bronchiolitis was defined as the presence of poorly defined small, multifocal nodules or air-trapping areas characterized by hyperlucency. Bronchopneumonia was defined as the presence of focal nodular opacities and patchy areas of consolidation involving one or more segments of a single or multiple lobes. Lobar pneumonia was defined as the presence of focal dense opacification of most the entire lobe. Children with chronic lung disease, congenital heart diseases, immune deficiency, muscular disease, neurometabolic disease, hospital-acquired pneumonia, and children who had undergone tracheostomy and/or home ventilation devices were excluded from the study.

RT-MPCR tests were conducted on 23 pathogens including AdV, HboV, RSV, PIV 1, 2, 3, 4, IFV A, B, RV, enterovirus, hMPV, CoV-OC43, CoV-229E, CoVNL63, human parechovirus, HcoV, SARS-CoV-2, *M. pneumonia, L. pneumonia, S. pneumonia, C. pneumonia,* and *Bordetella pertussis.*

Statistical Analysis

All analyses were performed using the SPSS 23.0 statistical software package (IBM SPSS Statistics). Categorical variables were expressed as numbers (n) and percentages, whereas continuous variables were summarized as mean with standard deviation or as median with minimum-maximum where appropriate. Chi-square tests were used to compare categorical variables between groups. The normality of distribution for continuous variables was tested using the Kolmogorov-Smirnov test. For continuous variables that had normal distribution, >2-group comparisons were performed using One-Way ANOVA. For the pairwise corrections of the ANOVA, we used the Bonferroni correction. The statistical level of significance for all tests was defined as a p-value of <0.050.

The study was approved by the Ethics Committee of Medeniyet University Göztepe Training and Research Hospital (approval date: 16.03.22; approval number: 2022/0150) before the experiment was started and was conducted in accordance with the principles set forth in the Helsinki Declaration.

Results

Of the 247 children diagnosed with LRTIs, 153 (61.9%) were male. The mean age of the patients was 2.93±4.09 (0.1-17.7) years, and 148 (59.9%) of them were under 2 years old. The most common symptoms at admission were cough (74.5%), fever (46.6%), and wheezing (29.1%). High-flow nasal cannula (HFNC) oxygen therapy was administered to 66 patients (26.7%) with respiratory distress (**Table 1**).

At least one pathogen was detected in 218 (88.3%) of the nasopharyngeal swap specimens. Of the detected pathogens, 74.9% (n=185) were viruses, 7.7% (n=19) were bacteria, and 5.7% (n=14) were both bacteria and viruses. The leading pathogens were RSV (27.1%), HBoV (21.1%), RV (15.8%), and SARS-CoV-2 (15.4%). In addition, RSV (37.9%) and HBoV (25.8%) were the most commonly identified pathogens in patients requiring HFNC (**Table 2**).

When the pathogens were evaluated in terms of their distribution according to age, RSV (80.6%), HBoV (57.7%), RV (51.3%), PIV-3 (68.6%), and *H. influenzae* (85.7%) were most commonly detected in children

under 2 years of age, whereas SARS-CoV-2 was predominantly found in children over 10 (47.4%) and under 2 years of age (44.7%). The comparison of the incidence of viruses according to age showed that the incidence of RSV and *H. influenza* was significantly higher in children under 2 years old based on statistical comparisons (p<0.001 and 0.026, respectively). While the incidence of SARS-CoV-2 was significantly higher in children over 10 years of age, the incidence of HBoV was significantly lower in children over 10 years of age based on statistical comparison (p<0.001 and p=0.022, respectively). In addition, the incidence of RV was significantly higher in children between the ages of 2 and 5 than in children under the age of 2 and over the age of 10 (p=0.047) (**Table 3**).

Comparing clinical and laboratory results indicated by pathogens detected as virus, bacteria, or virus and bacteria, there was no significant difference in terms of clinical results, radiographic results, neutrophil count, neutrophil/lymphocyte ratio, and C-reactive protein levels among the pathogens. The white blood cell count was significantly higher in children who tested positive for both virus and bacteria in their respiratory tract specimens than in children who tested positive for only virus, and the lymphocyte count was significantly higher in children who detected virus in their respiratory tract specimens (p=0.013 and p<0.01, respectively) (**Table 4**).

While empirical antibiotic therapy was started for 80.2% (n=198) of patients at the time of initial diagnosis, only 19.8% (n=49) of patients were not given antibiotics. The rate of starting empirical antibiotic therapy in patients with a virus identified in their respiratory tract specimens was 80.5% (n=145).

There was no significant difference in the duration of hospitalization according to pathogens and the patients' gender (p=0.341, p=0.774), however there was longer hospitalization with children over the age of 10 years (p=0.011).

Highlights

- Lower respiratory tract infections (LRTIs) are one of the most common causes of hospitalization in the early childhood period
- Using real-time multiplex polymerase chain reaction, at least one pathogen was identified in 88.3 % of patients with LRTIs
- Viruses were responsible for 74.9% of LRTIs
- Respiratory syncytial virus (24.7%) and human bocavirus (21.1%) were the most common viruses causing LRTIs
- Bacteria were detected in 7.7% of patients, and *Haemophilus influenzae* was the most common etiological agent.

Discussion

LRTIs are an important cause of morbidity and mortality in children aged under five years, especially in developing countries. In European and North American countries, the incidence of pneumonia has been reported to be 34-40% in children aged under five years and 7% in adolescence.[15] In Türkiye, Saka Umit et al.[16] reported that 81% of children hospitalized with pneumonia were aged 5 years. Similarly, in our study, the rate of children hospitalized with LRTI aged 5 years was high (82.6%).

In many studies, it has been reported that LRTIs are more common in males. Michelow et al.[6] reported that 62% of patients with LRTIs were male, and Aksoy et al.[17] reported that 65.5% were male. In contrast, Saka Umit et al.[16] reported that 46.7% of patients with LRTIs were male. In our study, males comprised 61.9% of the study group.

Etiologic pathogens of LRTIs vary according to patient age. RSV is the most common viral pathogen, especially in infants; it is responsible for 30-67% of hospitalizations of children with pneumonia.[2,10] *S. pneumoniae* is the

Table 1. *Demographic and clinical characteristics of 247 children with lower respiratory infections*

	n (%)		n (%)
Age (year)		**Symptoms during the hospital admission**	
1ay-<2	148 (59.9)	Cough	184 (74.5)
		Fever	115 (46.6)
		Wheezing	72 (29.1)
		Nasal congestion	52 (21.1)
2-<5	56 (22.7)	Dyspnea	46 (18.6)
5-10	21 (8.5)	Tachypnea	32 (13)
>10	22 (8.9)	**Auscultation findings**	
		Crepitation	141 (57.1)
Sex (Male/Female)	153/94 (61.9-38.1)	Prolonged expiration/sibilant rhonchi	96 (38.9)
Gestational age		Using accessory respiratory muscles	151 (61.1)
37 weeks	189 (76.5)	Decrease in breath sounds	18 (7.3)
<37 weeks	58 (23.5)	None	11 (4.5)
Route of delivery		**HFNCO**	66 (26.7)
Vaginal delivery	94 (38.1)	**Admission time (day)**	6.13±2.93 (2-20)
Cesarean section	153 (61.9)		

