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EDITORIAL

From Evidence to Clinic, from Local to Global: A Journey of Continuous Development

Dear Readers,

The dynamic nature of pediatric emergency and intensive care medicine keeps us on a continuous journey of learning and adaptation. Every new day brings a new clinical question, an unexpected diagnosis, or a study that reshapes our evidence-based practice. This dynamism is one of the most challenging, yet also most rewarding, aspects of our profession. In this issue of the Journal of Pediatric Emergency and Intensive Care Medicine, we are delighted to present a wide range of valuable studies that reflect the different stages of this ongoing journey, spanning from local to global contexts.

The last few months have witnessed significant developments in our field. Foremost among these is undoubtedly the publication of the American Heart Association's (AHA) 2025 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care.[1] As the product of a five-year cycle, these guidelines form the cornerstones of our resuscitation practice. Given the importance and scope of the topic, in addition to our traditional editorial in this issue, we are also presenting a special editorial titled "The 2025 AHA Guidelines for Pediatric Resuscitation: From Technical Updates to Holistic Care." In that piece, we have analyzed in detail the key changes compared to the 2020 guidelines and the underlying paradigm shifts. We believe this approach will allow for the in-depth examination the subject deserves and will serve as a valuable reference for clinicians.

The content of this issue once again showcases the breadth and depth of our field. Our issue begins with a comprehensive review from Indonesia that addresses the problems of critically ill children, offering us a global health perspective. Following this, the valuable study by Yousef et al. from Saudi Arabia and Egypt, which examines survival in pediatric in-hospital cardiac arrests, reinforces the timeliness and importance of the subject, especially in this period when new resuscitation guidelines have just been released.

A single-center retrospective cohort study by Güngör et al. from Ankara, comparing the clinical outcomes of coronavirus disease-2019 and influenza, provides data of high practical value for clinicians during the current respiratory virus season. Meanwhile, the study by Adak et al. from Mersin once again brings to the forefront the role of inferior vena cava diameter measurement in assessing the fluid status of children in intensive care units.

Large-scale, long-term studies from our country are also a highlight of this issue. The 11-year national emergency department cohort study by Vatansever et al. which develops a risk model for hospitalization and mortality in children with cyanotic congenital heart disease, is an excellent example of how valuable local data can be and how it can shed light on our clinical decision-making processes. Similarly, the prospective study by Tepedelen Bozdağ et al. from Aydın offers an evidence-based perspective on a common surgical emergency by identifying predictive factors for acute and complicated appendicitis in children.

Toxicology and rare conditions, an integral part of our clinical practice, are also represented in this issue through case reports. Cases of sibutramine-induced serotonin syndrome and baclofen poisoning from Malaysia offer important lessons on managing unexpected toxicities, while a case of high-dose cytarabine-related toxic encephalopathy from Kahramanmaraş raises our awareness of the complex side effects of oncological treatments.

Finally, the study by Tekbıyık et al. from Istanbul, which examines the clinical profile of children and adolescents referred for psychiatric admission after an emergency psychiatric evaluation, reminds us once again of the fact that physical and mental health are a whole and of the critical role our emergency departments play at this intersection.

Each article in this issue contributes to our common goal of integrating evidence-based medicine principles into clinical practice, learning from experiences in different geographies, and ultimately, providing better care to the children we serve. We wish you all an enjoyable and enlightening reading.

Sincerely,

Prof. Dr. Hayri Levent Yılmaz

Editor-in-Chief

Journal of Pediatric Emergency and Intensive Care Medicine

Reference

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Editorial: The 2025 AHA Guidelines for Pediatric Resuscitation: From Technical Updates to Holistic Care

Editörden: 2025 AHA Pediyatrik Resüsitasyon Kılavuzları: Teknik Güncellemelerden Bütüncül Bakıma

Hayri Levent Yılmaz

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Scientific progress generally manifests through cumulative and evolutionary steps rather than sudden, revolutionary leaps. Each new guideline presents a synthesis of these steps, refining our existing knowledge and guiding our clinical practice. The publication of the American Heart Association's (AHA) 2025 Guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care is the most recent example of this evolutionary process.[1] The updates, particularly in pediatric basic life support (PBLS) and pediatric advanced life support (PALS), not only introduce technical changes compared to the 2020 recommendations but also reveal significant developments in our perspective on the science and practice of resuscitation in children.

Upon reviewing these new guidelines, the first notable change is at the structural and conceptual level. The reorganization of PBLS and PALS, which were combined into a single part in the 2020 guidelines, into separate parts (parts 6 and 8) in 2025 demonstrates a deeper recognition of the unique complexity and specialized nature of pediatric resuscitation.[1] This separation promises a more targeted approach in both education and practice settings. Similarly, the consolidation of the chain of survival concept, which previously had different versions for various populations and scenarios, into a single, universal 6-link chain emphasizes the universality of resuscitation's core principles while providing standardization and simplicity in training.[1] This approach reflects the philosophy of building population-specific nuances (such as the newly introduced 7-link chain of survival for neonatal care) upon a solid foundation of fundamental principles.

The 2025 guidelines also underscore the importance of the language used, moving beyond technical applications. The removal of terms like "rescue breaths" to create a clear distinction between "breaths" and "ventilations" and the adoption of the term "lay rescuer" to encourage action, replacing the passive connotation of "bystander" highlight a commitment to enhancing clarity in communication and promoting community involvement.[1] These and other key conceptual advancements are summarized in Table 1.

From Technique to Philosophy: The Evolution in Basic Life Support

Updates in PBLS clearly demonstrate the progression of evidence-based practice. The 2020 guidelines opened the door for compression-only CPR, in line with the trend in adults.[2] However, the 2025 guidelines more strongly emphasize, based on large observational studies, that the best outcomes in pediatric out-of-hospital cardiac arrests are achieved with conventional CPR (chest compressions and breaths).[1] This approach is based on population-specific physiology, underscoring the fact that pediatric arrests, unlike adult arrests, are often due to respiratory causes.

Another significant change occurred in the infant chest compression technique. The 2-finger technique, an acceptable option in 2020, is no longer recommended in 2025 due to

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Table 1. Selected conceptual advancements between the 2020 and 2025 guidelines

Concept	2020 approach	2025 approach and its reflected advancement
Organization	PBLS and PALS were combined into a single part.	PBLS and PALS were performed in separate parts. Advancement: A clearer recognition of the specialized nature of pediatric resuscitation.
Chain of survival	Four different versions (adult/pediatric, IHCA/OHCA).	A single, universal 6-link chain. Advancement: Emphasis on universal principles and simplicity in education.
Terminology	Mixed and less action-oriented terms (e.g., bystanders).	Standardized, clear, and action-oriented terms (e.g., lay rescuers). Advancement: A goal is to improve communication quality and community engagement.

PBLS: Pediatric basic life support, PALS: Pediatric advanced life support, IHCA: In-hospital cardiac arrest, OHCA: Out-of-hospital cardiac arrest

its lower efficacy.[1] Simulation and observational data have shown that the 2-thumb-encircling hands or 1-hand technique provides a more effective compression depth.[1] This change demonstrates a commitment to removing techniques that do not meet the evidence-based quality metrics.

Goal-directed Resuscitation: New Horizons in Advanced Life Support

Innovations in PALS signal an evolution from a "protocol-driven" approach to a more goal-directed understanding of resuscitation guided by physiological data.

Although early epinephrine administration was recommended in 2020, uncertainties regarding timing existed.[2] The 2025 guidelines reduce this ambiguity by providing more aggressive and clear timing recommendations for both non-shockable and shockable rhythms (e.g., as early as possible for non-shockable rhythms).[1] This shows that pharmacological intervention is shifting from a reactive step to a proactive strategy.

Perhaps one of the most innovative approaches is the recommendation to use physiological parameters to assess CPR quality. For patients with invasive arterial blood pressure monitoring, the establishment of specific diastolic blood pressure targets during CPR (≥25 mmHg for infants, ≥30 mmHg for children) shifts the quality of resuscitation from subjective assessments to objective, measurable targets.[1] Similarly, the post-arrest goal of maintaining systolic and mean arterial pressures at or above the 10th percentile for age symbolizes a transition from the general aim of "stabilizing the patient" to the specific task of "achieving age-specific, evidence-based hemodynamic targets."[1]

In the field of neuroprognostication, a more cautious and holistic approach has been reinforced. The 2025 guidelines, more strongly than in 2020, emphasize the need to avoid making irreversible decisions based on a single examination finding, biomarker, or imaging result, stating that a multimodal assessment incorporating multiple data points is essential (COR 1, LOE B-NR).[1] This approach aligns significantly with the multimodal assessment principles gaining traction in neurocritical care and reflects an ethical stance that recognizes the potential risks of a "poor prognosis" label for patients.

Conclusion: The Pursuit of Holistic Care and Equity

When evaluated as a whole, the changes in the 2025 AHA Guidelines reveal that pediatric resuscitation is no longer viewed merely as a series of technical interventions performed at the moment of cardiac arrest. It is now considered a holistic process that begins with pre-arrest prevention and includes high-quality CPR, goal-directed advanced life support, comprehensive post-arrest care, and ultimately, physical, cognitive, and emotional recovery. This process is embodied by the integration of "recovery" the sixth link, into the chain of survival.[1]

Furthermore, the guidelines' strong emphasis on health disparities provides an important roadmap for future research and clinical practice. The 2025 guidelines show that the principle that every child has the right to access the highest quality of care, regardless of race, ethnicity, socioeconomic status, or geographic location, is now more firmly placed at the center of resuscitation science.[1]

In conclusion, the 2025 guidelines invite us to be not only better technicians but also better clinicians, better systems thinkers, and more equitable care providers. This is a promising development, indicating the continued progress of evidence-based, patient-centered, and ethically grounded care in the field of pediatric resuscitation.

Keywords: Cardiopulmonary resuscitation, pediatric advanced life support, heart arrest, practice guideline, child

Anahtar Kelimeler: Kardiyopulmoner resüsitasyon, çocuklarda ileri yaşam desteği, kalp durması, uygulama kılavuzu, çocuk

Footnotes

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1. Del Rios M, Bartos JA, Panchal AR, Atkins DL, Cabañas JG, et al. Part 1: executive summary: 2025 American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2025;152:s284-312.
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Review / Derleme

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Unveiling the Problems of Critically Ill Children in Indonesia: A Narrative Review

Endonezya'da Kritik Durumdaki Çocukların Sorunlarının Ortaya Çıkarılması: Anlatımsal Bir Derleme

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Abstract

The mortality rate of children in Indonesia is still high when compared to that in developed countries. The mortality rate of children in Indonesia remains high due to various factors. Efforts to reduce child mortality should focus on improving family understanding of health risks, enhancing access to quality healthcare services, and addressing social and environmental determinants of child health. The aim of this study was to describe the problems from upstream to downstream of critically ill children in Indonesia, thus Indonesia can work towards lowering the children's mortality rate of children. The PubMed, Cochrane, and Embase databases were meticulously examined utilizing specific search terminologies. Original articles, meta-analyses and systematic reviews in the English and Indonesian languages describing the problems of critically ill children in Indonesia were selected. Relevant references in some of these articles were included as well. The problem of high mortality of children treated in intensive care units in Indonesia is not only due to limited pediatric intensive care unit (PICU) capacity, limited equipment, and unqualified resources. However, it is necessary to identify various underlying factors including family factors, socio-economic status, community culture, referral systems, knowledge of health workers, and health facilities at both primary and secondary levels. A critical concern is that external factors influencing the hospital environment are infrequently or never evaluated for their effects on the referral system, which is essential for ensuring that critically ill pediatric patients are not presented for care too late. The high mortality rate of critically ill children in Indonesia is influenced by many factors, including parents' awareness of pediatric emergencies, the socio-cultural and family economy, community, the ability of primary care providers to identify emergencies and provide initial care, referral system communication and the availability of beds and facilities in the PICU.

Keywords: Critically ill, children, Indonesia

Öz

Endonezya'da çocuk ölüm oranı, gelişmiş ülkelerdeki çocuk ölüm oranına kıyasla hala yüksektir. Çocuk ölüm oranını düşürmeye yönelik çalışmalar ailelerin sağlık riskleri konusundaki farkındalığını artırmaya, kaliteli sağlık hizmetlerine erişimi geliştirmeye ve çocuk sağlığının sosyal ve çevresel belirleyicilerini ele almaya odaklanmalıdır. Bu çalışmanın amacı, Endonezya'da kritik durumda olan çocukların sorunlarını tanımlamak ve böylece Endonezya'nın çocuk ölüm oranını düşürmeye yönelik çalışmalar yapabilmesini sağlamaktır. PubMed, Cochrane ve Embase veri tabanları, belirli arama terminolojileri kullanılarak titizlikle incelendi. Çalışmaya Endonezya'daki kritik durumdaki çocukların sorunlarını anlatan İngilizce ve Endonezce dillerinde yazılmış orijinal makaleler, meta-analizler ve sistematik incelemeler seçildi. Bu makalelerin bazılarının ilgili referansları da dahil edildi. Endonezya'da yoğun bakım ünitelerinde tedavi gören çocukların yüksek ölüm oranı sorunu, sadece çocuk yoğun bakım ünitesi (ÇYBÜ) kapasitesinin sınırlı olması, ekipman yetersizliği ve niteliksiz kaynaklardan kaynaklanmamaktadır. Bununla birlikte, ailesel faktörler, sosyo-ekonomik faktörler, toplum kültürü, sevk sistemleri, sağlık çalışanlarının bilgisi ve hem birincil hem de ikincil düzeydeki sağlık tesisleri gibi çeşitli altta yatan faktörlerin belirlenmesi gerekmektedir. Hastane ortamını etkileyen dış faktörlerin sevk sistemi üzerindeki etkilerinin nadiren değerlendirilmesi veya hiç değerlendirilmemesi önemli bir sorundur. Çünkü bu durum kritik durumdaki çocuk hastaların tedaviye geç kalmamalarını sağlamak için çok önemlidir. Endonezya'da kritik durumda olan çocukların yüksek ölüm oranı ebeveynlerin pediyatrik acil durumlar konusundaki farkındalığı, sosyo-kültürel ve aile ekonomisi, toplum, birinci basamak sağlık hizmetleri sağlayıcılarının acil durumları tespit etme ve ilk yardım sağlama becerisi, sevk sistemi iletişimi ve ÇYBÜ'de yatak ve tesislerin mevcudiyeti gibi birçok faktörden etkilenmektedir.

Anahtar Kelimeler: Kritik durum, çocuklar, Endonezya

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Introduction

The mortality rate of children in Indonesia is still high when compared to the mortality rate of children in developed countries. Data from UNICEF shows that in Indonesia, the average mortality rate of children aged 1-11 months old, 1-4 years old, 5-14 years old is 7.64 per 1000 children, 3.35 per 1000 children, and 4.73 per 1000 children, respectively. From 2002 to 2022, there was a decrease in the mortality rate of children under 5 years old, from 71 per 1000 live births in 2002 to 37 per 1000 live births.[1] This is in contrast to the mortality rate of children in developed countries, such as the United Kingdom (UK). In the UK, the average mortality rate for children aged 1-11 months old, aged 1-4 years old, and aged 5-14 years old is 0.86 per 1000 children, 0.54 per 1000 children, and 0.71 per 1000 children, respectively.[2] This is in accordance with the condition of pediatric patients who are treated in a pediatric intensive care unit (PICU) in Indonesia. In a retrospective analysis conducted on pediatric patients who experienced septic shock at the PICU of Dr. Sardjito Hospital in Yogyakarta, the average patient mortality was 88.2%.[3] Meanwhile, in a prospective study in 2020, septic shock pediatric patients at the PICU of Dr. Sardjito Hospital, had an average mortality of 55.7%[4]. The mortality rate of septic shock patients decreased compared to the previous study in the same place in 2013, which was 60%.[5] In addition to septic shock, the mortality rate of critically ill pediatric patients affected by conditions such as dengue shock syndrome (DSS) is also still high. The average mortality rate of DSS at the PICU of a certain hospital, Surabaya, Indonesia is 52.2%.[6] The high mortality rate of critically ill children in Indonesia is likely due to complex problems from upstream to downstream, such as low knowledge of parents in recognizing emergencies in children, inadequate ability of doctors in primary care to stabilize patients before they obtain care at referral hospitals, inefficient referral systems, uneven distribution of skilled doctors, and incomplete equipment in referral hospitals.[7,8] This work provides an overview of the problems behind the high mortality rate in critically ill pediatric patients in Indonesia.