HFNCO; High-flow nasal cannula oxygen

Table 2. *Results of respiratory samples analyzed by real-time multiplex polymerase chain reaction*

Pathogens	All patients (n=247) n (%)	Patients treated with HFNCO (n=66) n (%)
Virus	185 (74.9)	50 (75.8)
Bacteria	19 (7.7)	4 (6.1)
Virus + bacteria	14 (5.7)	3 (4.5)
RSV	67 (27.1)	25 (37.9)
HBoV	52 (21.1)	17 (25.8)
RV	39 (15.8)	9 (13.6)
SARS-CoV-2	38 (15.4)	5 (7.6)
PIV-3	35 (14.2)	9 (13.6)
H. influenzae	28 (11.3)	7 (1.6)
S. pneumonia	5 (2)	-
CoV OC43	5 (2)	-
IFV A	3 (1.2)	-
hMPV	2 (0.8)	-
AdV	1 (0.4)	-
Negative samples	29 (11.7)	9 (13.6)

RSV; Respiratory syncytial virus, HBoV; Human bocavirus, RV; Rhinovirus, SARS-CoV-2; Severe acure respiratory syndrome coronavirus 2, PIV 3; Parainfluenza viruses 3, CoV; Coronaviruses, IFV A; Influenza viruses A, hMPV; Human metapneumovirus, AdV; Adenovirus, HFNCO; High-flow nasal cannula oxygen

Table 3. *Distribution of pathogens analyzed by real-time multiplex polymerase chain reaction according to the age groups*

	<2 year	2-<5 year	5-10 year	>10 year	p*
RSV (n=67) n (%)	54 (80.6)[a]	10 (14.9)[b]	1 (1.5)[b]	2 (3)[b]	**<0.001**
HBoV (n=52) n (%)	30 (57.7)[a]	15 (28.8)[a]	7 (13.5)[a]	0 (0.0)[b]	**0.022**
RV (n=39) n (%)	20 (51.3)[a]	15 (38.5)[b]	3 (7.7)[a,b]	1 (2.6)[a]	**0,047**
SARS-CoV-2 n (%)	17 (44.7)[a]	2 (5.3)[a]	1 (2.6)[a]	18 (47.4)[b]	**<0.001**
PIV-3 (n=35) n (%)	24 (68.6)[a]	7 (20)[a,b]	4 (11.4)[a]	0 (0.0)[b]	0.172
H. influenzae (n=28) n (%)	24 (85.7)[a]	3 (10.7)[b]	1 (3.6)[a,b]	0 (0.0)[b]	**0.026**
S. pneumonia (n=%) n (%)	3 (60)	1 (20)	0 (0.0)	1 (20)	0.788
CoV OC43 (n=5) n (%)	2 (40)	2 (40)	1 (20)	0 (0.0)	0.497
IFV A (n=3) n (%)	1 (33.3)	1 (33.3)	1 (33.3)	0 (0.0)	0.364
hMPV (n=2) n (%)	1 (50)	1 (50)	0 (0.0)	0 (0.0)	0.790
AdV (n=1) n (%)	1 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0.880

*Chi-square or Fischer's-exact test.
[a,b]; Indicate the differences between the groups
RSV; Respiratory syncytial virus, HBoV; Human bocavirus, RV; Rhinovirus, SARS-CoV-2; Severe acure respiratory syndrome coronavirus 2, PIV 3; Parainfluenza viruses 3, CoV; Coronaviruses, IFV A; Influenza viruses A, hMPV; Human metapneumovirus, AdV; Adenovirus

most common cause of bacterial pneumonia in the whole age group.[3,9,10,18] A systematic review published before the use of conjugated pneumococcal and *H. influenzae* type B vaccines reported that *S. pneumoniae* and *H. influenzae* were the most common bacterial agents. RSV is present in 15-40% of viral pathogens, and IFV A-B, PIV, hMPV, and AdV have been reported as other common viral pathogens.[19] The frequency of viral pathogens in the etiology of pneumonia has begun to increase after the use of conjugated pneumococcal and *H. influenzae* type B vaccines.[20] In a recent study conducted in South Africa, at least one virus was found to be the causative agent in 87% of the cases.[21] In another study conducted in the Netherlands, viruses were identified in 72% of pneumonia.[22] At least one viral agent was found in 41.8% and 67.8% of patients in studies conducted in Türkiye.[23,24] In our study, in 80.6% of the cases, at least one virus was identified. In our country, viral pathogens are increasingly predominant because of the high coverage of pneumococcal and *H. influenzae* type B conjugate vaccination.

The COVID-19 outbreak caused by SARS-CoV-2 started in December 2019 and became a pandemic spreading world.[25] The clinical manifestations of the disease range from asymptomatic infection to acute respiratory distress syndrome. Most children show asymptomatic or mild symptomatic disease.[26-28] According to a recent review conducted in USA, which included of the 82.798 children with laboratory confirmed SARS-CoV-2 infection, 66% of the cases were asymptomatic, 27% were mild, 5% were moderate, and 2% were severe diseases requiring intensive care unit (ICU) admission.[26] In our study, SARS-CoV-2 was responsible for 15.4% of the LRTIs, and most of the infected children were under two or older than 10 years. Because of the expectation of severe clinical manifestation, infants with SARS-CoV-2 infection were hospitalized with fever rather than significant respiratory symptoms. In contrast, children older than 10 years were mainly admitted with fever and parenchymal infiltration on radiography. In our study, none of them required ICU admission.

Table 4. *Comparison of the clinical and laboratory finding according to the etiological pathogens*

	Virus (n=185)	Bacteria (n=19)	Virus+bacteria (n=14)	p
Fever n (%)	88 (47.6)	10 (52.6)	7 (50)	0.547*
Cough n (%)	139 (75.1)	15 (78.9)	9 (64.3)	0.784*
Wheezing n (%)	56 (30.3)	5 (26.3)	5 (35.7)	0.686*
Crepitation n (%)	107 (57.8%)	12 (63.2%)	8 (57.1%)	0.901*
Prolonged expiratory phased/sibilant rhonchi n (%)	75 (40.5%)	3 (15.8%)	5 (35.7%)	0.105*
WBC x10^3/mm^3 mean ± SD	12.45±7.15	15.89±5.86	17.22±9.47	**0.013****
Neutrophil x10^3/mm^3 mean ± SD	7.72±6.04	9.59±8.87	9.15±6.69	0.372**
Lymphocyte x10^3/mm^3 mean ± SD	6.37±2.87	3.35±2.44	4.51±2.87	**<0.001****
NLR	2.5±4	4.09±4.9	3.72±4.83	0.413**
CRP (mean ± SD)	22.98±38.5	11.06±14.57	15 ±23.16	0.314**
Finding of chest X-ray Bronchiolitis Bronchopneumonia Lobar pneumonia	67 (89.3) 109 (82) 9 (90)	7 (9.3) 12 (9) 0	1 (1.3) 12 (9) 1 (10)	0.208*

*Chi-square or Fischer's-exact test
**One-Way ANOVA
WBC; White blood cell, NLR; Neutrophil/Lymphocyte ratio, CRP; C-reactive protein, SD; Standard deviation

RSV is the most common cause of LRTIs, particularly in infants. Do et al.[22] (24%) and Iwane et al.[29] (20%) reported that RSV was the most frequently detected viral agent in their studies. In the studies conducted in Türkiye, RSV was reported as a causative agent of LRTIs in 61.2% of pediatric cases by Akçalı et al.[23] and 44.7% by Tanır et al.[30] In our study, RSV was again the most common viral agent with a rate of 27.1%. RSV was most frequently observed in children under the age of 5 years as the cause of LRTIs. Appak et al.[31] reported that the age relation was significant for RSV, which was most frequently identified (89%) in children under 5 years of age. Similarly, 80.6% of RSV infections were detected in patients younger than 2 years of age, and this rate was statistically significant. According to our study, the occurrence of LRTs caused by RSV was found to be less frequent than that in previous studies conducted with infants or children under 10 years of age. This result may be due to prolonged community isolation due to the COVID-19 pandemic to save infants from droplet infections.

Since its definition in 2005, the prevalence of HBoV has been reported to be 2-21.5%, especially in children aged under three years with upper and LRTIs.[32] Its prevalence in children aged under two years with bronchiolitis was reported as 1.8-37.1%, whereas a meta-analysis published in 2020 has been reported as 13%.[33-36] Sancaklı et al.[24] detected HBoV in 2.3% of children with LRTIs. In our study, HBoV was detected in 21.1% of children with LRTIs.

Sancaklı et al.[24] reported that RV was the most common pathogen in children with LRTIs and had a higher prevalence in children aged 3 years. A study from China also reported RV as the most common viral pathogen in LRTIs.[25] However, in our study, RV was the third most common pathogen. On the other hand, similar to the literature, it was most frequently observed in children under 2 years of age.

Parainfluenza virus is an important cause of upper and LRTIs at all ages. It can lead to more serious symptoms, especially in infants and during early childhood.[37-40] There are four serotypes of PIV, namely PIV1,2,3,4. PIV-3 is the most common and is often associated with pneumonia and bronchiolitis.[40] Zhao et al.[41] found PIV in 31.12% of cases, Iwane et al.[29] 7%, and Howard et al.[40] in 6.6%. In addition, Etemadi et al.[42] reported the rate of PIV to be 4.8% in hospitalized children under 5 years of age with LRTI, and they reported PIV3 in 50% of these cases. Sancaklı et al.[24] reported PIV in 2.3% of children with LRTI. On the other hand, in our study, PIV was the causative agent in 14.2% of the cases, and all were type 3. In addition, its infection was most frequently identified (88.6%, n=31) in children under 5 years of age in our study, which was consistent with the literature.

With the use of the RT-MPCR test for identifying respiratory tract pathogens, researchers have reported that more than one agent was detected in the same patient. Co-infection with more than one pathogen was reported in up to 51.8% of patients.[23,43,44] Akçalı et al.[23] reported that 10.4% of patients had co-infection with RSV-rhinovirus, RSV-coronavirus, rhinovirus-coronavirus, and RSV-rhinovirus-coronavirus. In our study, 21.5% (n=53) of patients were co-infected with more than one pathogen. PIV and RV were the most common pathogens associated with co-infection. Howard et al.[40] detected co-infections in 50% of PIV infections, mainly with RV, RSV, and AdV, and 16% of them as bacterial agents. Etemadi et al.[42] reported that 37.5% of PIV cases had co-infection. In our study, 57.1% (n=20) of PIV patients had co-infection most commonly with HBoV (n=9; 25.7%), RSV (n=7; 20%), and RV (n=6; 17.1%). Co-infection was detected in 48.7% (n=19) of RV infections, and the most common pathogens co-infected with RV were RSV (n=8; 20.5%), PIV (n=6; 15.4%), and HBoV (n=4; 10.3%). Appak et al.[31] reported that RSV was responsible for 25.2% of the coinfections. In another study, Frobert et al.[45] reported that RSV (24.3%) was the most commonly detected virus in co-infections. In our study, 38.8% (n=26) of RSV infections were co-infected with other pathogens such as RV (n=8; 11.9%), PIV (n=7; 10.4%), HBoV (n=7; 10.4%), and *H. influenzae* (n=6; 9%). Co-infection of HBoV with other viruses was reported as 51.7% in a study conducted in Rome.[46] In this study, RSV and RV were the viruses that

most commonly co-infected with HBoV, MPV, PIV, and others.[46] In our study, 38.5% (n=20) of HBoV was co-infected with the other pathogens. PIV 3 (n=9; 17.3%) was the most co-infected pathogen with HBoV, and the others were RSV (n=7; 13.5), RV (n=4; 7.7%), and *H. influenzae* (n=2; 3.8%).

There are some limitations to our study. First, our study has the limitations of any retrospective study. Second, the study was conducted only with hospitalized patients, and there were no data on outpatients. Third, the RT-MPCR test was able to identify only 23 respiratory tract pathogens.

Conclusion

In our study, we detected a positive pathogen ratio of 88.3% using RT-MPCR in 24 h. Most pathogens responsible for LRTIs were viruses. Although the study was conducted during the last period of the COVID-19 pandemic, after longtime community isolation, RSV was still the leading cause of LRTIs in children. It was remarkable that HBoV was the second leading pathogen. Identifying the causative pathogens of LRTIs in a short time will be important for avoiding unnecessary antibiotic usage.

Ethical Approval: The study was approved by the Ethics Committee of Medeniyet University Göztepe Training and Research Hospital (approval date: 16.03.22; approval number: 2022/0150) before the experiment was started and was conducted in accordance with the principles set forth in the Helsinki Declaration.

Informed Consent: The study was designed retrospectively no written informed consent form was obtained from the patients.

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Maternal Obesity and ADHD: An Original Review of Evidence and Potential Mechanisms

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Abstract

This review explores the potential link between maternal obesity [body mass index (BMI) >30 during pregnancy] and the development of attention-deficit/hyperactivity disorder (ADHD) in offspring. This study assesses the strength of this association by examining epidemiological studies and investigating possible biological mechanisms, including inflammation, oxidative stress, hormonal changes, prenatal programing, and epigenetic modifications. In addition, the review considers moderating variables and discusses the public health implications, with the objective of providing valuable insights into addressing this complex relationship for future clinical approaches and public health policies. This original review conducted a comprehensive literature search in August 2023 using various databases and keywords related to maternal obesity and ADHD. English articles published from 2005 to 2023, including case-control studies, cross-sectional studies, cohort studies, and reviews were considered. Multiple authors independently conducted searches, screened titles/abstracts, and extracted data to ensure rigorous methodology. Initially, 414 articles were retrieved from various databases and managed using Zotero. After eliminating 96 duplicates, 318 articles remained for screening on Rayyan. Of these, 47 papers met the eligibility criteria and underwent full-text review for inclusion in the study. Multiple studies suggest a positive correlation between maternal obesity and ADHD symptoms in children. Additionally, maternal obesity is associated with other neurodevelopmental disorders and behaviors in offspring, including heightened motor and anxiety behaviors. The complex relationship between maternal obesity and ADHD necessitates further investigation. Although existing research indicates associations, causality remains unconfirmed. Genome-wide association studies reveal shared genetic pathways, supported by rodent models. Human studies must address confounding factors. Promising interventions exist but require validation. Comprehensive research encompassing genetic, environmental, and metabolic factors is crucial for understanding the full impact of maternal obesity on neurodevelopmental outcomes.