Rationale and Knowledge Gap

The high mortality rate of critically ill children in Indonesia is likely attributable to various complex issues from upstream to downstream, such as parents' limited knowledge in recognizing emergencies in children, the capability of doctors in primary care to stabilize patients before they receive care at referral hospitals, and referral systems that have not been optimally implemented. Additionally, the ability of doctors and the availability of complete equipment in referral hospitals are not evenly distributed. The issue is that few clinicians or policymakers have investigated the gap between the realities on the ground and existing theories. Based on human development index (HDI) data from the United Nation, Indonesia is ranked 112 out of 192 countries. Indonesia belongs to the high HDI category. Following after the recommendation on the use of artificial intelligence (AI), there was a significant impact on the HDI ranking.[9] The technology recommendation is likely to be implemented. Therefore, there is a need to identify problems at the levels of family, socio-cultural context, society, primary health facilities, and referral facilities. One approach to identifying these issues is to develop this narrative review, which can be followed by research in locations that have not been extensively studied.

Objective

We aim to create a narrative review discussing all the problems that can contribute to the high mortality rate of critically ill children in Indonesia from upstream to downstream, so that we can provide recommendations to the Indonesian government to carry out comprehensive interventions. We hope that this narrative review will prompt the Indonesian government to take definitive actions to reduce the mortality of critically ill pediatric patients, starting from the family, community, primary health facility, to referral health facility levels. We present this article in accordance with the narrative review reporting checklist (Table 1).

Materials and Methods

A literature review using the databases PubMed and Google Scholar was performed utilizing search terms "critically ill children, upstream to downstream children health problem, critically ill patients in Indonesia, mortality critically ill children in Indonesia, pediatric critically ill referral cases, pediatric patients in primary health care, pediatric patients in referral hospital, referral systems in Indonesia, emergencies in children, transport system, healthcare facilities" (Table 1). This search was performed from September 2023 to January 2024.

Discussion

The Problem of Parental Knowledge in Recognizing Emergencies in Children

Delays in emergency treatment are still common in children. The management is essential both at the pre-hospital stage and when it has been treated at a health facility. In the pre-hospital phase, if parents are unable to carry out early treatment of emergencies in children, it can increase mortality and morbidity. Therefore, it is essential to provide parents with knowledge about emergencies in children.[10-13] Emergency recognition and knowledge are the keys to reducing child mortality and morbidity, which should start at the level of parents, doctors in primary care, and doctors in referral

hospitals. Recognizing emergencies in critically ill patients is crucial for determining the right management and should be done as soon as possible (Table 2). A study on pediatric patients who experienced septic shock found that when fluid resuscitation was administered in under 30 minutes, the mortality was 40%. If fluid resuscitation was given between 30 and 60 minutes, mortality increased to 58%. If fluid resuscitation was given after more than 60 minutes, mortality increased to 73%. Early recognition of emergencies followed by treatment as soon as possible can reduce mortality in pediatric patients who experience septic shock.[14]

Parents' knowledge about emergencies involving children in Indonesia has not been widely studied, but a study in Malaysia found that older parents and female parents have knowledge about emergencies involving children and respond positively to children with emergencies.[15] Knowledge about child emergencies in Indonesia may differ from that in Malaysia. This is due to Indonesia's large population, varied levels of education, and very diverse socio-cultural background, which require further research. Studies on efforts to improve parents' knowledge about emergencies in children were conducted in Indonesia through training and education. Aspects taught

Table 1. Search strategy summary

Item	Specification
Date of search	September 1, 2023 to January 15 2024
Databases and other sources searched	PubMed, Google Scholar
Search terms used	Critically ill children, upstream to downstream children health problem, critically ill patients in Indonesia, mortality critically ill children in Indonesia, pediatric critically ill referral cases, pediatric patients in primary health care, pediatric patients in referral hospital, referral sytems in Indonesia, emergencies in children, transport system, healthcare facilities.
Timeframe	Literature published until search date.
Inclusion and exclusion criteria	Inclusion: English language, Bahas Indonesia language, focused on the above search term in problem critically ill in children starting from the family, community, primary health facility to referral health facility levels. Exclusion: Non critically ill children's health problems.
Selection process	Selection of references was agreed upon all authors.

Table 2. Recognition of emergencies in children can reduce child mortality

Study	Method	Subject	Result	Conclusion
Simbila et al.[11]	Prospective cohort study	Four hundred and forty critically ill children were enrolled in the study (aged 28 days-14 years)	• 26.5% children died within 30 days of presentation. • 64.6% presented late (after 48-h). • 35.4% presented early (before 48-h).	Risk of the hospital mortality is 1.3 times higher for children who present late to the ED.
Tsegaye et al.[12]	Unmatched case-control study conducted at specialized hospital in Ethiopia	All children who died within 24-h of admission to the emergency department for the case groups. All children who survived 24-h emergency unit admission in all comprehensive specialized hospitals of the south region for the control group.	• Delayed diagnosis and treatment [AOR=2.088, 95% of CI (1.128, 3.864)] were signifcantly associated with pediatric emergency mortality. • Acute respiratory distress syndrome [AOR=2.804, 95% of CI (1.487, 5.250)] were signifcantly associated with pediatric emergency mortality. • Dehydration [AOR=3.323, 95% of CI (1.260, 8.761)] were signifcantly associated with pediatric emergency mortality. • Meningitis [AOR=5.282, 95% of CI (2.707, 10.310)] were signifcantly associated with pediatric emergency mortality. • Sepsis [AOR=4.224, 95% of CI (2.220, 8.040)] were signifcantly associated with pediatric emergency mortality. • Accidental injury [AOR=3.603, 95% of CI (1.877, 6.916)] were signifcantly associated with pediatric emergency mortality. • Duration of sign/symptoms [AOR=5.481, 95% of CI (2.457, 12.230)] were signifcantly associated with pediatric emergency mortality.	Delayed diagnosis and treatment, acute respiratory distress syndrome, dehydration, meningitis, sepsis, accidental injury, and duration of signs/symptoms were significantly associated with pediatric emergency mortality.

Table 2. Continued

Study	Method	Subject	Result	Conclusion
Wise[13]	Electronic survey conducted by British Paediatric Surveillance Unit	The British Paediatric Surveillance Unit carried out an electronic survey of 4.075 paediatric consultants, representing over 90% of all of those working in the UK and Ireland.	• Delays in emergency department visits may have contributed to deaths of 9 children. • Causes included sepsis, malignancy, and metabolic disease.	Delays in attending emergency departments may have contributed to deaths.
Devaraj[15]	The study utilized a cross-sectional design	Parents attending health talks at the Faculty of Medicine and Health Sciences, Universiti Putra Malaysia between June 2019 to November 2019.	• Parents have good knowledge, attitudes and practices towards childhood emergencies. Older age and female parents showed higher knowledge and positive attitudes.	Older parents have more knowledge on childhood emergencies. Female parents exhibit positive attitudes towards managing children's emergencies.
Sulissia et al.[16]	One group pretest and posttest design	Fifty five respondents (parents of students at TK Aisyiyah 11 Palembang).	• There is an increase in knowledge about the knowledge of early treatment of seizures in children.	There is an effect of educational videos on parents' knowledge in early handling of children at Aisyiyah 11 Palembang Kindergarten, so parents should always update their knowledge about the handling through online and offline video media.
Siregar and Damanik[17]	Observational analytic with cross sectional design	Forty parents who have children under five years in Tanjung Pasir Village, Simalungun Regency.	• Majority of respondents had less knowledge as many as 17 people (42.5%). • Negative attitudes as many as 24 people (60%). • There was a relationship between parental knowledge and attitude in the first treatment of febrile seizures in children (p-value 0.000).	Knowledge was related to parents' attitudes about the first treatment of febrile seizures in children. Good knowledge will lead to a good attitude in the first treatment of febrile seizures in children at home. It is expected that health workers, especially nurses, provide increased health education to increase knowledge and attitudes of parents about the first treatment of children with febrile seizures.
Wibawati et al.[18]	One group pretest posttest design	A sample of Forty respondents using an acidental sampling technique.	• The distribution of the frequency of knowledge before counseling was carried out as many as 25 (62.5%) had poor knowledge, while after counseling there were 36 respondents (90%) had good knowledge.	There is an effect of health education about first aid on the level of knowledge of parents in handling injuries to toddler.
Feri and Juartika[19]	One group pretest and posttest design	Thirty mothers in Marga Rahayu Village.	• An increase in mother's knowledge and skills about diarrhea. • Before the training it was 38.2 and after attending the training it increased to 83.67. • An increase knowledge and skills about diarrhea of 45%.	Training on managing children with diarrhea at home is effective in increasing mothers' knowledge in managing diarrhea at home.
Anestia et al.[20]	Cross sectional design	Sixty five respondents.	• 86.2% of parents had good knowledge about DHF disease and 84.6% made efforts to prevent the disease. • There is a relationship between parental knowledge and efforts to prevent DHF in children.	Good knowledge will form the best prevention efforts from parents to prevent their children from declining health, especially DHF disease.

AOR: Aortic regurgitation, CI: Confidence interval, ED: Emergency department, DHF: Dengue hemorrhagic fever

include febrile seizures, choking and cardiopulmonary resuscitation. The results of this study showed significant differences in knowledge about emergencies in children, which included aspects of febrile seizures, choking, and cardiopulmonary resuscitation before and after education.[7] This is in accordance with a previous study which conducted research on parents' knowledge of handling children with febrile seizures. Parents are given educational videos about the early treatment of children with seizures. In this study, we prove that providing education through learning videos can increase parents' knowledge about how to handle the emergency of children who have febrile seizures.[16]

Low levels of parental knowledge have a significant relationship with the occurrence of negative attitudes when dealing with children who have febrile seizures.[17] Several other studies also prove that training and counseling methods for parents can increase parents' knowledge about emergencies in children, such as handling injuries in toddlers, recognizing dangers, and managing diarrhea in children at home.[18,19] In both of these studies, there was a significant increase in knowledge level after training or counseling. Increasing parents' knowledge about emergency prevention is equally important for an effort to reduce child mortality and morbidity due to emergencies among children. In an Indonesian study, it was found that good knowledge of dengue hemorrhagic fever (DHF) has a significant relationship with DHF prevention.[20] The problem is that efforts to comprehensively and systematically equalize knowledge about emergency situations in children do not yet exist. Training and education for parents about emergencies in children should be carried out by the government so that the initiative can cover all parents throughout Indonesia.

A study in Indonesia demonstrated that educating parents about the recognition of emergencies effectively increases their ability to handle children's emergencies, thereby potentially reducing the death rate. Future research should explore the correlation between education level and emergency response effectiveness to tailor interventions.[21] A limitation of this study is that the population sample only covers one area. Thus, this can be developed for multicenter studies to enable wider research.

One recommendation that can be made, apart from providing education about emergencies to children and parents, is developing emergency response technologies. Through AI, technology that can be easily used by parents to recognize emergencies in children can be developed. One idea for developing AI in recognizing emergencies in children, is to apply the pediatric assessment triangle (PAT) method in the form of AI videos. Parents can record videos of their children who are sick and enter them into the PAT application, so they can conclude whether their children are in a serious condition. This method certainly requires measurable validation. However, it could become a target for scientific studies.

Social and Cultural Aspects of the Family and the Surrounding Environment in Responding to Emergencies in Children

The high mortality and morbidity rates in children are, one of which is related to parents delaying bringing their children to the doctor or emergency room. The problem of delay is not only because parents do not recognize a child's emergencies, but is also related to socio-cultural aspects, such as the extended family asking that the child be taken to receive alternative medicine. Financial constraints can also cause parents to be late in bringing children to the hospital. Transportation costs and expensive living costs in hospitals often make parents delay bringing their children to the hospital.[22,23] According to research conducted in Vietnam and Africa, poor patients tend to take children in emergency conditions to under-resourced facilities. This causes delays in taking children to referral hospitals.[24,25] The problem of late referrals is influenced not only by socio-cultural aspects, such as families preferring to take sick children to a traditional healer rather than to a doctor, but also by financial issues, which are a consideration for parents who are reluctant to take sick children to the doctor. One of the recommendations is that the government should provide treatment and transport services for patients at a low cost or even for free. This will make the burden lighter for parents when taking their children to the doctor for treatment or to the hospital.

Knowledge of Health Workers in Primary Health Facilities in Recognizing and Managing Pediatric Patients who Experience Emergencies

Another problem that plays a role in increasing child mortality and morbidity is the lack of knowledge of health workers in recognizing emergencies in children in the emergency department (Table 3). A previous study in Indonesia found that only 18.1% of health workers had high knowledge about acute diarrhea with dehydration, with the remaining 45.5% having moderate knowledge and 36.4% having low knowledge about it in children. However, most health workers are able to properly manage acute diarrhea with dehydration (72.7%).[26] A strategy to overcome the lack of equal knowledge of health workers about pediatric emergencies is to conduct training for doctors or nurses. A study proves that nurses who are given emergency training experience a significant increase in their knowledge.[27] In Indonesia, primary care provided by Puskemas or primary care clinics covers 86% of the total health care facilities. Doctors in primary care play an important role as gatekeepers and coordinators of health services. Therefore, doctors working in primary care health facilities need to receive training to improve their knowledge. However, special

training for doctors working in primary care in Indonesia is still not well programmed (Table 3).[28,29] In addition to providing continuous training on pediatric emergencies to doctors, primary health care facilities must also be equipped with infrastructure that supports the management of pediatric emergencies. The problem that occurs is that pediatric patients often have to delay referral to health facilities with a PICU, because the PICU at the referral hospital is still full. One of the recommendations is that the government can provide oxygen therapy facilities for children experiencing respiratory distress at community health centers (CHCs), such as with continuous positive airway pressure (CPAP) or high flow nasal cannula (HFNC), so that respiratory failure can be prevented. The success rate of therapy at referral hospitals will increase because delays in therapy can be minimized. Another recommendation is that the government can provide hemodynamic monitoring tools that are simple yet possess high sensitivity and specificity in monitoring hemodynamic disorders in shocked children at CHCs. Patients can still be treated for shock early and adequately at the CHC before they are referred. This will certainly help reduce the mortality of pediatric patients in referral hospitals.

Limited Pediatric Intensive Care

Limited space in the intensive room of referral hospitals in Indonesia is often a problem that can increase the risk of death of children in referral hospitals. In 2020, the number of PICU beds in Indonesia was 1653, for 270.2 million Indonesians. Based on data from the Indonesian Central Bureau of Statistics, the number of children in Indonesia in 2020 was 88.673.000.[30] Therefore, 1 PICU bed serves 53.644 Indonesian children. When compared to the situation in the United States (US) and the UK, the availability of PICU beds in Indonesia remains significantly limited. In the US, one PICU bed is for 10.000 children, while in the UK, one PICU bed is for one thousand children. Even so, the situation in Indonesia is slightly better than in Pakistan, where there is 1 PICU bed for 500.000 children under the age of 14 years.[31]

The limited number of beds in the PICU results in patients not being able to be referred from the referring hospital, thus requiring treatment at their facilities with makeshift arrangements. It is not only the problem of bed availability that causes child patients to be delayed in being referred. Even when a child has received a place of care, many other factors cause children to not be referred to hospitals that have PICU facilities. Based on research conducted in Yogyakarta, out of 494 critically ill patients, only 398 were admitted, and 98 were refused admission to the PICU. Some reasons for being rejected at referral hospitals include a lack of available PICU beds (84%), patients not being transportable (9%), patients not meeting the priority criteria (5%), patients being terminal or palliative (1%), and the referring hospital being too far (1%).[32]

Factors Affecting the Outcomes of Critically Ill Children Treated in the Referral Hospital

The problem of high child mortality in the PICU in Indonesia occurs because patients who enter the PICU were late and did not get adequate treatment before being referred. Critically ill patients treated at the PICU of the referral hospital often face several challenges. These include patients with hemodynamic disorders who did not receive adequate treatment at the previous hospital and respiratory distress patients who did not receive adequate treatment due to incomplete equipment at

Table 3. Knowledge of health workers in primary health facilities in recognizing and managing pediatric patients who experience emergencies

Study	Method	Subject	Result	Conclusion
Yosi[26]	Analytic study with cross-sectional design	Forty four health workers in 2 hospitals, 1 clinic and 4 health centers in Pontianak city.	• Physicians's knowledge level about acute watery diarrhea is 36.4% low, 45.5% moderate, 18.1% high and the treatment is 27.3% bad and 72.7% good. • Corelation score between physicians's knowledge and treatment (r) 0.615 and p=0.000	There is a meaningful relation between physicians's knowledge level towards the treatment of 1-5 years old dehydrated children with acute watery diarrhea in Pontianak's emergency units.
Ekawati et al.[28]	Semi-structured interviews with a topic guide	The participants were GPs practicing in Yogyakarta primary care clinics who were recruited using purposive-maximum variation sample design.	• Almost all the GP participants were unfamiliar with the primary care training program. • GP partisipants were also pessimistic if the training could change the health service in the country while it lacked resources and infrastructures. • Exposure to the training brought positive insights that it could improve the doctors' knowledge and skills in primary care practice.	The government intention to establish PCP training is currently on the right tract.