Keywords: Maternal obesity, attention deficit hyperactivity disorder, neurodevelopmental disorders, overweight

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Introduction

Maternal obesity, defined as having an excessive body weight with a BMI >30 during pregnancy, has emerged as a significant global public health concern. In recent years, the prevalence of maternal obesity has surged, raising concerns about its potential impact on infant neurodevelopment. Among various neurodevelopmental disorders, attention-deficit/hyperactivity disorder (ADHD) has gained particular attention because of its widespread prevalence and enduring effects.[1] Understanding the possible link between maternal obesity and ADHD is essential for identifying modifiable risk factors and developing targeted interventions to improve the neurodevelopmental outcomes of children.

Investigation into the potential connection between these two conditions holds significant importance, considering the escalating rates of maternal obesity and the high prevalence of ADHD among children.[2] Uncovering a substantial association could have profound implications for public health strategies aimed at reducing the prevalence and impact of ADHD. Identifying maternal obesity as a potential risk factor for ADHD would underscore the significance of early interventions during pregnancy and postnatally, thereby mitigating the risk of neurodevelopmental challenges. Moreover, unraveling the mechanisms underlying this connection could provide insights into the pathophysiology of ADHD and open new avenues for therapeutic interventions.

The primary objective of this review is to provide a comprehensive overview of existing research on the potential links between maternal obesity and ADHD in offspring. By systematically examining epidemiological studies, animal research, and mechanistic investigations, we ascertain the strength of this association and uncover plausible biological mechanisms. This review seeks to clarify how maternal obesity might influence offspring neurodevelopment and its potential relevance to ADHD risk. Through meticulous analysis and synthesis of current evidence, we contribute to the understanding of how maternal obesity during pregnancy may contribute to the emergence of ADHD in children.

The specific aims of this review are as follows: (1) summarize findings from epidemiological studies that have investigated the association between maternal obesity and ADHD; (2) explore potential biological mechanisms, such as inflammation, oxidative stress, and hormonal changes during pregnancy, that could elucidate the maternal obesity- ADHD link; (3) investigate studies on prenatal programming and epigenetic modifications as potential explanatory factors; (4) identify potential moderating variables that could influence the strength of the maternal obesity-ADHD association; and (5) discuss the public health implications of this association and consider potential preventive measures. By achieving these goals, this review intends to offer valuable insights into the complex interplay between maternal obesity and ADHD, guiding future clinical approaches and public health policies.

Material and Method

Search Strategy and Inclusion Criteria

This original review was conducted in August 2023 to investigate the potential link between maternal obesity and the development of ADHD in offspring. The authors performed a search through PubMed, Scopus, Scielo, Cinahl, Web of Science, and ScienceDirect using the following keywords: “Maternal Obesity”, “Maternal Overweight”, “Attention Deficit Disorders with Hyperactivity”, “ADHD”, “Attention Deficit Hyperactivity Disorder”, “Attention Deficit-Hyperactivity Disorder”, “Attention Deficit-Hyperactivity Disorders”, “Deficit-Hyperactivity Disorder Attention”.

The inclusion criteria for articles considered in this review were as follows:

Publication Language: Articles published in the English language were included.

Publication Date: Articles published from 2005 to 2023 were considered to ensure coverage of recent research and developments.

Study Design: Various types of studies were included, such as case-control studies, cross-sectional studies, cohort studies, and review articles. These diverse study designs were chosen to capture a wide range of evidence on the topic.

Selection Process

Two authors independently conducted the literature searches, ensuring a comprehensive search across the specified databases. Duplicate articles were automatically detected and removed using Zotero. After eliminating duplicates, the remaining 318 articles underwent further screening on Rayyan. During this screening process, three authors independently evaluated the titles and abstracts of these articles, excluding any literature that did not meet the inclusion criteria. The reasons for exclusion at this stage included studies not related to maternal obesity and ADHD, non-English articles, and those published before 2005.

Following the title and abstract screening, the full text of 47 papers was reviewed to determine their eligibility for inclusion in the study. These full-text reviews were conducted to ensure that the selected articles contained detailed and relevant information regarding the potential link between maternal obesity and ADHD. The screening process is visually depicted in **Figure 1**.

Data Analysis

Three authors independently extracted data from the 47 included studies. Data extraction encompassed key information such as study design, sample size, participant characteristics, methodologies, main findings, and any information pertinent to the review’s objectives. This approach ensured that a comprehensive and thorough assessment of the literature was performed.

By following this methodological process, we aimed to identify and select articles that were most relevant to the objectives of this review, thereby providing a robust foundation for our analysis of the association

between maternal obesity and ADHD and the potential mechanisms underlying this relationship.

Results

A comprehensive search and screening process were conducted to identify relevant articles for this review. A total of 414 articles were initially retrieved from various databases, which were then managed using Zotero. After eliminating 96 duplicate articles, 318 articles remained for screening on Rayyan. Following a rigorous screening process, 47 papers were identified as meeting the eligibility criteria and underwent full-text review for inclusion in the study. A summary of the results is visually depicted in **Table 1**.

Highlights

- Maternal obesity is a global public health concern with rising prevalence, raising concerns about its potential impact on attention-deficit/hyperactivity disorder (ADHD).
- This review examines the potential link between maternal obesity and ADHD, exploring biological mechanisms and epidemiological evidence.
- Findings suggest a potential association between maternal obesity and ADHD but lack causality confirmation.
- Shared genetic pathways and biological mechanisms may contribute to this association.
- Future research should prioritize randomized controlled trials and comprehensive investigation of confounding factors.