GP: General practitioner, PCP: Primary care physician

the referring hospital, such as the absence of HFNC, CPAP, or ventilators. Additionally, infection remains a significant problem for children in Indonesia, as the detection of sepsis faces many obstacles (Table 4). Hemodynamic disorders in critically ill children in Indonesia are caused by several factors, including DSS, sepsis shock, hypovolemic shock, and other causes. An Indonesian study obtained results from a total of 239 shock patients: 55 experiencing DSS, 136 with sepsis shock, 1 with obstructive shock, and the remaining could not be classified as the type of shock.[3]

DSS cases are prevalent in Indonesia. For example, in Yogyakarta, from January to December 2016, of the 271 patients admitted to the PICU, 97 (35.7%) were DSS patients.[33] Meanwhile, DSS cases in Malang, Indonesia (January-December 2016, out of 100 patients): 92% are classified as DHF grade III and 8% of patients are classified as DHF grade IV.[34] A study in Indonesia stated that the mortality rate of DSS patients was 5.5%. The predictive factors of mortality in DSS patients are fluid overload, disseminated intravascular coagulation (DIC), acute kidney injury (AKI), and unresolved shock upon admission to the PICU.[35] Those predictors are associated with monitoring, and determining inadequate fluid resuscitation. Efforts are made to minimize this condition by finding effective hemodynamic monitoring methods to determine patients with shock who do and do not respond to fluid. Studies in Indonesia aim to find hemodynamic monitoring methods in pediatric patients experiencing shock by determining the response to fluid administration using ultrasound cardiac output monitoring (USCOM) compared to the electrical cardiometry monitor (ICON) hemodynamic monitoring tool.[36] The determination of shock patients who respond to fluid resuscitation is by using the stroke volume variation parameter which has a sensitivity of 72.7% and specificity of 70%.[37] Hypovolemic shock is dominant in DSS. However, some studies have found that DSS patients also experience myocardial dysfunction or cardiomyopathy, so USCOM can help DSS patients unresponsive to fluid resuscitation and requiring inotropic vasopressor drugs. The USCOM parameter used to determine the need for inotropic support is the Smith-Madigan inotropic index, while the parameter used to determine the afterload condition of patients who experience DSS is the systemic vascular resistance index (SVRI).[33,34]

The problem in Indonesia is the use of non-invasive hemodynamic monitoring devices such as USCOM and ICON is only available in referral hospitals. This causes patients in referring hospitals to be resuscitated with fluids based on clinical parameters only. This situation sometimes causes children with DSS to fluid overload, because it is difficult to determine whether pediatric patients have reached a normovolemic state, are still hypovolemic, or have experienced overload due to fluid resuscitation. Shock that is not resolved promptly can also cause complications such as AKI and DIC.[35]

Another problem faced by pediatric patients in Indonesia who experience hemodynamic disorders is septic shock. A prospective study in Indonesia conducted for 6 months found that 52 pediatric patients experienced sepsis shock, of whom only 23 patients survived (44.2%).[4] The high mortality of septic shock patients in developing countries such as Indonesia is related to several factors, including fluid overload, the need for mechanical ventilation support, the use of vasoactive drugs, and congenital anomalies.[38]

The strategy to reduce the mortality rate of shock patients in children is to use several monitoring tools, namely clinical, macrocirculation, and microcirculation parameters. Clinical parameters that can be used as a monitoring tool for pediatric patients experiencing septic shock are heart rate, systolic blood pressure, body temperature, mean arterial pressure (MAP), capillary refill time, Glasgow Coma scale, and diuresis. Macrocirculation hemodynamic parameters include cardiac index (CI), stroke volume index, SVRI measured using USCOM, while microcirculation hemodynamic parameters include lactate, bicarbonate, and base excess. Research in Indonesia found that a strong pulse after fluid resuscitation at 6 hours, MAP more than 50th percentile at 12 hours, and SVRI at 24 hours are strong predictors of survival in septic shock patients. If we resuscitate pediatric patients who have septic shock, then within 6 hours the pulse must be strong, and within 12 hours, the MAP must be more than the 50th percentile; then the child has a greater chance of survival. This can be applied at the referrer hospital or at the first health facility if you get a pediatric patient who has septic shock but has not been admitted to the PICU.[4] Based on non-invasive hemodynamic monitoring using USCOM, pediatric patients in Indonesia who experience sepsis shock are mostly hypodynamic, where CI is normal, preload, inotropy and afterload are still abnormal.[39] Resuscitation can be carried out at the first referral hospital or health facility, targeting the study results, and monitored using clinical parameters, macro-circulation parameters with non-invasive hemodynamic monitoring tools such as USCOM, and micro-circulation parameters using arterial blood gas (AGB) tests. The government should facilitate the availability of hemodynamic monitoring in hospitals in Indonesia, as well as provide laboratory equipment to conduct AGB tests. This will help monitor the hemodynamics of pediatric patients and reduce pediatric mortality. A study in Indonesia has proven that fluid resuscitation of pediatric patients who experience sepsis shock using the ultrasound-guided fluid resuscitation protocol can prevent fluid overload and reduce child mortality at 72 hours. This is compared to pediatric patients who experience sepsis shock and resuscitation using the American College of Critical Care Medicine protocol (Table 4).[40] The problem of

Table 4. The problem of high children mortality with hemodynamic problem in PICU in Indonesia

Study	Method	Subject	Result	Conclusion
Rusmawatiningtyas and Nurnaningsih[3]	A retrospective study	Two hundred thirty nine shock cases from all types, from all PICU admissions between November 1, 2011 to June 30, 2014.	• From 239 cases, there were 55 cases related to dengue shock syndrome; 136 case of septic shock, 38 cases who failed to meet the criteria for septic shock, and 1 case of obstructive shock. • The median length of PICU stay was 4 days. A total of 48.5% of the subjects were in need of crystalloid and colloid fluid in a median amount of 40 mL/kg. • The median time required to complete the initial resuscitation was 60 minutes. • Mechanical ventilator support in the first 24-h was required in 79.4% of the cases. • Fluid overload of >10% (FO >10%) was found in 58.8% of the subjects.	The mortality rate in pediatric septic shock in our unit is very high. There is a higher incidence of fluid overload in non-survival group.
Yuliarto et al.[34]	A retrospective observational study	Pediatric patients who were between one month to 18 years old, presented with clinical criteria for DHF grade III and IV based on WHO classification of dengue fever in 2011, and admitted to the Saiful Anwar General Hospital, Malang-Indonesia, from January 2016 to December 2016.	• Among 100 patients, 92 patients were classified as DHF grade III and 8 patients were DHF grade IV. 74 patients were in the restrictive group and 24 patients were in the liberal group. • No significant differences were observed between length of stay in PICU (p=0.09), and duration of ventilator use between liberal and restrictive group. • The restrictive group had 53% lower mortality compared to the liberal group (p=0.18). • There were no significant differences in hemodynamic parameters between two groups based on measurement with USCOM which were preload component (SVV) (p=0.89), inotropy components (SMII) (p=0.07), SVRI (p=0.85) as well as the CI (p=0.66).	This study showed that there is no difference in clinical outcomes (length of mechanical ventilation and length of PICU stay), and hemodynamic parameters (preload, inotropy, afterload, and CI) in dengue shock syndrome patients who receive restrictive or liberal fluid resuscitation.
Armenda et al.[35]	A prospective observational study	Consecutive sampling method from 97 children admitted to the PICU with DSS from 1 January 2016 to 31 July 2016.	• Ninety-seven (35.7%) among them had a primary diagnosis of DSS on PICU arrival. Slightly more than three-quarter (76.7%) of DSS patients arrived in PICU with clinically shock condition (group 1) while the rest (23.3%) showed no clinical sign of shock (group 2). This study found that in group 1, patients had received less intravenous fluid prior to their admissions to the PICU compared to group 2 patients (6.90 vs. 7.52 mL/kg BW/h). Three patients in group 1 had not received any fluids before they were admitted to this hospital because of difficulties in obtaining intravenous access.	• Only a small percentage of DSS patients with clinically shock admitted to the PICU were fluid responsive.
Yuliarto et al.[34]	A prospective study	Fifty two subjects were aged 1 month to 18 years who were diagnosed with septic shock based on clinical and laboratory findings according to the Surviving Sepsis Campaign Guidelines from August to December 2020 at the PICU in Dr. Saiful Anwar Hospital, Malang, East Java, Indonesia.	• There was a significant correlation between the outcomes of the pediatric septic shock patients 72-h after fluid resuscitation and clinical, macrocirculatory hemodynamic, and microcirculatory laboratory parameters. • After the 6th hour of observation, strong pulse was predictive of survival, with 88.2% AUC. At the 12th hour of observation, MAP >50th percentile for age was predictive of survival, with 94% AUC. • Macrocirculatory hemodynamic parameters include blood pressure, CI, MAP, and SVRI. Microcirculatory laboratory parameters include serum lactate, central venous pressure, central venous oxygen saturation ($ScvO_2$), mixed venous oxygen saturation ($ScvO_2$), HCO_3, and base excess.	Pediatric patients with septic shock, the treatment target in the first 6-h is to improve strength of pulse, and that in the first 12-h is to improve MAP >50th percentile for age to limit mortality.

Table 4. Continued

Study	Method	Subject	Result	Conclusion
Rusmawatiningtyas et al.[38]	A retrospective observational study	Patients' data from 1st January 2014 to 31st December 2019 who had been diagnosed with sepsis and admitted to the PICU in our tertiary hospital (Dr. Sardjito Hospital, Yogyakarta, Indonesia). The definition sepsis using the Goldstein 2005 criteria.	• Higher risk of mortality in PICU was associated fluid overload percentage of >10% (HR: 9.6, 95% CI: 7.4-12.6), the need of mechanical ventilation support (HR: 2.7, 95% CI: 1.6-4.6), vasoactive drugs (HR: 1.5, 95% CI: 1.2-2.0) and the presence of congenital anomaly (HR: 1.4, 95% CI: 1.0-1.9). • On the contrary, cerebral palsy (HR: 0.3, 95% CI: 0.1-0.5) and post-operative patients (HR: 0.4, 95% CI: 0.3-0.6) had lower mortality.	PICU mortality in pediatric patients with sepsis is associated with fluid overload percentage of >10%, the need for mechanical ventilation support, the need of vasoactive drugs, and the presence of congenital anomaly. In septic patients in PICU, those with cerebral palsy and admitted for post-operative care had better survival.
Yuliarto et al.[43]	A prospective observational study	Fifty shock patients from January to September 2014 in an emergency department and PICU, at Dr. Cipto Mangunkusumo General Hospital, Jakarta City, Indonesia.	• Fifty patients were included with 25 of them are male. The median age was 35 months (1 month-18 years old). • Septic shock was the most (60%) clinical type of shock, due to pneumonia, meningitis, malignancy, and post-surgery condition. • The survival rate at PICU discharge was 74%. • Based on normal hemodynamic values for age, at 1st hour, all of low CI patients had low SMII, while 6/7 were in fluid-refractory shock and high afterload. In the normal CI group, the majority (19/33) were in fluid-refractory shock; more than half (10/19) had low SMII. In the high CI group, the majority (6/10) were in fluid-responsive shock, and most of them (4/6) had normal SMII. At the 6th hour, 5/7 and 18/33 subjects in groups 1 and 2, respectively, still revealed low SMII (with various afterload levels). Conversely, most subjects in group 3 (6/10) revealed normal SMII along with various afterload levels.	Most pediatric shock patients were hypodynamic. Even when the CI was normal, the preload, inotropy, and afterload may still be abnormal. It represented the inotropy as a key to hemodynamic.

FO: Fluid overload, PICU: Pediatric intensive care unit, DHF: Dengue hemorrhagic fever, WHO: World Health Organization, USCOM: Ultrasonic cardiac output monitor, SVV: Stroke volume variation, SMII: Smith-madigan inotropy index, SVRI: Systemic vascular resistance index, DSS: Dengue shock syndrome, HR: Heart rate, CI: Cardiac index, CI: Confidence interval, AUC: Area under the curve, MAP: Mean arterial pressure

septic shock lies not only in establishing the diagnosis but also in hemodynamic monitoring, as well as in adequately managing and treating the patients. Hemodynamic monitoring is crucial to anticipate fluid overload during fluid resuscitation in patients with septic shock. One of the consequences of fluid overload during resuscitation is prolonged use of mechanical ventilation.[41,42]

High PICU mortality rates are also associated with pediatric patients with respiratory distress, but inadequate oxygen therapy treatment. A study conducted in Indonesia over 5 months of observation found that 35 pediatric patients who entered the PICU had respiratory failure: 37.1% had respiratory failure type 1, 37.1% had respiratory failure type 2, and 25.7% had mixed type respiratory failure. Of the patients who developed respiratory failure, 28.6% died.[44] High mortality rates can be prevented by providing patients referred by hospitals with non-invasive oxygen therapy, such as CPAP or HFNC. However, this situation has not materialized in Indonesia. Oxygen therapy is expected to improve the outcomes so that patients who are transferred to referral hospitals do not experience prolonged hypoxia. Another study obtained results for 4 years of observation. Of the 366 patients who entered the PICU: 100 patients (27.3%) experienced pediatric acute respiratory distress syndrome.

Patients who use invasive mechanical ventilation are more than patients who use non-invasive mechanical ventilation, which is 80% and 20%, respectively.[45] A non-invasive therapeutic modality, HFNC, is proven to provide excellent outcomes. HFNC can reduce excessive breathing effort by several mechanisms, including reducing work of breathing, reducing energy expenditure, improving lung component and muco-ciliary function, and providing positive pressure on the airway.[46] Currently, research is needed to determine the effectiveness of HFNC in critically ill children in Indonesia.

Infection is also a problem for critically ill children that can affect the outcomes and can increase child mortality. A study conducted in Surabaya, observed over a 5-year period (2011-2016) in the PICU presented results showing that, among 1138 patients with positive microbial cultures; 44.6% came from blood, 19.15% from urine, 11.59% from sputum, 8.96% from feces, 7.5% from cerebrospinal fluid, 4.04% from endotracheal tube (ETT), 2.89% from pus swab, and 1.41% from pleural fluid. Most microorganism communities are dominated by Gram-negative bacteria. The most abundant bacteria are *Burkholderia cepacia* in blood, *Escherichia coli* (*E. coli*), in urine, *Pseudomonas aeruginosa* in sputum, *E. coli* in feces, *Staphylococcus cohnii* in cerebrospinal fluid, *Klebsiella pneumoniae* extended-spectrum beta-lactamase in ETT, *Staphylococcus aureus* in pus swab, and *Stenotrophomonas maltophilia* in pleural fluid. Some antibiotics that are still sensitive to these bacteria include amikacin, cefoperazone-sulbactam, linezolid, vancomycin, and carbapenem groups. Pneumonia is the most common disease that causes positive microorganism cultures.[47] In another study in Jakarta, Indonesia, observations conducted over one year resulted in a total of 486 blood cultures, 410 of which were sterile. Culture results were positive; 64 microorganisms were Gram-positive, and 12 microorganisms were Gram-negative. Gram-positive bacteria consist of *Staphylococcus hominis*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, and *Staphylococcus aureus*. Gram-negative bacteria consist of *Salmonella typhi* and *Acinetobacter baumannii*. The appropriate antibiotics for Gram-positive bacteria were vancomycin (95.2%), gentamycin (68.3%), cotrimoxazole (44.4%), cefotaxime (31.7%), and ceftriaxone (31.7%). Antibiotics for Gram-negative bacteria consist of meropenem (84.6%), cotrimoxazole (84.6%), amikacin (61.5%), gentamycin (53.8%), and cefepime (46.2%).[48]

The study conducted in Yogyakarta, aimed to predict infections caused by Candida. Patients in PICU are divided into two groups, namely those infected with Candida and those who are not infected with Candida. From the results obtained in this study, from 43 patients infected with Candida, 7 had candidemia.[49] The problem faced by doctors working in PICU is the lack of specific antibiotic guidelines for PICU; not all hospitals have these guidelines Therefore, easy-to-understand guidelines are needed in managing infection in the PICU, so that people have no difficulty determining which antibiotics or antifungals will be used for pediatric patients with infections.

Another problem for critically ill children is the outcomes of patients post-treatment in the PICU. A study conducted in Malang, Indonesia that examined neurocognitive predictor factors and psychological disorders in children after treatment in PICU obtained results from 53 critically ill patients aged 4-18 years, treated in PICU for more than 24 hours and alive, neurocognitive problems, pro-social behavior improved after 3 months of treatment in the PICU, but in children aged 4-5 years neurocognitive abnormalities continued to occur, especially in boys, coming from families of low socio-economic level, incomplete family members, having previously had neurological problems or disorders and and in postoperative patients.[50] Post-PICU treatment causes detriments to the quality of life, both in patients and their families. The patient's family was shown to experience significant depression, anxiety, and stress after their child received treatment in the PICU compared to before the treatment. In the meantime, children's quality of life and functional level decline despite post-PICU treatment. The severity of neurological disease is significantly associated with decreased functional status.[43] Until now, efforts to improve PICU services have focused on increasing the capacity of human resources, both pediatricians and nurses. Trainings between pediatric intensive care doctors, general pediatricians, and nurses are carried out every year in the PICU-NICU update program held by the Indonesian Pediatric Society's Emergency and Pediatric Intensive Therapy coordination work unit. This training aims to improve the skills of pediatric intensivists, general pediatricians, and PICU nurses. Apart from that, the Indonesian Pediatric Society's Emergency and Pediatric Intensive Therapy coordination work unit also collaborates with pediatric intensivist doctors in Southeast Asia, Asia and the world to carry out scientific development.

In the end, it can reduce mortality in infants and children. Another problem is that blood, urine, and fecal cultures are only available in the laboratory of referral hospitals, but few referring hospitals and primary health facilities are equipped to culture microorganisms. This prevents primary health facility or referring hospital doctors from finding out what microorganisms cause infections in patients, thus hindering them from provideing adequate treatment. The government must have a policy that facilitates primary health facilities and referring hospitals to carry out blood culture examinations, urine, feces, swabs, and other cultures. This ensures that if the patient cannot be referred to a referral hospital with intensive care facilities, antibiotics that are culturally appropriate can be given immediately.

Conclusion

To enhance the quality of PICU services and decrease child mortality and morbidity rates, efficacy does not solely rely on proficient medical practitioners and resources available at tertiary care hospitals; it also depends on the ability to execute emergency interventions in children effectively. It also necessitates consideration of factors such as parental aptitude in identifying pediatric emergencies, socio-economic and

cultural influences, competence of healthcare professionals in primary care settings in recognizing and managing pediatric emergencies, availability of hospital beds at referral facilities, and the implementation of optimal protocols at referral hospitals. This ensures that the patient being transferred has attained stabilization at the referring institution or primary healthcare center through appropriate interventions.

Footnotes

Authorship Contributions

Concept: K.T.K., Design: S.Y., Data Collection or Processing: C.M., Analysis or Interpretation: K.T.K., Literature Search: S.Y., T.K., Writing: K.T.K., T.K.

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Against the Clock: Survival in Pediatric in-hospital Cardiac Arrest

Zamana Karşı: Hastane İçi Pediyatrik Kardiyak Arrest Durumunda Hayatta Kalma

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Abstract

Introduction: Pediatric in-hospital cardiac arrest (IHCA) is associated with high morbidity and mortality, yet factors influencing survival are incompletely understood. The aim of the study is to evaluate factors affecting immediate and short-term survival in IHCA, focusing on cardiopulmonary resuscitation (CPR) duration, initial rhythm, and arrest location.

Methods: This retrospective cohort study included 365 patients aged 1 day to 14 years with IHCA who presented at the King Faisal Specialist Hospital & Research Center, Jeddah, Saudi Arabia between 2013 and 2022. Key resuscitation variables such as CPR duration, initial rhythm, and arrest site were analyzed. The primary outcomes were the return of spontaneous circulation (ROSC) and 28-day survival. Demographic and clinical data, including comorbidities and post-ROSC organ failure, were recorded. Multivariate logistic regression identified independent survival predictors.

Results: The 28-day survival rate was 25.2%. Longer CPR duration was linked to reduced ROSC and 28-day survival [odds ratio (OR)=1.11 per minute; p<0.001]. Median CPR duration was 7 minutes for ROSC compared to when ROSC was not achieved, which was 27 minutes (p<0.001). CPR lasting more than 15 minutes was likely to result in no ROSC, with a strong prediction accuracy of 82%, meaning it correctly identified cases 82% of the time, (p<0.001). IHCA in the emergency department (ED) was associated with ROSC failure (OR=4.12; p=0.006). Initial bradycardia was associated with better survival than asystole or pulseless electrical activity (p=0.031). There was no significant association between CPR duration and post-ROSC organ failure (p>0.05).

Conclusion: CPR duration, initial rhythm, and arrest location significantly influence immediate and 28-day survival in pediatric IHCA. These findings support the need for optimized, rhythm-specific resuscitation strategies, particularly for ED arrests requiring prolonged CPR. Future research should investigate strategies to reduce CPR duration and enhance survival.

Öz

Giriş: Hastane içi pediyatrik kardiyak arrest (HİKA), yüksek morbidite ve mortalite ile ilişkilidir, ancak hayatta kalmayı etkileyen faktörler tam olarak ortaya konulmamıştır. Çalışmanın amacı, kardiyopulmoner resüsitasyon (CPR) süresi, ilk ritim ve arrest lokasyonuna odaklanarak HİKA'da acil ve kısa vadeli hayatta kalmayı etkileyen faktörleri değerlendirmektir.

Yöntemler: Bu geriye dönük kohort çalışması, 2013 ile 2022 yılları arasında Suudi Arabistan'ın Cidde kentindeki King Faisal İhtisas Hastanesi & Araştırma Merkezi'ne başvuran, 1 gün ile 14 yaş arası HİKA'lı 365 hastayı içerdi. CPR süresi, ilk ritim ve arrest lokasyonu gibi önemli resüsitasyon değişkenleri analiz edildi. Birincil sonuçlar, spontan dolaşımın geri dönüşü (ROSC) ve 28 günlük sağkalımdı. Komorbiditeler ve ROSC sonrası organ yetmezliği dahil olmak üzere demografik ve klinik veriler kaydedildi. Çok değişkenli lojistik regresyon ile bağımsız sağkalım belirleyicileri tanımlandı.

Bulgular: Yirmi sekiz günlük hayatta kalma oranı %25,2 idi. Uzun CPR süresi, düşük ROSC ve 28 günlük hayatta kalma oranı ile bağlantılıydı [olasılık oranı (OO)=1,11/dakika; p<0,001]. ROSC için medyan CPR süresi 7 dakika iken, ROSC elde edilemediğinde bu süre 27 dakikaydı (p<0,001). On beş dakikadan uzun süren CPR'nin ROSC ile sonuçlanma olasılığı yüksekti ve bu durumun tahmin doğruluğu %82 idi, yani olguların %82'sinde doğru bir şekilde tespit edildi (p<0,001). Acil serviste (AS) HİKA, ROSC başarısızlığı ile ilişkiliydi (OO=4,12; p=0,006). Başlangıçtaki bradikardi, asistoli veya nabızsız elektriksel aktiviteye göre daha iyi hayatta kalma ile ilişkiliydi (p=0,031). CPR süresi ile ROSC sonrası organ yetmezliği arasında anlamlı bir ilişki yoktu (p>0,05).

Sonuç: CPR süresi, başlangıç ritmi ve arrest lokasyonu, pediyatrik HİKA'da acil ve 28 günlük hayatta kalma oranını önemli ölçüde etkilemektedir. Bu bulgular, özellikle uzun süreli CPR gerektiren AS arrestleri için, ritimlere özgü optimize edilmiş resüsitasyon stratejilerinin gerekliliğini desteklemektedir. Gelecekteki araştırmalar, CPR süresini kısaltmak ve hayatta kalma oranını artırmak için stratejiler üzerinde durmalıdır.

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Abstract

Keywords: Cardiopulmonary resuscitation, in-hospital pediatric cardiac arrest, survival rates

Öz

Anahtar Kelimeler: Kardiyopulmoner resüsitasyon, hastane içi pediyatrik kardiyak arrest, hayatta kalma oranları

Introduction

Pediatric in-hospital cardiac arrest (IHCA) is a critical condition that requires prompt professional management to enhance survival rates.[1-3] Although infrequent, IHCA is linked to considerable morbidity and mortality.[4,5] High-quality cardiopulmonary resuscitation (CPR) is defined as chest compressions with sufficient depth (≥4 cm in infants and ≥5 cm in children), rate (100-120 compressions/min), minimal pauses, complete chest recoil, and adequate ventilation, according to American Heart Association (AHA) Guidelines.[6] The quality and timing of CPR, initial cardiac rhythm, and the location of the arrest are certain factors that affect patients' survival.[7,8] According to AHA Guidelines, high-quality CPR is characterized by proper compression depth, rate, and minimal interruptions that significantly improve survival outcomes.[9] Bradycardia shows better outcomes than other initial rhythms, such as asystole and pulseless electrical activity (PEA), given that interventions remain timely and efficient.[8,10-15]

Adult cardiac arrests have been extensively studied in the literature, particularly regarding the effects of initial rhythm, CPR duration, and arrest location-whether out-of-hospital, in the emergency department (ED), or within specialized units. Several studies have shown that arrests occurring in specialized units, such as the pediatric intensive care unit (PICU) and neonatal intensive care unit (NICU), are associated with better outcomes.[16-19] Given the importance of effective resuscitation and post-resuscitation efforts, alongside the absence of agreement on CPR duration effects and cut-off limits in terms of outcomes, further research is warranted.[8,20,21] Therefore, this research aims to evaluate the effect of CPR duration, initial presenting cardiac rhythm, and arrest location on survival outcomes in pediatric IHCA. In addition, it seeks to identify predictors and factors that influence improved IHCA survival rates. By examining whether prolonged resuscitation is beneficial or detrimental, this study bridges a gap in clinical literature. The findings will provide evidence-based insights for medical stakeholders to inform CPR guidelines, support long-term improvement of pediatric IHCA outcomes, and enhance post-resuscitation care strategies.

Materials and Methods

Study Design and Population

The study adopted a retrospective design, analyzing data from 365 pediatric patients who experienced IHCA at King Faisal Specialist Hospital & Research Center, Jeddah, Saudi Arabia, and received CPR by pediatric advanced life support-certified teams. Patients were aged 1 day to 14 years, and data were collected at our center between January 2013 and December 2022. Those who experienced out-of-hospital cardiac arrest or required extracorporeal CPR following return of spontaneous circulation (ROSC) were excluded to maintain focus. Although the overall sample was substantial, subgroup analyses-particularly comparisons across arrest types-were limited by statistical power. All CPR interventions adhered to the latest AHA Guidelines, sustaining a compression rate of 100-120 per minute, achieving adequate depth, allowing full chest recoil, and minimizing interruptions.[22]

Ethical Considerations

The Institutional Review Board approved the study protocol at King Faisal Specialist Hospital & Research Center, Jeddah, Saudi Arabia (approval number: IRB 2032-82, date: 21.07.2023). Informed consent was waived for this research due to the retrospective nature of the studies. The study strictly adhered to institutional and national data-protection policies before data collection. To ensure confidentiality, all medical records were de-identified prior to analysis and access was restricted solely to authorized investigators. This research also complied with institutional rules and national guidelines for the use of patient records in retrospective studies.

Data Collection

Data were collected from participants' medical records, including demographic information (age, gender, and postnatal history), clinical characteristics, reasons for hospital admission, and indications for NICU or PICU care. We also recorded details of each cardiac arrest: type, cause, and location (operating room, ED, inpatient ward, NICU, or PICU), as well as the electrocardiography rhythm at arrest [bradycardia, asystole, PEA, or pulseless ventricular tachycardia/fibrillation (VT/VF)]. Resuscitation details were reviewed, including CPR duration (time from collapse to ROSC or death), medications

administered, procedures performed, and outcomes. Finally, we assessed achievement of ROSC, mortality, 28-day survival, and incidence of new organ failure following ROSC.

Study Outcomes

The primary outcome was ROSC, defined as the return of a palpable pulse with sustained circulation for at least 20 minutes. Secondary outcomes included survival to hospital discharge and survival rates at 28 days; identification of common factors leading to hospital or PICU admission that precipitated cardiac arrest; survival stratified by initial cardiac rhythm; and the incidence of new organ failure post-ROSC, along with its impact on survival.

Definitions

The cardiac arrest phase is defined as the duration from the cardiac arrest onset to the initiation of effective CPR. Therefore, prompt identification of worsening conditions by rapid response teams is essential for effective intervention.[23,24] CPR is defined as the administration of chest compressions and assisted ventilation in response to cardiac arrest or significant bradycardia accompanied by inadequate perfusion.[25] The post-resuscitation phase is defined as the critical period after ROSC, necessitating rigorous monitoring for complications, including multi-organ failure and other adverse outcomes. Multi-organ failure is defined as the dysfunction of two or more organ systems, resulting in an inability to maintain spontaneous activity.

Statistical Analysis

The data analysis of the current research was performed using SPSS version 26.0 (IBM Corp., Armonk, NY). Normality evaluations of continuous variables were conducted through the Shapiro-Wilk test, and these variables were reported as the median and interquartile range (IQR), while categorical data were presented as frequencies and percentages. Comparative analyses were performed through the Mann-Whitney U test to compare CPR duration between two groups, whereas the Kruskal-Wallis test facilitated comparisons between more groups. Pairwise comparisons were conducted using the Bonferroni correction, and chi-square and Fisher's exact tests were employed to compare proportions across categorical groups. Furthermore, receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic capability of CPR duration in predicting ROSC achievement/non-achievement. In multivariate logistic regression, variables significant in bivariate analysis ($p<0.05$) were included in the models to determine independent predictors of ROSC achievement and 28-day survival. All subsequent tests were conducted at a $p<0.05$ significance level.

Results

Demographic and Clinical Characteristics

The research included 365 pediatric patients who experienced IHCA between 2013 and 2022. The median age of the patients was 6 months (IQR: 1 to 36 months), with 55.1% of the population being male. In accordance with participant demographics, age and gender did not correlate with ROSC achievement.

Location of First Cardiac Arrest

Patients with arrests in the emergency room (ER) showed significantly lower ROSC rates ($p=0.001$) compared to patients whose arrests occurred in PICUs, NICUs, wards, or operating rooms, as shown in Table 1. This may be related to the nature of most ER settings, which affect the resuscitation process as they are often over-stressed and resource limited.

Rhythm at the Time of Arrest

Cardiac rhythm, at the time of arrest, showed a stronger association with ROSC outcomes. Most patients with bradycardia showed poor perfusion (69%), followed by asystole (16.7%), PEA (10.1%), and pulseless VT/VF (4.1%). Patients with bradycardia showed better outcomes ($p=0.031$) in comparison to patients with asystole ($p=0.003$), as shown in Table 1.

CPR Duration and ROSC

Approximately 46% of patients did not achieve ROSC after the first cardiac arrest, with a 25.2% survival rate after 28 days. The CPR duration significantly correlated with the achievement of ROSC. The median CPR duration was 7 minutes (IQR: 4-15 minutes) among patients who achieved ROSC, as compared to a median CPR duration of 27 minutes (IQR: 20-44 minutes) among patients who did not achieve ROSC ($p<0.001$). Shorter CPR durations showed a stronger association with better outcomes, as indicated by the ROC curve analysis. ROC curve analysis showed that CPR duration of more than 15 minutes is a strong predictor of non-ROSC, with 0.866 [95% confidence interval (CI): 0.827-0.899] area under the curve at 82.0% accuracy, 87.0% sensitivity, 77.2% specificity, and $p<0.001$, as shown in Tables 2 and 3 and Figures 1 and 2.