Few studies have examined the relationship between maternal obesity and ADHD risk in offspring. In a systematic review published by Sullivan et al.,[3] an association between maternal obesity and several mental health disorders, mainly ADHD, has been found. Similarly, a cohort study of 331 women who were enlisted from antenatal hospital facilities and clinics in Durham-North Carolina between April 2005 and June 2011 reported their offspring's ADHD symptoms at a mean age of 3 years. In this cohort, Fuemmeler et al.[4] found a positive correlation between pre-pregnancy BMI (especially a BMI ≥35) and total ADHD symptoms (B=0.17, p=0.001), attention deficit behavior (B=0.08, p<0.001), hyperactive-impulsive behavior (B=0.09, p=0.02), and executive functioning concern (B=0.38, p=0.02). Additionally, the authors revealed that, when compared to mothers with adequate gestational weight gain (GWG), mothers with less than adequate weight gain noted increased impulsivity and hyperactivity (B=2.04, p=0.02). However, greater than adequate GWG was statistically significantly associated with challenging behaviors related to working memory (B=0.08, p=0.046), and planning and organizing (B=0.07, p=0.01).[4] In an integrated analysis, van der Burg et al.[5] demonstrated that, via an inflammatory state, maternal obesity increased the risk of neurodevelopmental disorders in children mostly ADHD, autism, psychosis, and intellectual disability. Moreover, in a prospective cohort study, Buss et al.[6] evaluated 174 children [mean age =7.3±0.9 (standard deviation) yrs, 55% girls] for symptoms of ADHD with maternal pre-pregnancy BMI being a possible predictor. In this study, it was shown that while maternal GWG was not significantly associated with ADHD symptoms, pre-pregnancy BMI was significantly associated with ADHD symptoms after controlling for potential confounding variables [F (1,158)=4.80, p=0.03]. They also assessed the severity of ADHD symptoms in children of obese, overweight, and normal weight with the former showing increased symptom severity (p=0.02).[6]

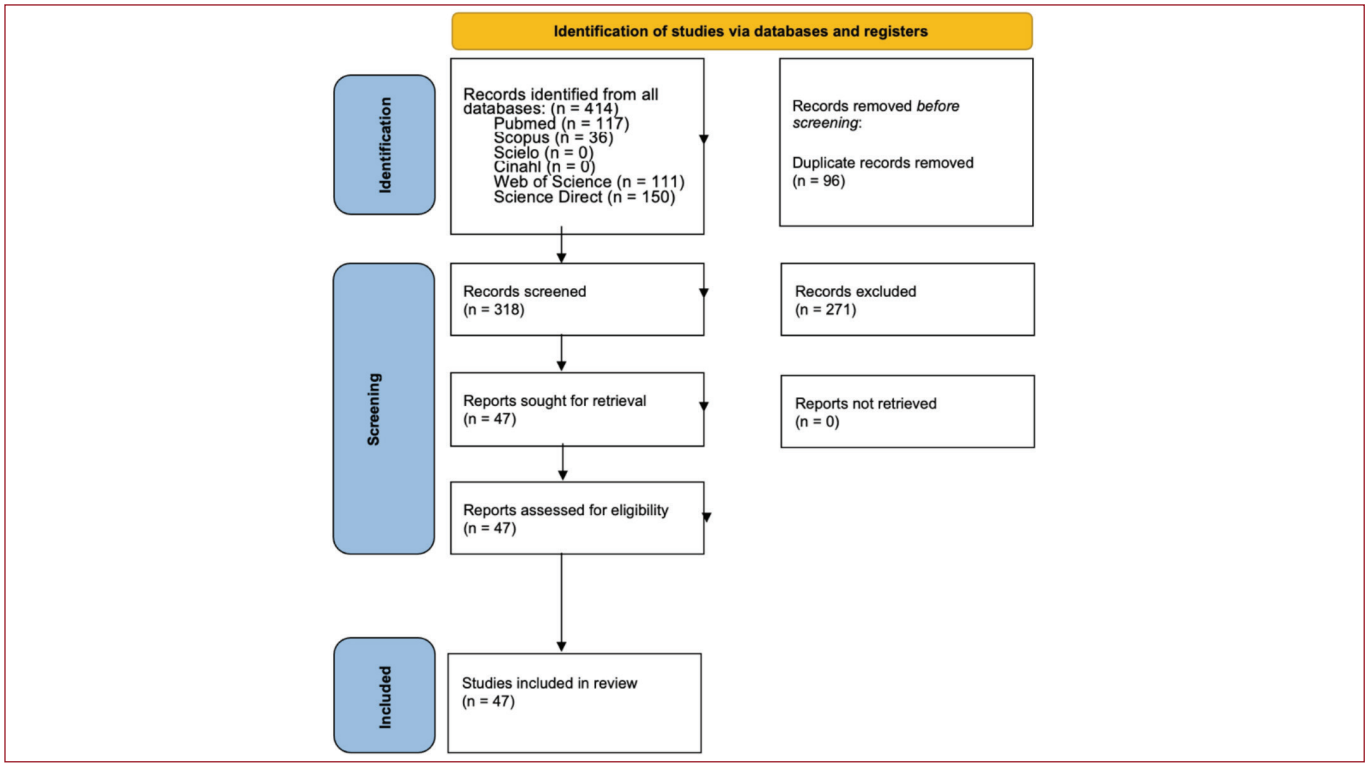

Figure 1. PRISMA flow diagram of literature screening for maternal obesity and ADHD

ADHD; Attention-deficit/hyperactivity disorder

In another prospective study by Casas et al.[7] it was found that both maternal and paternal underweight and obesity were linked to an increase in ADHD-related symptoms in pre-school children, but the associations were not statistically significant. The type of diet itself has been assessed in an experiment by Raygada et al.[8] In this experiment, three strains of mice were fed either control of high n-6 Polyunsaturated fatty acid (PUFA) diets throughout gestation. It was determined that in utero exposure to a high (n-6) PUFA diet increases locomotor activity [among female (t=4.6, df=17, p<0.0003) and males (t=3.1, df=18, p<0.006) mice] and aggression [(among females χ^2=5.3, df=1, p<0.025) and males (t=5.4, df=16, p<0.0001)] in offspring.[8] Similarly, many studies revealed an association between maternal obesity and various neurodevelopmental disorders, other than ADHD per say. In fact, in an animal-model systematic review, authors revealed that maternal obesity was positively correlated with heightened motor [with a standardized mean difference (SMD) of 0.34 (0.10; 0.58)] and anxiety [SMD 0.47 (0.16; 0.79)] behaviors in offspring.[9] Similarly, a study conducted by Peleg-Raibstein et al.,[10] demonstrated that mice born to high fat diet mothers stayed in the maze for an average of time of 24.84% (±3.86) compared to the control group who spent 41.19% (±6.26) of time in the maze.

Discussion

Prevalence and Trends in Maternal Obesity and ADHD

Recent years have witnessed increased attention from researchers and medical professionals toward the prevalence and trends of maternal obesity and ADHD. The link between maternal obesity and adverse outcomes for both mothers and fetuses has propelled it into a prominent public health concern. Studies have demonstrated associations between maternal obesity and heightened risks of gestational diabetes, hypertension, and delivery complications.[11] Furthermore, maternal obesity could contribute to the emergence of juvenile obesity and long-term health issues in offspring. In addition, the prevalence of ADHD, characterized by symptoms of impulsivity, hyperactivity, and inattention, has surged. While the intricate relationship between maternal obesity and ADHD in offspring involves multifaceted factors, recent evidence suggests the plausibility of such a connection.[9]

Association Between Maternal Obesity and ADHD

According to Karhunen et al.[12], children born to obese mothers might face an elevated risk of developing ADHD later in life. While precise causal mechanisms remain elusive, theories suggest that metabolic disturbances, hormonal imbalances, and inflammation induced by maternal obesity during pregnancy could influence fetal brain development, thereby contributing to neurodevelopmental disorders such as ADHD.[1] Prenatal exposure to an obesogenic environment could also trigger enduring epigenetic changes in the child's DNA.[13] This highlights the importance of recognizing maternal obesity as a modifiable risk factor that could impact neurodevelopmental outcomes in the next generation. Comprehensive interventions targeting maternal health, diet, and lifestyle throughout pregnancy could play a pivotal role in minimizing ADHD risk among offspring.

Table 1.
Table showing the main findings concerning maternal obesity and its correlation to ADHD

Authors	Models used	Study design	Maternal factor	Child outcome
Sullivan et al.[3] (2012)	Human and animal	Systematic review	Obesity in pregnancy	Increased risk of developing several behavioral disorders, mainly ADHD
Fuemmeler et al.[4] (2019)	Human	Cohort study	Pre-pregnancy BMI >35 and GWG	Pre-pregnancy BMI >35 was associated with higher ADHD symptoms and worse behavior. Greater than adequate GWG was associated with worse working memory and planning behavior
Menting et al.[9] (2019)	Animal	Systematic review	Maternal obesity	Increased offspring locomotor activity and anxiety, but not memory performance
van der Burg et al.[5] (2016)	Human and animal	Systematic review	Maternal obesity and inflammation	Increased neurodevelopmental disorders, mainly ADHD
Peleg-Raibstein et al.[10] (2012)	Animal	Prospective cohort	High-fat diet	Increased anxiety-like behavior
Field[34] (2014)	Human	Case control	Omega-3 fatty acids deficient diet	An n3FA deficient diet may be an important factor in the rising incidence of ADHD and partial prevention through diet and supplements may be possible.
Raygada et al.[8] (1998)	Animal	Prospective cohort	(n-6) PUFA rich diet	In utero exposure to a high (n-6) PUFA diet subsequently increases locomotor activity and aggression
Buss et al.[6] (2012)	Human	Prospective cohort	Pre-pregnancy BMI	2.8-fold increase in the prevalence of ADHD among children of obese compared to those of non-obese mothers
Casas et al.[7] (2017)	Human	Prospective cohort	Pre-pregnancy obesity	Both maternal and paternal obesity were associated with an increase in ADHD-related symptoms

ADHD; Attention-deficit/hyperactivity disorder

Biological Mechanisms Underlying the Maternal Obesity and ADHD Link

Several biological mechanisms contribute to the potential association between maternal obesity and ADHD risk in offspring. Inflammation emerges as a crucial player in programing brain development,[14] as obesity triggers chronic inflammation through cytokine release, including C-reactive protein (CRP) and interleukin-6.[15,16] Similarly, maternal obesity is associated with heightened inflammatory markers, especially CRP.[17] These markers, notably cytokines, mediate communication between the immune and central nervous systems.[18] In addition, obese women's placentas have more CD68+ and CD14+ cells and pro-inflammatory cytokines than non-obese women.[19] These markers disrupt the integrity of the placenta and endothelium, damaging the serotoninergic (5-HT), dopaminergic (DA), and melanocortinergic neural circuits.[3,14]

The serotonergic pathway, which is pivotal for neural development, particularly serotonin's role in synaptogenesis and neurogenesis, is disrupted.[20,21] Newborns of obese mothers display reduced serotonin levels,[3] and diminished serotonin synthesis correlates with ADHD symptoms, particularly impulsivity and hyperactivity.[22,23]

Inflammatory interference with the serotonergic system, as indicated by studies on the impact of cytokines on serotonin neuronal fibers, contributes to this disruption.[24] A similar inflammatory mechanism disrupts the DA and melanocortinergic pathways, impairing the central reward system and eating behaviors.[14]

Metabolic hormone-induced programming, driven by maternal obesity, exposes offspring to elevated nutrient (fatty acid, glucose) and metabolic hormone levels (leptin mainly).[14] Brain regions governing behavior house leptin receptors, which are linked to metabolic hormone-induced brain development disruption.[25]

Epigenetics also contributes, as evidenced by maternal obesity-induced epigenetic changes in gametes and fetuses[26], alongside mitochondrial dysfunction.[27] The gut- brain axis, via altered gut microflora and short-chain fatty acids, also influences neurodevelopment.[27] Genetic and metabolic pathway[28,29] overlap between obesity and neurodevelopmental disorders emphasize shared pathways.[1] Environmental exposure during early pregnancy, alongside postnatal factors, affects brain development.[30,31]

Despite robust animal support.[14] Human research on the maternal obesity- ADHD link requires addressing confounders such as genetics and the postnatal environment.[1] Variables such as socioeconomic status, micronutrient deficiencies, and emotional distress should also be considered.[5] More research is necessary to clarify the mechanisms underlying the association between maternal obesity and ADHD.[4]

Role of Animal Studies in Determining the Pathophysiology Underlying the Maternal Obesity and ADHD Link

Animal studies have proven pivotal in understanding the mechanisms linking maternal obesity to offspring ADHD risk.[1] Inflammation induced by maternal obesity disrupts vital brain circuits that govern behavior.[14] Impaired serotonergic pathways are evidenced by elevated inhibitory auto-receptor levels in rodent high-fat diet progeny.[10] Placental dysfunction due to high-fat diets correlates with inflammation and impaired blood flow,[3] mirroring findings in sheep and rodents.[32] Neural inflammation in rodents that consume high-fat diets disrupts neurogenesis.[3,33]

Clinical and Public Health Recommendations

PUFAs, encompassing omega-3 and omega-6, present potential treatments for maternal obesity-associated neurodevelopmental issues. Omega-3 PUFAs alleviate brain inflammation and enhance serotonin signaling.[14] Insufficient omega-3 fatty acids during pregnancy are linked to higher ASD and ADHD risks.[34] Preliminary human studies suggest that omega-3 supplementation reduces inflammation in maternal bodies and placentas.[35] A retrospective analysis of data from the Nurses' Health Study II suggested that maternal intake of high levels of omega-6 PUFAs was associated with a 34% reduction in the risk of ASD,[36] which goes against what has been shown in animal studies: that maternal diet rich in omega-6 PUFAs during gestation and lactation produced autism-like traits in offspring sociability.[8] Metformin's effects on maternal obesity's impact on offspring neurodevelopment require further exploration. Two randomized controlled trials have been conducted involving metformin therapy for pregnant women with obesity and no existing diabetes. In one of these trials, there was no observed influence of maternal metformin on the outcomes examined in relation to both maternal and neonatal aspects.[37] However, another trial demonstrated that the use of maternal metformin notably decreased the extent of maternal weight gain and the occurrence of preeclampsia.[38] Neither study has yet reported any long-term effects on neurodevelopment in offspring.