Post-ROSC Organ Failure

After ROSC from the first cardiac arrest, the most common new organ failure was cardiovascular (18.8%), followed by respiratory (16.2%). However, no significant association was reported between CPR duration and the occurrence of new organ failure post-ROSC ($p>0.05$). This unexpected result may be influenced by factors not fully accounted for in this study, such as variations

Table 1. Association between patient's characteristics of studied patients with cardiac arrest 2013-2022 and achievement of ROSC

Variables	Total (n=365)	Achieving ROSC (n=197; 54%)	Not achieving ROSC (n=168; 56%)	p-value
Age (months): median (IQR)	6.0 months (1-36)	6.0 months (2-36)	4.50 months (1-36)	0.185
Gender				
Male	201 (55.1%)	108 (54.8%)	93 (55.4%)	0.918
Female	164 (44.9%)	89 (45.2%)	75 (44.6%)	
Preterm or full term				
Term	282 (77.3%)	150 (76.1%)	132 (78.6%)	0.581
Preterm	83 (22.7%)	47 (23.9%)	36 (21.4%)	
Location of first cardiac arrest				0.009
ICU	246 (67.4%)	135 (68.5%)	111 (66.1%)	0.617
NICU	71 (19.5%)	44 (22.3%)	27 (16.1%)	0.168
ER	32 (8.8%)	8 (4.1%)	24 (14.3%)	0.001
Ward	12 (3.3%)	7 (3.6%)	5 (3.0%)	0.995
Operation room	4 (1.1%)	3 (1.5%)	1 (0.6%)	0.747
Cause of hospital admission				
Cardiac	173 (47.4%)	89 (45.2%)	84 (50.0%)	0.358
Respiratory	103 (28.2%)	59 (29.9%)	44 (26.2%)	0.426
Prematurity	61 (16.7%)	36 (18.3%)	25 (14.9%)	0.386
Hematology/oncology	48 (13.2%)	31 (15.7%)	17 (10.1%)	0.113
GIT	45 (12.3%)	27 (13.7%)	18 (10.7%)	0.386
Neurological	33 (9.0%)	21 (10.7%)	12 (7.1%)	0.243
Sepsis	2 (0.5%)	1 (0.5%)	1 (0.6%)	0.999
Cause of ICU admission				
Post operative	113 (31.0%)	65 (33.0%)	48 (28.6%)	0.362
Respiratory failure	112 (30.7%)	59 (29.9%)	53 (31.5%)	0.741
Shock	82 (22.5%)	45 (22.8%)	37 (22.0%)	0.852
Prematurity	46 (12.6%)	28 (14.2%)	18 (10.7%)	0.315
Arrythmia	25 (6.8%)	17 (8.6%)	8 (4.8%)	0.145
Sepsis	15 (4.1%)	9 (4.6%)	6 (3.6%)	0.632
Convulsion	6 (1.6%)	2 (1.0%)	4 (2.4%)	0.420
Organ system affected before first cardiac arrest				
Cardiovascular	207 (56.7%)	108 (54.8%)	99 (58.9%)	0.430
Respiratory	121 (33.2%)	72 (36.5%)	49 (29.2%)	0.135
Neurological	69 (18.9%)	40 (20.3%)	29 (17.3%)	0.459
Hepatic	67 (18.4%)	40 (20.3%)	27 (16.1%)	0.298
Renal	48 (13.2%)	29 (14.7%)	19 (11.3%)	0.336
Sepsis	27 (7.4%)	16 (8.1%)	11 (6.5%)	0.567
Rhythm at time of first arrest				0.017
Brady with poor perfusion	252 (69.0%)	146 (74.1%)	106 (63.1%)	0.031
Asystole	61 (16.7%)	22 (11.2%)	39 (23.2%)	0.003
PEA	37 (10.1%)	22 (11.2%)	15 (8.9%)	0.596
Pulseless VT or VF+	15 (4.1%)	7 (3.6%)	8 (4.8%)	0.562
Duration of CPR in minutes				
Median (IQR)	18.0 minutes (7.0-30.0)	7.0 minutes (4.0-15.0)	27.0 minutes (20.0-40.0)	<0.001

ROSC: Return of spontaneous circulation, IQR: Interquartile range, ICU: Intensive care unit, NICU: Neonatal intensive care unit, ER: Emergency room, GIT: Gastrointestinal tract, PEA: Pulseless electric activity, VT: Ventricular tachycardia, VF+: Ventricular fibrillation

in pre-existing conditions, ICU management strategies, or sample size limitations. Additionally, this study did not perform a separate analysis of individual organ systems, which may have masked potential relationships between CPR duration and specific types of organ dysfunction. Future research should examine each organ system separately to better understand how resuscitation efforts influence post-ROSC outcomes.

Survival Beyond 28 Days

In the current study, the survival rate after 28 days was 25.2%. The median age was 4 months (IQR: 3-36) in the survival group, as compared to 8 months (IQR: 1-36) in the non-survival group (p=0.031). The median CPR duration for patients surviving more than 28 days was 5 minutes, as compared to 20 minutes for patients who did not survive (p<0.001). Patients with primary arrest in ER and NICU showed the highest mortality rates (p=0.032 and p=0.036, respectively). Notably, PICU patients showed better survival rates (p=0.002). Furthermore, patients with hepatic failure and sepsis showed higher mortality rates (p=0.032 and p<0.001, respectively), as shown in Table 4.

Table 2. Diagnostic criteria for duration of CPR in prediction of not achieving ROSC

Validity measures	Diagnostic criteria Duration of CPR
AUC (95% CI)	0.866 (0.827-0.899)
Cut-off	>15.0 min
Accuracy %	82.0%
Sensitivity %	87.0%
Specificity %	77.2%
PPV⁺ %	76.4%
NPV^ %	87.4%
p-value	<0.001

CPR: Cardiopulmonary resuscitation, ROSC: Return of spontaneous circulation, AUC: Area under the curve, CI: Confidence interval, PPV⁺: Positive predictive value, NPV^: Negative predictive value

Table 3. Comparison between duration of CPR and achievement of ROSC

Outcome	Duration of CPR in first arrest Median (IQR)
Not achieved ROSC (n=168, 46.0%)	27.0 minutes (20.0-40.0)
Less than 24-h survival (n=64, 17.5%)	10.0 minutes (5.0-15.0)*
Less than 5-day survival (n=17, 4.7%)	10.0 minutes (5.0-40.0)*
Less than 28-day survival (n=24, 6.6%)	6.0 minutes (3.0-20.0)*
More than 28-day survival (n=92, 25.2%)	5.0 minutes (3.0-13.0)*
p⁺	<0.001

CPR: Cardiopulmonary resuscitation, ROSC: Return of spontaneous circulation, IQR: Interquartile range, *: Significant in comparison to not achieving ROSC group by Pairwise comparison with Bonferroni correction, ⁺: Kruskal-Wallis test compares median duration between groups

Multivariate Logistic Regression Analysis

Multivariate logistic regression analysis was performed to identify independent predictors of both return of ROSC and 28-day survival. For ROSC, the analysis revealed that ER arrests (OR=4.12, 95% CI: 1.49-11.41, p=0.006) and increased CPR duration (OR=1.11 per minute, 95% CI: 1.08-1.14, p<0.001) were significantly associated with failure to achieve ROSC.

For 28-day survival, prolonged CPR duration remained a significant predictor of poor outcomes (OR=1.11, 95% CI: 1.07-1.14, p<0.001). Conversely, in the case of post-operative conditions (OR=0.27, 95% CI: 0.14-0.52, p<0.001) or arrhythmia (OR=0.21, 95% CI: 0.06-0.61, p=0.005) as

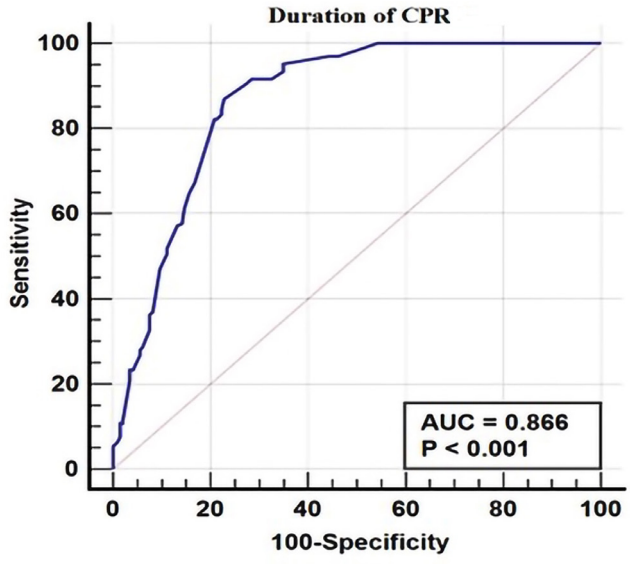

Figure 1. ROC curve for the ability of duration of CPR in the prediction of not achieving ROSC
ROC: Receiver operating characteristic, ROSC: Return of spontaneous circulation, CPR: Cardiopulmonary resuscitation, AUC: Area under the curve

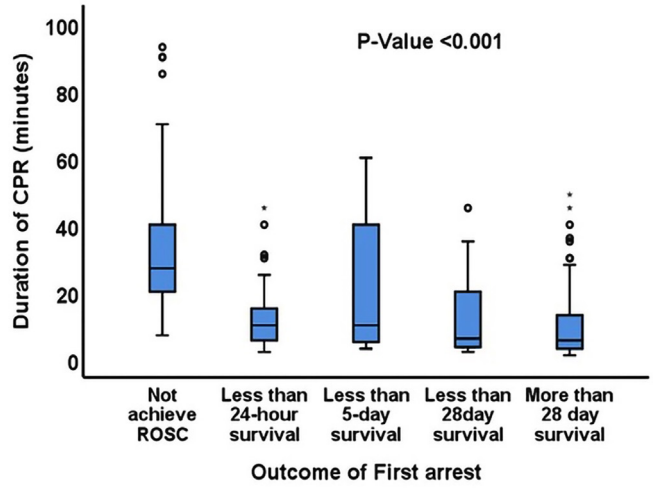

Figure 2. Boxplot for the CPR duration according to arrest outcome
ROSC: Return of spontaneous circulation, CPR: Cardiopulmonary resuscitation

Table 4. Association between patient's characteristics of studied patients with cardiac arrest 2013-2022 and mortality

Variables	>28 days survival (n=92)	Died (n=273)	p-value*
Age (months): median (IQR)	8.0 months (3-36)	4.00 months (1-36)	0.031
Gender			
Male	49 (53.3%)	152 (55.7%)	0.687
Female	43 (46.7%)	121 (44.3%)	
Preterm or full term			
Term	75 (81.5%)	207 (75.8%)	0.275
Preterm	17 (18.5%)	66 (24.2%)	
Location of first cardiac arrest			0.028
PICU	74 (80.4%)	172 (63.0%)	0.002
NICU	11 (12.0%)	60 (22.0%)	0.036
ER	3 (3.3%)	29 (10.6%)	0.032
Ward	3 (3.3%)	9 (3.3%)	0.999
Operation room	1 (1.1%)	3 (1.1%)	0.999
Cause of hospital admission			
Cardiac	50 (54.3%)	123 (45.1%)	0.123
Respiratory	26 (28.3%)	77 (28.2%)	0.992
Prematurity	12 (13.0%)	49 (17.9%)	0.275
Hematology/oncology	9 (9.8%)	39 (14.3%)	0.269
GIT	13 (14.1%)	32 (11.7%)	0.543
Neurological	10 (10.9%)	23 (8.4%)	0.479
Sepsis	0 (0.0%)	2 (0.7%)	0.410
Cause of PICU admission			
Post operative	46 (50.0%)	67 (24.5%)	<0.001
Respiratory failure	23 (25.0%)	89 (32.6%)	0.172
Shock	14 (15.2%)	68 (24.9%)	0.054
Prematurity	9 (9.8%)	37 (13.6%)	0.346
Arrythmia	11 (12.0%)	14 (5.1%)	0.025
Sepsis	1 (1.1%)	14 (5.1%)	0.128
Convulsion	1 (1.1%)	5 (1.8%)	0.999
Organ system affected before first cardiac arrest			
Cardiovascular	58 (63.0%)	149 (54.6%)	0.156
Respiratory	26 (28.3%)	95 (34.8%)	0.249
Neurological	19 (20.7%)	50 (18.3%)	0.620
Hepatic	10 (10.9%)	57 (20.9%)	0.032
Renal	14 (15.2%)	34 (12.5%)	0.498
Sepsis	0 (0.0%)	27 (9.9%)	<0.001
Rhythm at time of first arrest			
Bradycardia with poor perfusion	62 (67.4%)	190 (69.6%)	0.692
Asystole	12 (13.0%)	49 (17.9%)	0.275
PEA+	16 (17.4%)	21 (7.7%)	0.008
Pulseless VT or VF	2 (2.2%)	13 (4.8%)	0.279
Duration of CPR in minutes			
Median (IQR)	5.0 minutes (3.0-13.0)	20.0 minutes (10.0-32.5)	<0.001

*: Chi-square/Fisher's exact tests compare proportions between groups, PICU: Pediatric intensive care unit, NICU: Neonatal intensive care unit, ER: Emergency room, GIT: Gastrointestinal tract, PEA+: Pulseless electric activity, VT: Ventricular tachycardia, VF: Ventricular fibrillation, IQR: Interquartile range

the cause of PICU admission, the results showed a higher association with improved odds of survival, as shown in Table 5.

Discussion

The study evaluated the interplay between CPR duration, initial presenting cardiac rhythm, and arrest location on survival outcomes in pediatric IHCA over ten years. The findings underscore the pivotal role of timely, effective resuscitation in this vulnerable population and highlight the need to enhance both resuscitation and post-resuscitation care. Prolonged CPR duration was significantly associated with poorer outcomes, including lower rates of return of ROSC and reduced 28-day survival. These results align with prior studies demonstrating the critical impact of resuscitation quality on pediatric IHCA outcomes.[19-21]

The findings do not show a significant relation between prolonged CPR and post-ROSC organ failure. This contradicts published data in adults, which may be related to different physiological responses and varied age-specific management protocols.[2] However, other factors may play an essential role, such as pre-existing clinical conditions and the quality of post-arrest care. According to Mally et al.[25] the location of arrests appears to be a significant factor influencing outcomes, as arrests in ER exhibited worsened outcomes in comparison to arrests in specialized units such as NICUs and PICUs.[14] This difference emphasizes the distinctive challenges encountered in resource-limited ERs and reinforces the necessity of protocol optimization alongside the allocation of resources within such environments.[8,14] Conversely, the results showed no significant correlation between younger age and ROSC, contradicting previous research findings that showed an association between younger age and increased mortality.[8]

The outcomes of this research align with current literature;[3,12,13,20] the initial cardiac rhythm correlated with the research outcomes. Bradycardia with poor perfusion exhibited more favorable outcomes than asystole, highlighting the value of rhythm evaluation and targeted measures.

This highlights the necessity of enhancing healthcare infrastructure in anticipation of possible future worldwide disasters.[3,8,20,26] The 28-day survival rate of 25.2% aligns with previous studies, underscoring the significant effectiveness of the post-ROSC phase in specialized care environments such as NICUs and PICUs.[8,20,26,27] Thus, it highlights the crucial role of targeted interventions and post-resuscitation strategies.[28]

Table 5. Multivariate logistic regression analysis

Factors associated with not achieving ROSC return of spontaneous circulation (ROSC)				
	OR	**95% CI**		**p-value**
		Lower	**Upper**	
Age in months	1.00	0.99	1.01	0.917
Location of first cardiac arrest at ER	4.12	1.49	11.41	0.006
Rhythm at time of first arrest				
Asystole	1.45	0.54	3.87	0.453
Bradycardia with poor perfusion	1.03	0.47	2.26	0.940
Duration of CPR in first arrest to achieve ROSC in minutes	1.11	1.08	1.14	<0.001
Factors associated with less than 28 days mortality				
Age in months	1.002	0.99	1.01	0.667
Location of first cardiac arrest				
At emergency room	2.41	0.37	15.50	0.352
At ICU	0.89	0.22	3.61	0.881
At NICU	1.91	0.40	9.01	0.411
Cause of PICU admission				
Post operative	0.27	0.14	0.52	<0.001
Shock	1.97	0.92	4.21	0.080
Arrythmia	0.21	0.06	0.61	0.005
Duration of CPR in first arrest to achieve ROSC in minutes	1.11	1.07	1.14	<0.001
Organ system affected before first cardiac arrest				
Hepatic	1.74	0.28	10.77	0.548

OR: Odds ratio, CI: Confidence interval, dependent variable: less than 28 days mortality, ROSC: Return of spontaneous circulation, ER: Emergency room, CPR: Cardiopulmonary resuscitation, ICU: Intensive care unit, NICU: Neonatal intensive care unit, PICU: Pediatric intensive care unit

The current research highlights numerous clinically actionable targets, such as shortening CPR duration, especially in ER environments. Enhanced team collaboration, continuous uninterrupted chest compressions, and prompt resource access are vital. Furthermore, identifying initial cardiac rhythms and executing rhythm-specific actions are necessary for improving outcomes. The multivariate analysis in the current study revealed significant predictors of pediatric IHCA clinical outcomes. Arrests in ER were significantly correlated with ROSC failure (OR=4.12), aligning with the results of Mally et al.[25] Also, prolonged CPR duration significantly correlated with 28-day survival and ROSC (OR=1.11 per minute duration), indicating the value of timely interventions.[8] Multivariate regression indicated that longer CPR duration was statistically related to reduced ROSC rates and reduced 28-day survival. However, this relationship does not necessarily indicate a direct cause-and-effect relationship. Instead, longer CPR may serve as a marker of the severity of underlying diseases and not an independent predictor for poor outcomes. This is consistent with previous studies indicating that longer CPR duration tends to be a marker of increased illness severity rather than a direct cause of poor outcomes.[29] As a result, multivariate logistic regression was performed in the study, controlling important variables, including the initial cardiac arrest rhythm, site of arrest, and reason for PICU admission (Table 5). The findings suggested that although CPR time continued to be significantly related to ROSC and survival, other clinical variables, including the presenting arrest rhythm and site of the event, also contributed significantly to outcomes.

Better ROSC odds were noted in arrests caused by arrhythmias and in post-operative patients admitted to ICUs, implying possible underlying protective mechanisms. The 28-day survival rate in the current study conforms to the trends reported by Kienzle et al.[27] highlighting the necessity of tailored and optimized post-ROSC care. However, the results offer a solid basis for future studies that could incorporate a multi-center research design and integrate further evaluation of targeted interventions to improve CPR quality and duration, especially across ER environments, while further exploring the interaction between factors that influence long-term survival rates and post-arrest quality of life.