Grasping the connections between prenatal influences and developmental aspects associated with ADHD and deficient self-regulation is crucial. This understanding is vital because childhood problems in these areas, regardless of an official diagnosis, can increase the chances of engaging in harmful behaviors in adulthood[39,40] and lead to substantial economic burdens.[41-43]

Guidance for healthcare providers and policymakers involves recognizing the link between prenatal influences and ADHD/self-regulation issues, which necessitates targeted interventions. Adequate prenatal care and lifestyle adjustments can reduce the risk of neurodevelopmental disorders. Adequate GWG is crucial, with deviations linked to ADHD symptoms.[39]

Intergenerational Effects and Translational Implications

The influence of both maternal and paternal BMI on offspring cognitive development deserves consideration.[6,44,45] For instance, a Danish national birth cohort study with 1783 mothers revealed that higher pre-pregnancy BMI in both parents correlated with lower IQ in their offspring. These associations remained significant even after adjusting for potential influencing factors, suggesting an impact beyond

the intrauterine environment.[41] However, in contrast, research from two birth cohort studies in Spain and Greece indicated that the effect of maternal BMI on infant cognitive development was more pronounced than that of paternal BMI.[42] This observation aligns with the idea of maternal-specific or intrauterine effects. Additionally, a study involving two cohorts-one British (N=5,000) and the other Dutch (N=2,500)-indicated inconsistent associations between pre-pregnancy overweight in parents and their child's cognitive abilities.[7] Hence, while interpreting these findings, it is important to consider potential hidden genetic and familial factors that might confound the results, as well as the ongoing brain maturation process that extends into early adulthood. Recent genome-wide association studies (GWAS) have revealed over 200 genetic regions linked to traits related to type 2 diabetes and obesity.[46-48] Similarly, neurodevelopmental and psychiatric conditions, ranging from moderately heritable ones such as depressive and anxiety disorders, as well as eating and sleeping disorders, to highly heritable ones including ASD, ADHD, bipolar, and psychotic disorders, have been identified.[49] Notably, an elevated susceptibility to obesity has been observed in children with ADHD or ASD.[50,51] One plausible explanation is the existence of shared genetic or metabolic pathways between obesity and neurodevelopmental disorders. The genetic locations identified in GWAS linked to obesity are found in proximity to genes implicated in appetite control, energy balance, and mood management.[52-54] Moreover, the gene encoding the β2-Adrenoceptor, a G protein-coupled receptor, is not only associated with circulatory, muscle, and digestive systems but is also connected to insulin resistance[55] obesity/diabetes,[56] and psychiatric conditions such as autism.

Future Directions for Research

Future studies should address gaps in understanding the maternal obesity- ADHD relationship. An emphasis on randomized controlled trials is needed to determine whether early dietary interventions can prevent mental health disorders in offspring.

Conclusion

The intricate relationship between maternal obesity and ADHD necessitates further investigation. In this review, we conducted a comprehensive examination of existing research to understand the potential links between maternal obesity and ADHD in offspring. While our analysis of the existing literature indicates associations between maternal obesity and ADHD, it is essential to acknowledge that causality remains unconfirmed. GWAS have shed light on shared genetic pathways between maternal obesity and neurodevelopmental disorders, and rodent models have provided valuable insights into the potential mechanisms underlying this association. However, human studies must address various confounding factors, including genetics and the postnatal environment. Socio-economic status, micronutrient deficiencies, and emotional distress are factors that should be considered in future research. Promising interventions have been identified, such as the use of PUFAs and omega-3 supplementation. These interventions show potential in mitigating the effects of maternal obesity on neurodevelopment. However, their effectiveness and safety need further validation through rigorous studies. In conclusion, the effects of maternal obesity on brain development have received significant attention, but it is recommended that future research be shaped to provide a more comprehensive understanding of the ADHD-maternal obesity relationship. Addressing the complex interplay between maternal obesity and ADHD requires multifaceted research that encompasses genetic, environmental, and metabolic factors. By doing so, we can better clarify the mechanisms underlying this association and identify effective interventions that can improve neurodevelopmental outcomes in the next generation. This ongoing research will be essential for developing targeted approaches to mitigate the risk of ADHD in offspring and improve public health strategies.

Ethical Approval: Not necessary.

Informed Consent: Because the study was designed retrospectively no written informed consent form was obtained from the patients.

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Case Report

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Unexpected Tumor Rupture in a Case of Treatment-naïve Neuroblastoma - A Mortality Experience from a Tertiary Medical Institution

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Abstract

Neuroblastoma (NBL) is one of the most common extracranial neoplasms in children. Mortality is often attributed to treatment-related adverse events, sepsis secondary to immunocompromised status, and multi-organ failure resulting from advanced illness. Cases of NBL initially presenting with life-threatening events are rare. Here, we present a fatal NBL case that initially manifested profound anemia and coagulopathy, which later progressed to hemorrhagic shock due to tumor rupture.

Keywords: Mortality, neuroblastoma, oncology, pediatrics

Introduction

Neuroblastoma (NBL) is a major contributor to extracranial neoplasms in children. Mortality is linked to treatment-related adverse events, serious bacterial infection secondary to immunocompromised status, and multi-organ failure resulting from advanced illness. Rarely do patients succumb to extensive disease before the initiation of treatment or during the disease diagnostic stage. We present a mortality case of treatment-naïve NBL to emphasize the urgency of a precise diagnosis.

Case Reports

A 1-year and 7-month-old boy was admitted to the hospital because of a pale appearance. One month prior to hospitalization, the patient appeared pale and was brought to the outpatient department of pediatric hematology for a survey. In addition to the pale appearance, a distended abdomen was reported. Laboratory evaluations revealed profound anemia and coagulopathy, prompting admission for detailed examinations.

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During hospitalization, computed tomography (CT) revealed a right heterogeneous mass (size: 10.9*10.3*8.0 cm) located in the retroperitoneal region (**Figure 1**). To differentiate from the tumor nature, 24-h urine vanillylmandelic acid (VMA) and catecholamine were collected. Bone marrow (BM) aspiration was performed and was negative for malignancy. However, on the second day of hospitalization, immediately after completing urine sampling, an event of hypotension with a disturbed conscious status occurred. The prompt survey revealed evidence of anemia and coagulopathy progression, thereby diagnosing uncontrolled tumor bleeding. Life-saving management, including fluid resuscitation, blood component transfusion, and intravenous coagulation factor 7a infusion, was performed. Because of his critical condition, he was referred to the pediatric intensive care unit for intensive treatment.

Upon stabilization of vital signs, an emergent CT scan revealed profound hemoperitoneum (**Figure 2**). A salvage operation was performed for bleeding control and tumor resection. Under laparotomy, a huge tumor encapsulated the kidney, adrenal gland, and inferior vena cava. Dissection was performed cautiously. However, refractory hypotension and massive bleeding persisted despite vasopressor use and transfusion of blood components. Cardiopulmonary resuscitation (CPCR) was initiated when cardiac arrest occurred. Unfortunately, his vital signs were unresponsive to high-quality CPCR. His family decided on palliative care after an explanation of his bleak prognosis. The patient succumbed to the illness on the third day of hospitalization. Further histology of the resected tumor and urine catecholamine report confirmed the diagnosis of NBL.