Study Limitations

The retrospective design of this study restricts the researcher from establishing a causal relationship between CPR time, initial cardiac rhythm, and IHCA survival outcomes. Furthermore, although the overall sample size of 365 children is large, the statistical power for subgroup analyses, especially comparisons between various arrest types and resuscitation environments (PICU vs. NICU), is still limited. As the study was conducted at a single center, future multicenter studies could improve generalizability.

Conclusion

This study sheds light on key determinants of outcomes in IHCA, addressing significant gaps in existing literature. The research findings emphasize the critical influence of CPR duration, initial cardiac rhythm, and arrest location on both immediate and short-term survival, thus highlighting the pressing need for refined resuscitation strategies, particularly in high-risk scenarios such as ER arrests and cases that require extended CPR. The observed rhythm-specific variations in outcomes reinforce the necessity of tailored, rhythm-focused interventions. The analysis of 28-day survival rates underscores ongoing challenges and the imperative need for improved post-resuscitation care. These insights serve as a robust foundation for developing targeted protocols aimed at enhancing outcomes in pediatric IHCA.

Ethics

Ethics Committee Approval: The Institutional Review Board approved the study protocol at King Faisal Specialist Hospital & Research Center, Jeddah, Saudi Arabia (approval number: IRB 2032-82, date: 21.07.2023).

Informed Consent: Informed consent was waived for this research due to the retrospective nature of the studies.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.Y., M.H., A.G., H.A., A.A., Concept: A.Y., M.H., A.G., H.A., A.A., Design: A.Y., M.H., A.G., H.A., A.A., Data Collection or Processing: A.Y., M.H., A.G., H.A., A.A., Analysis or Interpretation: A.Y., M.H., A.A., Literature Search: A.Y., M.H., A.G., H.A., A.A., Writing: A.Y., A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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Children in the Shadow of Viruses: Comparative Clinical Outcomes of COVID-19 and Influenza - A Single-center Retrospective Cohort Study

Virüslerin Gölgesinde Çocuklar: COVID-19 ve İnfluenzanın Karşılaştırmalı Klinik Sonuçları - Tek Merkezli Geriye Dönük Kohort Çalışması

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Abstract

Introduction: Respiratory viruses are the most common cause of morbidity and mortality in children around the world. Unlike other viral respiratory diseases, recommendations for coronavirus disease-2019 (COVID-19) in children are mainly derived from adult data, and it has been difficult to differentiate COVID-19 from influenza by clinical manifestations that are earlier than viral identification. The study aims to compare clinical and laboratory characteristics that will enable healthcare workers to differentiate COVID-19 from influenza.

Methods: This retrospective cohort study, conducted at a tertiary academic hospital's pediatric emergency department from January 1, 2019 to December 31, 2021 focused on children with confirmed COVID-19 or influenza. We compared demographics, clinical features, laboratory/radiological findings, reatments, pediatric intensive care unit admissions, length of stay, mortality, and clinical outcomes between COVID-19 and influenza in pediatric populations, providing valuable insights into the two diseases during the specified period.

Results: Six hundred and sixty-one children with COVID-19 and 499 children with influenza infection were included. In the vital signs at triage, significantly higher fever, tachypnea, and tachycardia were found in patients with influenza (p=0.001). In terms of chest X-ray (CXR) characteristics, 82.2% of the children in the COVID-19 group had normal CXR (p=0.001) while the children in the influenza group had more patchy involvement (p=0.003) and consolidation (p=0.001). Platelet counts in the COVID-19 group were significantly higher than those in the influenza group (p=0.001). Regarding infection-related biomarkers, the C-reactive protein level in the influenza cohort was significantly higher than in the COVID-19 cohort (4.92 mg/L vs. 0.94 mg/L, p=0.001).

Öz

Giriş: Solunum yolu virüsleri, dünya genelinde çocuklarda morbidite ve mortalitenin en yaygın nedenidir. Diğer viral solunum yolu hastalıklarından farklı olarak, çocuklarda koronavirüs hastalığı-2019 (COVID-19) yönelik öneriler ağırlıklı olarak yetişkin verilerinden elde edilmiştir. Ayrıca, COVID-19'un influenza ile erken dönemde, viral tanı konulmadan önce, klinik belirtilerle ayırt edilmesi zor olmuştur. Bu çalışma, sağlık çalışanlarının COVID-19 ile influenzayı ayırt etmelerini sağlayacak klinik ve laboratuvar özellikleri karşılaştırmayı amaçlamaktadır.

Yöntemler: Bu geriye dönük kohort çalışması, 1 Ocak 2019-31 Aralık 2021, tarihleri arasında üçüncü basamak bir akademik hastanenin çocuk acil servisinde yürütülmüştür. Çalışmaya, COVID-19 veya influenza tanısı kesinleşmiş çocuklar dahil edilmiştir. COVID-19 ve influenza tanısı alan çocuk hastalar arasında demografik veriler, klinik özellikler, laboratuvar ve radyolojik bulgular, uygulanan tedaviler, çocuk yoğun bakım ihtiyacı, hastanede kalış süresi, mortalite ve klinik sonuçlar karşılaştırılmış, belirlenen dönemde iki hastalığa dair önemli veriler sunulmuştur.

Bulgular: Çalışmaya 661 COVID-19'lu ve 499 influenza enfeksiyonlu çocuk dahil edilmiştir. Triaj sırasında değerlendirilen yaşamsal bulgular incelendiğinde, influenza grubundaki hastalarda anlamlı derecede daha yüksek ateş, taşipne ve taşikardi saptanmıştır (p=0,001). Akciğer grafisi bulguları açısından COVID-19 grubundaki çocukların %82,2'sinde normal akciğer grafisi izlenirken (p=0,001), influenza grubundaki çocuklarda daha fazla yama tarzı tutulum (p=0,003) ve konsolidasyon (p=0,001) tespit edilmiştir. COVID-19 grubunda trombosit seviyeleri, influenza grubuna kıyasla anlamlı derecede daha yüksek bulunmuştur (p=0,001). Enfeksiyonla ilişkili

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Abstract

Conclusion: Our study objectively compares the severity of COVID-19 in children with influenza, a related serious respiratory illness with regular seasonal or pandemic outbreaks, and with a high patient count in both groups. Our study confirmed that influenza and COVID-19 cohorts are compared. Influenza is more symptomatic, associated with higher fever levels, more viral coinfection, longer and higher rates of hospitalization, greater need for respiratory support, and death.

Keywords: Children, influenza, COVID-19, pandemic

Öz

biyobelirteçler değerlendirildiğinde, influenza grubundaki C-reaktif protein seviyesi, COVID-19 grubuna kıyasla anlamlı derecede daha yüksek saptanmıştır (4,92 mg/L vs. 0,94 mg/L, p=0,001).

Sonuç: Çalışmamız, çocuk hastalarda COVID-19'un, düzenli mevsimsel veya pandemik salgınlarla ortaya çıkan ciddi bir solunum yolu hastalığı olan influenza ile objektif olarak karşılaştırmasını yapmaktadır. Bulgularımız, influenza grubunun COVID-19 grubuna kıyasla daha semptomatik olduğunu, daha yüksek ateş seviyeleri, daha fazla viral koinfeksiyon, daha uzun ve yüksek oranda hastane yatışı, daha fazla solunum desteği ihtiyacı ve daha yüksek mortalite ile ilişkili olduğunu doğrulamaktadır.

Anahtar Kelimeler: Çocuklar, influenza, COVID-19, pandemi

Introduction

The coronavirus disease-2019 (COVID-19) emerged as a global health crisis, marked by uncertainty and widespread transmission. While the World Health Organization has declared that COVID-19 is no longer a "global health emergency," the virus remains a public health concern due to its continued transmissibility.[1] As the pandemic declines, other respiratory viral infections are becoming increasingly prevalent, similar to past winter seasons. Early in the pandemic, it was noted that children were less affected by severe COVID-19 than adults.[2,3] However, their role in transmission remains unclear. Several studies have compared presentations of COVID-19 and influenza in adults.[4] Identifying clinical and laboratory features that allow healthcare professionals to distinguish COVID-19 from seasonal influenza is critical to effective containment, given the significant health, social and economic impact of COVID-19 worldwide. This distinction is particularly important in the pediatric population, as children are more susceptible to influenza due to behavioral factors, such as poor hygiene compliance and immature immune system responses. We conducted this study at our pediatric emergency outpatient clinic, which annually serves an average of 90.000 patients, in Ankara, Türkiye's capital, at its most comprehensive tertiary academic and university hospital. The objective of this study was to determine the differences between COVID-19 and influenza, particularly in pediatric patients. As the COVID-19 pandemic continues, it is critical for pediatricians to compare the demographic and clinical characteristics of the disease in children with influenza infections. COVID-19 can present with a wide clinical spectrum from asymptomatic to respiratory failure. The influenza viruses commonly encountered in children can present with similar symptoms. In this study, we focused on identifying clinical and laboratory characteristics that enable healthcare workers to differentiate COVID-19 from influenza.

Materials and Methods

This retrospective cohort study includes children admitted to the pediatric emergency department (PED) between January 1, 2019, and December 31, 2021, with COVID-19 or influenza confirmed by real-time polymerase chain reaction (RT-PCR) testing. Hacettepe University PED is in Ankara, the capital of Türkiye. Our PED is a referral tertiary academic hospital, serving approximately 90.000 patients annually. Data on patients' presenting complaints, physical examination findings, laboratory and radiological results, treatments and interventions, pediatric intensive care unit (PICU) admission, length of hospital stay, mortality, and clinical outcomes were extracted from medical records. Additionally, the results of COVID-19 RT-PCR and multiplex viral PCR panels for respiratory tract pathogens from nasopharyngeal swab samples, as well as complete blood count, C-reactive protein (CRP), and chest radiography findings, were recorded.

Viral tests were performed on all asymptomatic children with a history of COVID-19 or influenza exposure, as well as on patients who were admitted to the PED, general pediatric ward, or PICU, with a diagnosis of lower respiratory tract infection. Only patients with a positive viral respiratory panel were included in our study. Patients with missing or unavailable laboratory test results were excluded from the study. Respiratory specimens from each child were collected by qualified medical personnel within 24 hours of hospital admission. The extraction and detection of COVID-19 ribonucleic acid in nasopharyngeal swabs were performed according to the manufacturer's instructions using a commercial viral nucleic acid transport buffer and tubes (vNAT, Bioeksen, Türkiye), and an RT-PCR kit (Bio-Speedy severe acute respiratory syndrome-coronavirus-2 N RT-qPCR kit, Bioeksen, Türkiye). Patients with positive RT-PCR results for COVID-19 were classified as the COVID-19 PCR-positive group.

The study was approved by the Ethics Committee of Hacettepe University under registration code GO22/1242, date: 13.12.2022. The ethics committee reviewed our study and waived the need for informed consent, as all data and samples were analyzed retrospectively and collected as part of routine clinical practice in accordance with current guidelines.

To identify other viral respiratory pathogens, multiplex real-time PCR (Bosphore Respiratory Pathogens Panel kit v4, Anatolia Gene Works, Türkiye) was conducted on nasopharyngeal swabs following the manufacturer's protocol. The viral panel tested for adenovirus, respiratory syncytial virus (RSV) types A and B, influenza virus, parainfluenza virus types 1-3, human metapneumovirus, rhinoviruses, human coronaviruses (OC43, 229E, NL63), human bocavirus, and human polyomaviruses KI and WU. Patients who did not meet the collective and probable/definite case definitions or had incomplete data were excluded from the study. The severity of COVID-19 and influenza was classified based on clinical presentation, laboratory findings, and radiological imaging as follows:

Classification of Disease Severity[5,6]

Asymptomatic

No clinical symptoms or signs, with normal chest imaging, despite a positive viral PCR test.

In our hospital, COVID-19 tests were conducted on children with respiratory system symptoms or a contact history, to determine epidemiological characteristics. As a result, an asymptomatic patient group emerged.

Mild

Symptoms of an acute upper respiratory tract infection, including fever, fatigue, myalgia, cough, sore throat, runny nose, and sneezing, or gastrointestinal symptoms, such as nausea, vomiting, abdominal pain, and diarrhea. Physical examination findings may include pharyngeal congestion, but auscultation reveals no abnormalities.

Moderate

Presence of clinical signs of pneumonia, including fever and cough (initially dry, later productive), and possibly wheezing, shortness of breath, or lung crackles. However, there is no significant hypoxemia (pulse oxygen saturation >92%). Some patients may be asymptomatic, but thoracic computed tomography may reveal subclinical lung lesions.

The condition is severe, characterized by disease progression with dyspnea and central cyanosis. Oxygen saturation is less than 92%, accompanied by other manifestations of hypoxia.

Critical

Rapid progression to acute respiratory distress syndrome or respiratory failure. Patients may also develop sepsis, shock, encephalopathy, myocardial injury, or heart failure, coagulation dysfunction, or acute kidney injury. Multiorgan dysfunction can be life-threatening.

Chest radiography findings were categorized as follows: normal, patchy atelectasis and/or hyperinflation and/or bronchial wall thickening, focal consolidation, multifocal consolidation, diffuse alveolar changes.[7]

The vital signs of children were evaluated based on the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Pediatric Basic and Advanced Life Support, which are also used in our triage system.[8,9]

Statistical Analysis

The demographic information, clinical characteristics, laboratory results, and radiological findings of all patients were analyzed using the IBM SPSS Statistics 23.0 software for Windows. Quantitative data were presented as mean ± standard deviation and median (interquartile range), while qualitative data were expressed as frequencies and percentages. Associations between qualitative variables were assessed using cross-tabulations and the chi-square test. Quantitative variables were compared using the Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. A p-value of <0.05 was considered statistically significant.

Results

A total of 661 children diagnosed with COVID-19 and 499 children diagnosed with influenza were included in the study. Baseline clinical characteristics are presented in Table 1. The mean age of patients with COVID-19 was 117.8 months, which was significantly higher than that of patients with influenza, with a median of 51.8 months (p=0.001). There was no significant difference between the two cohorts in terms of gender distribution or the presence of underlying chronic diseases, including chronic respiratory diseases, neuromuscular disorders, epilepsy, obesity, asthma, type 1 diabetes mellitus, and pediatric hemato-oncological malignancies.

The body temperature of patients with influenza was significantly higher than that of patients with COVID-19 (≥38.1 °C, p=0.001). Compared to those with COVID-19, patients with influenza exhibited significantly higher prevalence of cough (p=0.001), respiratory distress (p=0.001), runny nose (p=0.001), abdominal pain, and nausea/vomiting (p=0.001), conjunctivitis (p=0.001), and rash (p=0.001). However, the prevalence of headache and loss of taste or smell was significantly higher in the COVID-19 cohort than in the influenza cohort (p=0.001).

Table 1. Comparison of baseline characteristics patients with influenza and COVID-19

	COVID-19 n (%)	Influenza n (%)	p-value
Gender			
Female	335 (50.6)	229 (45.8)	
Male	326 (49.4)	270 (54.2)	
Age (years, mean ± SD)	9.8±5.9	4.3±3.5	0.001
Presence of fever	427 (64.6)	449 (89.9)	0.001
≤37.5 °C	249 (37.6)	76 (15.3)	
37.6-38 °C	144 (21.7)	62 (12.4)	
38.1-39 °C	195 (31.5)	189 (37.8)	
>39 °C	31 (4.6)	171 (34.2)	
Presence of symptoms	603 (91.2)	482 (96.6)	0.001
Presenting symptoms			
Cough	282 (42.6)	352 (70.5)	0.001
Rhinorrhea	80 (12.1)	237 (47.4)	0.001
Nausea-vomiting	52 (7.8)	118 (23.6)	0.001
Fatigue	116 (17.5)	78 (15.6)	0.386
Sore throat	124 (18.7)	75 (15)	0.095
Muscle pain	81 (12.2)	69 (13.8)	0.429
Fast breathing	20 (3)	55 (11)	0.001
Diarrhea	77 (11.6)	53 (10.6)	0.583
Stomachache	28 (4.2)	49 (9.8)	0.001
Conjunctivitis	3 (0.4)	29 (5.8)	0.001
Headache	81 (12.2)	26 (5.2)	0.001
Rashes	5 (0.7)	21 (4.2)	0.001
Chest pain	10 (1.5)	2 (5.2)	0.064
Loss of taste and smell	34 (5.1)	14 (2.8)	0.001
Contact of index patient	380 (57.4)	105 (21)	0.001
Comorbid conditions	99 (14.9)	94 (18.8)	0.08
Cystic fibrosis	33 (4.9)	11 (2.2)	
Asthma	24 (3.6)	7 (1.4)	
Epilepsy	22 (3.3)	32 (6.4)	
Malignancy	9 (1.3)	9 (1.8)	
Genetic syndromes	6 (0.9)	10 (2)	
Diabetes mellitus type 1	3 (0.4)	-	
Obesity	-	2 (0.4)	
Other	1 (0.1)	5 (1)	
Autoimmune and autoinflammatory disease	1 (0.1)	7 (1.4)	
Congenital heart disease	-	8 (1.6)	
Immunodeficiency	-	3 (0.6)	
Vital sign on admission/triage			
Hypoxia	10 (1.5)	39 (7.8)	0.001
Fever	427 (64.6)	449 (89.9)	0.001
Tachypnea	9 (1.4)	27 (5.4)	0.001
Tachycardia	8 (1.2)	44 (8.8)	0.001
Hypotension	1 (0.2)	2 (0.4)	0.407

SD: Standard deviation, COVID-19: Coronavirus disease-2019

In the COVID-19 group, 57.3% of patients and their relatives reported a history of contact with a confirmed case, whereas this rate was 21% in the influenza group. Additionally, positive findings on respiratory system examination were observed in 28.7% of the influenza group compared to only 2.3% of the COVID-19 group (p=0.001). Upon triage and initial examination, patients with influenza exhibited significantly higher rates of fever, tachypnea, and tachycardia compared to those with COVID-19 (p=0.001).