Discussion

NBL is one of the most common extracranial neoplasms in children. Embryologically, NBL originates from primitive ganglion cells, which transform into the sympathetic nervous system and adrenal glands. Based on embryological origination and development, NBL can be recognized in areas of the abdomen, paraspinal sympathetic chains, adrenal glands, and rarely the renal parenchyma. Misdiagnosis of Wilms tumor (WT) as NBL may occur. Both NBL and WT can initially present as abdominal distention or mass; thus, laboratory and/or radiological evaluations are warranted. An accurate preoperative diagnosis is crucial because surgical timing and planning differ significantly.

In our case, a precise distinction between NBL and WT was challenging because of similarities in clinical and radiologic presentation. Previous studies have revealed that the presence of constitutional symptoms and intramural calcification are more likely to be associated with a diagnosis of NBL.[1,2] However, these characteristics were not observed in our case. Urinary VMA analysis possessed diagnostic value in differentiating NBL from WT. Unfortunately, we failed to disclose the result of the urinary VMA test before the progression of his disease. Serum neuron-specific enolase (NES) can be used as a rapid resulting marker. However, the sensitivity of NES is debated, and such testing is not available at our institution. BM involvement was reported to be more prevalent in cases of NBL than in WT. Nevertheless, BM sampling in our case was negative for malignancy. After a cautious and retrospective review of the CT scan at presentation, a small and hyperdense lesion could barely be traced. However, the challenge of distinguishing between calcification and minimal tumor bleeding remains.

The mortality in our case was mainly attributed to massive bleeding from a large tumor volume and

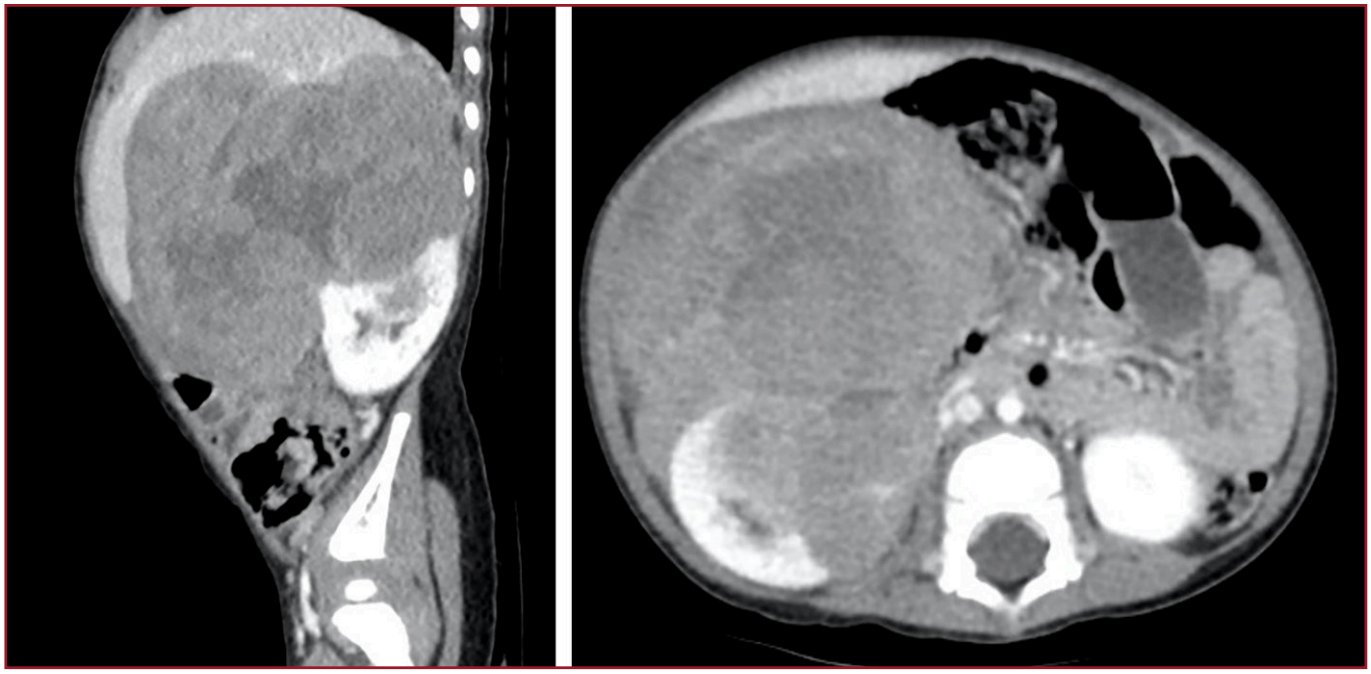

Figure 1. A computed tomography scan of the abdomen at presentation. A) A heterogeneous tumor at retroperitoneal space encases the adrenal gland and partial kidney, B) A heterogenous tumor displaces the inferior vena cava.

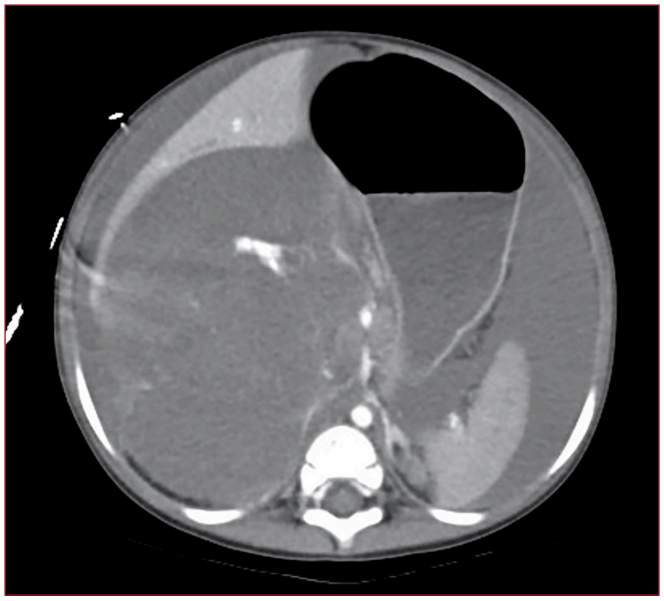

Figure 2. A computed tomography scan of the abdomen on the second day of hospitalization. The image reveals massive ascites with a small abdominal aorta, which is compatible with the status of hemoperitoneum.

coagulation dysfunction. This case highlights the importance of early and accurate diagnosis of NBL. Prompt cancer management decreases the tumor burden, resulting in a desirable disease outcome. In addition to typical differences in radiologic appearance, some studies advocated the use of different modalities to assist in the differential diagnosis. A lower apparent diffusion coefficient (ADC) value in diffusion-weighted imaging of magnetic resonance imaging was reported to be associated with the diagnosis of NBL relative to that of WT.[3] A positron emission tomography based CT scan was also reported to be helpful in the accurate localization of disease.[4] If clinically trapped in a diagnostic dilemma, physicians could turn to different imaging modalities for a precise diagnosis.

Author Contributions: Wan-Ju Lee: Concept, Design, Analysis or Interpretation, Literature Search, Writing.; Yi-Lun Wang: Surgical and Medical Practices, Concept, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Tsung-Yen Chang: Surgical and Medical Practices, Analysis or Interpretation, Literature Search, Writing.

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