Comparison of Radiologic and Laboratory Findings Between COVID-19 and Influenza

A total of 91.1% of patients in the COVID-19 cohort and 50.5% of those in the influenza cohort underwent chest radiography. Regarding chest X-ray (CXR) findings, 82.2% of children in the COVID-19 group had normal chest radiographs (p=0.001), whereas children in the influenza group exhibited significantly higher rates of patchy lung involvement (p=0.003) and consolidation (p=0.001). Platelet counts were significantly higher in the COVID-19 cohort than in the influenza cohort (p=0.001). Among infection-related biomarkers, CRP levels were significantly elevated in the influenza cohort compared to the COVID-19 cohort (4.92 mg/L vs. 0.94 mg/L, p=0.001). Regarding blood chemistry parameters, albumin and sodium levels were significantly higher in the COVID-19 cohort than in the influenza cohort (4.42 mg/dL vs. 4.02 mg/dL, p=0.01; 137.76 mmol/L vs. 135.92 mmol/L, p=0.011). Levels of aspartate aminotransferase (AST), alkaline phosphatase, serum creatinine, and creatine kinase (CK) were significantly lower in the COVID-19 pneumonia cohort compared to the influenza cohort (p=0.001) (Table 2).

The rate of viral coinfection was significantly higher in the influenza cohort than in the COVID-19 cohort (25.8% vs. 2.5%). The most commonly detected viral pathogens in the influenza cohort were respiratory RSV (20.2%) and rhinovirus (4.6%), (Table 3). Patients in the influenza cohort had more concurrent viral infections than COVID-19 patients. However, all patients with influenza with detected viral co-infections were in the mild disease group. The use of antibiotics and antiviral therapy (oseltamivir) was significantly more frequent among patients in the influenza cohort (p=0.001). Children in the influenza cohort required respiratory support more frequently than those in the COVID-19 cohort (p=0.07) and had a significantly higher need for high-flow nasal cannula therapy (p=0.022). Additionally, the influenza cohort exhibited higher hospitalization rates (p=0.001) and longer hospital stays (p=0.007) compared to the COVID-19 cohort.

Patients in the COVID-19 cohort were less symptomatic in terms of clinical severity, whereas children in the influenza cohort experienced mild, moderate, and severe and critical disease more frequently (p=0.001). Furthermore, the mortality

rate was higher in the influenza cohort (1.2%) than in the COVID-19 cohort (0.2%) (p=0.022) (Table 3).

Discussion

In this pediatric cohort study conducted at a tertiary referral hospital, we identified key factors associated with COVID-19 and influenza PCR-positive patients. Our findings confirm that influenza-infected patients have more severe symptoms, higher fever, higher rates of viral coinfection, longer hospital stays, higher hospitalization rates, greater need for ventilatory support, and significantly higher mortality.

This study provides an objective assessment of the severity of COVID-19 in comparison with influenza a similarly severe respiratory disease known for its seasonal outbreaks and pandemics. Worldwide, respiratory viruses remain a major cause of childhood morbidity and mortality. However, the differences between COVID-19 and other viral infections, particularly in the pediatric population, are not fully understood.[10] Recommendations for COVID-19 in children are derived predominantly from adult data, and without viral studies, it is difficult to differentiate COVID-19 from influenza through clinical findings alone. In meta-analyses and literature, fever and cough are the most common symptoms of COVID-19, and influenza in children. However, high fever, nasal congestion, rhinorrhea, vomiting, and muscle pain are more frequently observed in children with influenza compared to those with COVID-19. In contrast, diarrhea has been reported more commonly in children with COVID-19.[11,12] Notably, loss of smell and taste, which are characteristic symptoms of COVID-19 in adults, has been rarely reported in pediatric cases.[13] In our cohort, patients infected with influenza were significantly more symptomatic, with cough, fever, and rhinorrhea being more common among them. On the contrary, the frequency of nausea-vomiting, stomachache, and conjunctivitis in children with COVID-19 was less common than in patients with influenza. Skin rash was also less frequent in patients with COVID-19. Although erythematous rash or patchy exanthematous red rashes are dermal symptoms of COVID-19, childhood skin rashes are mostly similar to each other and do not contribute much to the differential diagnosis.[14] Although loss of taste and smell are common presenting symptoms in COVID-19 patients, these complaints were found to be less common (5.1%) in children than in adults and more common in patients with influenza.[13,15,16] This situation may be due to the difficulty children have expressing symptoms, such as loss of taste and smell, because infants and children have not fully developed the ability to recognize and express symptoms.

COVID-19 quickly became a pandemic spread quickly and easily among humans through oral and nasal droplets. As infected humans could be isolated due to pandemic measures, contact history was more manageable in the early period.[16] In our cohort, the history of contact for COVID-19 (57.4%) was

Table 2. Comparison of laboratory results in patients with COVID-19 and influenza patients

	Median (min-max)	Median (min-max)	p-value
Hemoglobin (g/dL)	13.4 (7.4-17.9)	12.4 (6.8-17.1)	0.331
Platelet (/mm³)	229000 (3800-570000)	209000 (18000-592000)	0.001
Leukocyte (/mm³)	6000 (400-23500)	6200 (500-25700)	0.485
Lymphocyte (/mm³)	1790 (90-14670)	2000 (100-12680)	0.121
Neutrophil (/mm³)	2965 (20-22000)	2950 (0-19100)	0.317
AST (U/L)	28 (6-526)	48 (16-547)	0.001
ALT (U/L)	17 (6-509)	21 (6-223)	0.06
BUN (mg/dL)	10.1 (2.2-30.1)	9.5 (2.5-46.2)	0.111
Creatinine (mg/dL)	0.5 (0.1-1.2)	0.4 (0.1-1.4)	0.49
Sodium (mg/dL)	138 (129-147)	136 (124-148)	0.011
Creatine kinase (mg/dL)	107 (26-301)	809 (0.3-36445)	0.001
CRP (mg/dL)	0.4 (0-22)	0.7 (0-41.0)	0.001
LDH (U/L)	244 (106-872)	343 (132-1478)	0.001
Total bilirubin (mg/dL)	0.3 (0.1-13.4)	0.3 (0.1-24)	0.173
PT (s)	12.1 (0.3-14.3)	12.5 (0.1-16.3)	0.396
APTT (s)	26.8 (21.6-32)	27.2 (21.6-112.7)	0.576
INR	1.0 (0.9-1.2)	1.1 (0.9-11)	0.019

AST: Aspartate aminotransferase, ALT: Alanin aminotransferaz, BUN: Blood urea nitrogen, CRP: C-reactive protein, LDH: Laktat dehidrogenaz, PT: Prothrombin time, APTT: Activated partial thromboplastin time, INR: International normalized ratio, COVID-19: Coronavirus disease-2019

Table 3. All results of respiratory samples, radiological findings and clinical characteristics in patients with COVID-19 and influenza

	COVID-19 n (%)	Influenza n (%)	p-value
Viral co-infection	17 (2.5)	129 (25.8)	0.001
RSV	1 (0.1)	101 (20.2)	
Human rhinovirus	9 (1.3)	23 (4.6)	
Coronavirus 229E	3 (0.4)	2 (0.4)	
Metapneumovirus	-	3 (0.6)	
Bocavirus	4 (0.6)	-	
Radiologic exam			
CT	25 (3.8)	-	n/a*
Chest X-ray	562 (91.1)	252 (50.5)	0.001
Chest X-ray findings			
Normal	504 (82.2)	42 (76.1)	0.001
Consolidation	13 (2.1)	24 (9.5)	0.001
Bilateral patchy infiltrates	6 (1)	10 (4)	0.003
Peribronchial thickening	44 (7.2)	22 (7.6)	0.435
Lung hyperaeration (bilateral)	-	4 (1.6)	n/a
Respiratory support	9 (1.4)	19 (3.8)	0.007
0_2 (nasal canula/mask)	8 (1.2)	9 (1.8)	0.405
High flow nasal canula	1 (0.2)	6 (1.2)	0.022
Intubation	1 (0.2)	4 (0.8)	0.094
Antibiotics	85 (12.9)	219 (43.8)	0.001
Oseltamivir	4 (0.6)	263 (52.7)	0.001
Disease severity			
Asymptomatic	50 (7.6)	11 (2.2)	0.001
Mild	589 (89.1)	373 (74.7)	0.001
Moderate	19 (2.9)	91 (18.2)	0.001
Serious-critical	3 (0.5)	24 (2.3)	0.001
Exitus	1 (0.2)	6 (1.2)	0.022
Length of stay (day)	2 (1-5)	4 (2-8)	0.007
Hospitalization	93 (14.1)	182 (36.5)	0.001
Transfer to PICU	2 (0.3)	5 (0.6)	0.128

*n/a: Not applicable, RSV: Respiratory syncytial virus, CT: Computed tomography, PICU: Pediatric intensive care unit, COVID-19: Coronavirus disease-2019

significantly higher than for influenza (2.8%), while in the study involving 8886 pediatric patients, this rate was found to be 71.3%.[17] The COVID-19 pandemic has overwhelmed healthcare systems. Therefore, it is important to evaluate patients in triage. There are few studies assessing vital signs in triage. In the triage, 43.1% of COVID-19 positive patients had tachycardia, 30.7% had fever, and 20.4% had hypoxia, which is relatively low in our patient group.[18] Only fever was detected in two-thirds of the COVID-19-positive children, and this rate was 89.9% in influenza-positive children. We also found tachycardia and tachypnea, at a higher rate in triage at admission. CRP levels have been found to be lower in COVID-19 patients compared to those with influenza.[13] While there is no significant difference in total white blood cell count, neutrophil levels have been reported to be lower in COVID-19 cases.[13] Findings from laboratory comparisons vary significantly. Some studies have reported higher levels of CRP, procalcitonin, alanin aminotransferaz, AST, and laktat dehidrogenaz in influenza patients; however, no significant difference in lymphocyte counts has been observed between the two groups.[19,20] We found no difference among patients regarding leukopenia, lymphopenia, and neutropenia. However, elevated CRP was significantly more common in the influenza cohort. There is substantial evidence suggesting that COVID-19 induces a milder inflammatory response in children compared to influenza. Although AST elevation, sodium elevation, and increased creatinine kinase values were more common, in the influenza patient group as biochemistry parameters, neither hemogram nor biochemistry change is indicative of disease differentiation. The underlying pathogenesis of this disorder remains unclear. Influenza is one cause of the benign acute childhood syndrome, so it is not surprising that elevated CK levels are detected in patients with influenza. In COVID-19 patients, coagulation parameters can be helpful in the timely treatment and prognosis, but thromboembolic events are rare in pediatric patients with COVID-19 infection.[21,22]

CXR are an important tool for clinical and epidemiological characteristics. Children are less studied than adults, and rapid diagnosis is challenging due to asymptomatic or mild episodes.[23] Although physicians tend to examine CXR to help diagnose COVID-19 cases of pneumonia, abnormalities in CXR were more often present in the influenza cohort. While 82.2% of the chest radiographs in the COVID-19 cohort were normal, this rate was 76% in the influenza group. Findings are non-specific, therefore, CXR cannot be used to screen for a condition or as a first-line diagnostic test. Therefore, national and international guidelines should be considered when taking CXR in children, and unnecessary radiation should be avoided. Although there are few studies on infections in children, the frequency of coinfection was 4.7% in children at the beginning of the pandemic, while in the systematic review and meta-analysis involving adult patients, 8.9% of the patients had coinfection, and it was 2.5% in our COVID-19 patient group.[24,25] Quick management with oseltamivir reduces the duration of symptoms and the risk of complications (bronchitis, otitis media, and pneumonia), and hospitalization, and decreases mortality among high-risk populations.[26] However, the use of respiratory viral tests remains controversial. Although it is recommended that the patient is immunocompromised, has chronic medical conditions, or is hospitalized, additional care should be considered. It can also be taken more frequently than typical

routine practices to determine the prevalence of diseases and to separate patient cohorts, especially in pandemic conditions such as COVID-19.[26,27] Respiratory PCR tests were taken before starting oseltamivir treatment. Despite this, 52.7% of the patients were started on oseltamivir. Therefore, we recommend starting antiviral therapy for non-severe patients with confirmed-influenza at high risk for severe or complicated illness. In the COVID-19 pandemic, there has been a dramatic shift in the patterns of traditionally seasonal respiratory viruses, which may be the result of changes in children.[28] In addition, due to restrictions and social isolation, other respiratory viruses, besides COVID-19, have started to be seen at all times of the year and have confused their routine seasonal calendar.[29] Therefore, the scope of our study is significant in evaluating the COVID-19 and influenza cases from the beginning of the COVID-19 pandemic until recently. Does COVID-19 present a milder course in children compared to influenza? The key question remains: which poses a greater risk? In our study, when clinical and treatment needs were compared, influenza was more severe and required extended hospitalization, and children with influenza needed more respiratory support. It is now better known that clinical symptoms of COVID-19 in children tend to be milder,[1,30] as supported by the results of our study. Six patients in the influenza group and one in the COVID-19 group died in our patient cohort. While the child who died in the COVID-19 group had an underlying immune deficiency, the three children in the influenza group were previously healthy with no known disease. The results of our study revealed that COVID-19 is commonly a mild disease in children, and a small proportion of children (3.4%) have a moderate to severe course, requiring intensive care support and long-term mechanical ventilation. Furthermore, we confirmed that fatal outcomes with COVID-19 in children are rare. As seen in our study, influenza continues to be a significant cause of mortality and morbidity in children; however, there was low circulation of influenza during the beginning of the COVID-19 pandemic.[30,31] 2023-2024 season in the US. In outpatient settings, children tested for influenza were more likely to have positive results compared to adults.[32] During the 2023-2024 influenza season, the mortality rate of children hospitalized with an influenza diagnosis was found to be 2.2%.[32] This unpredictable situation may be a reminder that influenza will be more challenging for children in the coming months. In all this chaos, children require more protection during the pandemic. Our findings emphasize the importance of vaccination programs for both influenza and COVID-19 to reduce disease burden in children.

Study Limitations

There are some limitations to our study. It is a single-center study. CXR were especially frequently taken at the beginning of the pandemic. We could not include point-of-care ultrasound examinations in our study due to the lack of standardization of lung ultrasound in COVID-19. Also, all children in both cohort groups were unvaccinated. In our study, we only used a viral respiratory tract panel, but not a bacterial panel because, given the volume of patients and the current standard of care, using bacterial panels is not particularly feasible in the emergency department (ED), where they are often not available to guide diagnosis and treatment. Given the presence of different COVID-19 variants during and after the pandemic, this factor could not be evaluated in the analysis. This limitation exists because variant identification was performed by the central government laboratory for epidemiologic surveillance through random sampling. The differentiation between bacterial and viral upper respiratory tract infections represents a significant challenge in clinical practice. To reduce the empiric use of antibiotics and improve outcomes, there is a need for improved diagnostics that can provide practitioners with rapid information regarding the underlying etiology, thereby enabling them to make more informed decisions. To have a global impact, including in low-income settings, such diagnostics should consider the recently defined target infections, as proposed by experts from academic centers and multicenter studies.[33]

Conclusion

In our pediatric cohort, influenza imposed a significantly greater clinical burden than COVID-19, presenting with higher peak fevers, more severe clinical presentation, increased rates of viral coinfections, prolonged hospital stays, greater need for ventilatory support, and notably higher mortality. These findings reaffirm that, while COVID-19 in children is generally mild and self-limiting, influenza continues to be a major driver of severe respiratory morbidity and mortality. Based on these results, several priorities emerge for pediatric emergency care: implementation of rapid, PCR-based viral diagnostics to guide isolation protocols and therapeutic interventions; reinforcement of seasonal vaccination strategies for both influenza and COVID-19 to mitigate preventable illness; and strengthening of multicenter research networks-particularly in vaccinated pediatric populations and utilizing standardized point-of-care tools-to better characterize emerging variants, guide targeted antiviral therapy, and refine triage algorithms. Strengthening these approaches has the potential to reduce unnecessary antibiotic use and alleviate resource burdens in overcrowded ED.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Hacettepe University under registration

code GO22/1242, date: 13.12.2022. The ethics committee reviewed our study and waived the need for informed consent, as all data and samples were analyzed retrospectively and collected as part of routine clinical practice in accordance with current guidelines.

Informed Consent: Informed consent was not required and therefore not obtained, as the study was conducted retrospectively and involved no direct patient intervention.

Footnotes

Author Contributions

Surgical and Medical Practises: E.G., Ö.T., Concept: E.G., A.Z.B., Ö.T., Design: E.G., H.Y., A.Z.B., Ö.T., Data Collection or Processing: E.G., H.Y., B.A., A.Z.B., A.A., Ö.T., Analysis or Interpretation: E.G., H.Y., B.A., A.Z.B., A.A., Ö.T., Literature Search: E.G., H.Y., B.A., A.Z.B., Ö.T., Writing: E.G., Ö.T.

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Evaluation of Fluid Status of Children in Pediatric Intensive Care Unit by Measuring Inferior Vena Cava Diameter

Pediatrik Yoğun Bakım Ünitesindeki Çocukların Sıvı Durumunun Inferior Vena Cava Çapı Ölçülerek Değerlendirilmesi

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Abstract

Introduction: The aim of this study was to determine the correlation between inferior vena cava (IVC) diameter, vena cava inferior collapsibility (cIVC) and vena cava inferior distensibility (dIVC) with other hemodynamic parameters to determine the fluid requirement or volume load of patients hospitalised in the pediatric intensive care unit.

Methods: Sixty-two patients aged 1 month-18 years were included in this study. IVC diameters were measured, collapsibility and distensibility were calculated to predict the fluid status of the patients. Physical examination findings, biochemical markers, perfusion indices (PI), pleth variability indices (PVI) were also evaluated.

Results: There were 33 girls and 29 boys, aged between 3-211 months. IVC minimum diameter (D_{min}) varied between 0.27 and 2.10 cm, while IVC maximum diameter (D_{max}) varied between 0.56 and 2.90 cm and there was a very strong relationship between D_{max} and D_{min} in the same direction (r=0.956, p<0.001). There was a positive correlation between D_{min} and cIVC or dIVC among patient groups according to mechanical ventilation (MV) support status. In contrast, there was a negative correlation between PI and PVI and cIVC in patients without MV support (r=-0.355, p=0.040; r=-0.404, p=0.018). There was a positive correlation between D_{min} and D_{max} (r=0.928, p<0.001). There was also a positive correlation between PVI and PI and a negative correlation between lactate (r=0.393, p=0.02; r=-0.272, p=0.033).

Conclusion: The high cIVC in spontaneously breathing patients may be associated with intravascular fluid loss. However, more patients are needed to comment on patients receiving MV support.

Keywords: Distensibility, collapsibility, fluid status, Inferior Vena Cava diameter

Öz

Giriş: Bu çalışmanın amacı çocuk yoğun bakım ünitesinde yatan hastaların sıvı gereksinimi veya hacim yükünü belirlemek için inferior vena cava (IVC) çapı, vena kava inferior kollapsibilitesi (cIVC) ve vena kava inferior distansibilitesi (dIVC) ile diğer hemodinamik parametreler arasındaki korelasyonu belirlemektir.

Yöntemler: Bu çalışmaya 1 ay-18 yaş arası 62 hasta dahil edildi. Hastaların sıvı durumlarını tahmin etmek için IVC çapları ölçüldü, kollapsibilite ve distansibiliteleri hesaplandı. Fizik muayene bulguları, biyokimyasal parametreleri, perfüzyon indeksi (PI), pleth variyabilite indeksi (PVI) de değerlendirildi.

Bulgular: Üç-211 ay arasında değişen yaşlarda 33 kız, 29 erkek çocuk vardı. IVC çaplarından minimum çap (D_{min}) 0,27 ile 2,10 cm arasında değişirken, maksimum çap (D_{maks}) 0,56 ile 2,90 cm arasında değişiyordu ve D_{min} ile D_{maks} arasında aynı yönde çok güçlü bir korelasyon vardı (r=0,956, p<0,001). D_{min} ile cIVC veya dIVC arasında, mekanik ventilasyon (MV) desteği alma durumuna göre hasta grupları arasında pozitif bir korelasyon vardı. Buna karşın, MV desteği almayan hastalarda PI ve PVI ile cIVC arasında negatif korelasyon mevcuttu (r=-0,355, p=0,40; r=-0,404, p=0,018). D_{min} ve D_{maks} arasında pozitif bir korelasyon vardı (r=0,928, p<0,001). PVI ve PI arasında da pozitif korelasyon ve laktat arasında negatif korelasyon vardı (r=0,393, p=0,02; r=-0,272, p=0,033).

Sonuç: Spontan soluyan hastalarda yüksek cIVC, intravasküler sıvı kaybı ile ilişkili olabilir. Ancak, MV desteği alan hastalar hakkında yorum yapabilmek için daha fazla sayıda hastaya ihtiyaç vardır.

Anahtar Kelimeler: Distansibilite, kollapsibilite, sıvı durumu, Inferior Vena Cava çapı

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Introduction

Ensuring hemodynamic stabilization is of vital importance in the management of critically ill patients admitted to the pediatric intensive care unit (PICU). The fluid, electrolyte, and acid-base equilibria must be maintained. If any of these three balances is disrupted, the body will not function normally. Maintaining hemodynamic balance reduces mortality and morbidity, especially for patients in PICU. In dehydration or shock, inadequate fluid resuscitation can cause tissue hypoperfusion and end-organ damage, while excessive fluid resuscitation can cause central venous pressure, hypertension, polyuria, peripheral oedema, hypoalbuminaemia, intracranial pressure, and mortality.[1-3]

Before making fluid management decisions in these individuals, clinicians should assess their hemodynamic condition. Dynamic methods like body weight loss, skin turgor, capillary refill time (CRT), systolic pressure change, heart rate, heart rate volume change, urine output, serum bicarbonate, lactate levels, and passive leg lift test can assess patients' hemodynamic status.[1,4,5] Recent studies have also employed perfusion index (PI), pleth variability index (PVI), and inferior vena cava (IVC) diameter measurement.[4] Measured IVC diameters and vena cava inferior distensibility (dIVC) in mechanically ventilator-dependent patients, and collapsibility in spontaneously breathing patients without mechanical ventilator (MV) support, can guide fluid management.[1,6] The aim of this study was to determine the correlation of IVC diameter, vena cava inferior collapsibility (cIVC), and dIVC with other hemodynamic parameters to assess the hemodynamic status, fluid requirement, or volume load of patients admitted to the PICU.

Materials and Methods

Selection of Patients

Between January 1, 2020, and June 1, 2020, pediatric patients aged 1 month to 18 years who were hospitalised in the PICU were included in the study. Among these patients, those with congenital heart disease, congenital vascular anomalies, pulmonary hypertension, pneumothorax/hemothorax, or cardiac tamponade; those who started inotropic therapy before hospitalisation; those who received MV support and had a positive end-expiratory pressure >8 cm H_2O; and those who had conditions that hindered ultrasonography (obesity, burns, wounds in the anterior chest dura, drains secondary to chest surgery) were not included in the study.

In addition, IVC diameters were measured collapsibility and distensibility were calculated, and physical examination findings and biochemical markers were also recorded. According to this information, it would be sufficient to reach at least 30% of the population for the best estimation. However, the aim is to reach at least 50% of the population in case of missing data. Accordingly, a minimum of 60 pediatric patients was calculated to be included in this study.[7] In accordance with these calculations, a total of 62 patients were included in the study.

Ethics Committee approval was obtained from Mersin University Clinical Research Ethics Committee, with the board (decision date: 08.01.2020 and decision no: 2020/26).

Assessment of Patients

The IVC diameter of the patients was measured during inspirium and expirium by a faculty member of the division of pediatric intensive care at the time of admission to the PICU. This was done using GE Logiq e ultrasound system ultrasonography device with the GE convex 4C-RS probe in our PICU. All measurements were performed by the same faculty member. The ultrasound probe was placed perpendicular to the long axis of the body just below the xiphoid bone level, and a cross-sectional image of the IVC and the aorta was obtained in B-mode. Afterwards, the junction of the IVC and right atrium, and the area where the hepatic veins join were visualised by turning the probe clockwise towards the patient's right shoulder. Switching to M-mode, IVC diameter was measured from the image taken 1-2 cm distal to the opening of the IVC into the right atrium in both inspiration and expiration. dIVC: [vena cava inferior maximum diameter (D_{max})-vena cava inferior minimum diameter (D_{min})/D_{min}]x100 and cIVC [cIVC: (D_{max}-D_{min})/D_{max}]x100 were calculated and recorded. Simultaneously, fever, pulse rate, blood pressure, oxygen saturation, and CRT, PI, PVI, blood count, blood biochemistry, blood gas parameters, ventilator parameters, demographic characteristics, and clinical problems of the patients were recorded.

Statistical Analysis

The data were analysed with Statistical Package for the Social Science (SPSS) 22. The mean, standard deviation, median, 1st and 3rd quartiles, number, and percentage were shown. The chi-square test determined the relationships between categorical variables. Normality was tested with Shapiro-Wilk. The Student's t-test was employed for variables that satisfied the normality assumption, and the Mann-Whitney U test for variables that did not. The statistical significance level was set at $p<0.05$.

Patients were categorized by diagnosis, chronic disease state, ventilation status, and pre-hospitalization fluid therapy. Results were compared between patient groups.

Results

There were 33 girls and 29 boys, aged between 3 and 211 months (median 70.5, interquartile range: 18.25-135.75). 17.7% of patients were 1-12 months old, 29% were 13-59 months old, 17.7% were 60-119 months old, and 35.5% were 120-216 months old. Patients who couldn't be included in all four diagnostic groups (electric shock, corrosive substance ingestion, drug intoxication, intrathecal treatment hospitalization) were defined as "other". Patients were hospitalized in the PICU for the following reasons: 16.1% due to neurological disease, 14.5% due to trauma, 43.5% due to infection/sepsis, 12.9% for surgery or for follow-up, and 12.9% for other reasons.

Table 1 presents the analysis from the study of physical examination findings of patient groups. There was no statistically significant difference between groups in terms of MV support and chronic illnesses. However, CRT and blood pressure values were significantly different in the group, identified as having an intravascular volume deficit during the clinical evaluation before hospitalization, fluid loaded compared to those who were not. CRT was prolonged in 53% of those who received fluid loading (p=0.025), and blood pressure was lower than the age-adjusted norm in 53.8% of the cases (p=0.039). A significant difference was found between the groups by diagnosis, only in terms of the pulse rate, according to age. Pulse rate increased with age in 40.7% of the patient group hospitalised due to infection/sepsis (p=0.029) (Table 1).

In terms of biochemical parameters, there was no significant difference between chronic disease status groups, but lactate levels differed between patients with and without MV support and between patients who received fluid loading before hospitalisation in the PICU and who didn't (p=0.018, p=0.022) (Table 2).

A statistically significant correlation was found between prolonged CRT and increased lactate (p<0.001), decreased pH (p<0.001), increased urea (p=0.021), increased creatinine (p=0.011), increased sodium (p=0.025), and urine density (p<0.001). A significant difference was shown among blood pressure value, lactate (p=0.02), pH (p=0.02), CO_2 (p=0.032), creatinine (p=0.032), sodium (p=0.030), and urine density (p<0.001) (Table 3).

IVC diameter D_{min} varied between 0.27 and 2.10 cm, while D_{max} varied between 0.56 and 2.90 cm, and there was a very strong relationship between D_{max} and D_{min} in the same direction (r=0.956, p<0.001). A linear correlation was found between patient age and IVC diameters (r=0.724, p<0.001 for D_{max}; r=0.646, p<0.001 for D_{min}).

Table 4 compares ultrasonographic and pulse oximetric data between groups based on concomitant chronic disease and MV support. D_{max}, D_{min}, and PVI differed significantly between chronic illness groups (p=0.003; p=0.12; p=0.030). The study compared patient groups based on MV supports for IVC measures, PVI, and PI. Significant differences were found mainly in respiratory variations of IVC (p<0.001).

Table 1. Distribution of physical examination findings between patient groups

Patient groups		CRT					Pulse rate (according to age)					$Ta_{systolic}$ (according to age)						
		Normal		Increased		p	Normal		Increased		p	$Ta_{systolic}$ normal		$Ta_{systolic}$ d decreased		$Ta_{systolic}$ increased		p
		n	%	n	%		n	%	n	%		n	%	n	%	n	%	
Mechanical ventilator support	Yes (n=28)	17	60.7	11	39.3	0.410	23	82.1	5	27.9	0.448	15	53.6	10	35.7	3	10.7	0.512
	None (n=34)	29	85.3	5	14.7		24	70.6	10	29.4		23	67.6	8	23.5	3	8.8	
Fluid loading before hospitalization	Done (n=13)	6	46.2	7	53.8	0.025*	8	61.5	5	38.5	0.324	6	46.2	7	53.8	0	0.0	0.039*
	Not done (n=49)	40	81.6	9	18.4		39	79.6	10	20.4		32	65.3	11	22.4	6	12.2	
Diagnosis groups	Neurological (n=10)	10	100	0	0.0	0.060	10	100	0	0.0	0.029*	7	70.0	1	10.0	2	20.0	0.313
	Trauma (n=9)	7	77.8	2	22.2		8	88.9	1	11.1		6	66.7	3	33.3	0	0.0	
	Infection/sepsis (n=27)	17	63.0	10	37.0		16	59.3	11	40.7		15	55.6	10	37.0	2	7.4	
	After surgery (n=8)	7	87.5	1	12.5		7	87.5	1	12.5		5	62.5	1	12.5	2	25.0	
	Others (n=8)	5	62.5	3	37.5		6	75.0	2	25.0		5	62.5	3	37.5	0	0.0	
Chronic diseases	Yes (n=39)	28	71.8	11	28.2	0.574	30	75.8	9	23.1	0.789	23	59.0	11	28.2	5	12.8	0.515
	None (n=23)	18	78.3	5	21.7		17	73.9	6	26.1		15	65.2	7	30.4	5	12.8	

CRT: Capillary refill time, $Ta_{systolic}$: Systolic blood pressure, *: Statistically significant

In addition, D_{min} was positively correlated with cIVC or dIVC in both groups, according to MV support status. Only the MV-supported group had a positive correlation between D_{max} and dIVC. However, PI and PVI were negatively correlated with cIVC in patients without MV support (r=-0.355, p=0.040; r=-0.404, p=0.018) (Table 5).

As a result, cIVC of patients with low PI and PVI measurements were high, which may be associated with intravascular volume loss.

Table 6 shows the correlations between IVC diameters, respiratory variability, PI, PVI, and biochemical parameters. A significant positive correlation exists between D_{min} and D_{max} (r=0.928, p<0.001). D_{min} is negatively correlated with cIVC and/or dIVC (r=-0.416, p=0.001). Creatinine is the only laboratory parameter that correlates positively with D_{min} and D_{max} (r=0.326, p=0.010 for D_{min}; r=0.340, p=0.005 for D_{max}).

Table 2. Evaluation of laboratory parameters of the patient groups according to fluid loading and MV support status before hospitalization

	Fluid loading before hospitalization			MV support		
	Yes (n=13)	No (n=49)	p	Yes (n=28)	No (n=34)	p
Lactate	7.462±5.807	4.302±3.834	0.789	6.554±5.833	3.658±2.238	0.018*
pH	7.368±0.098	7.383±0.066	0.975	7.372±0.091	7.386±0.054	0.484
CO_2 (mmHg)	44.323±10.702	42.276±10.785	0.771	44.954±11.804	40.853±9.503	0.135
HCO_3 (mmol/L)	24.169±6.498	23.559±4.504	0.283	24.039±5.985	23.397±3.932	0.614
BE (mmol/L)	-0.615±6.751	-0.514±3.980	0.885	-0.918±5.581	-0.221±3.729	0.559
Hemoglobin (g/dL)	16.885±24.426	9.657±1.917	0.433	12.600±18.744	9.997±2.121	0.424
Hematocrit (%)	28.38±5.32	29.51±5.59	0.839	28.04±4.11	30.29±6.31	0.096
White blood cell (x1/µL)	8680.00±4910.38	9506.80±4492.18	0.995	9124.64±5024.28	9505.38±4196.66	0.746
Urea (mg/dL)	75.31±112.03	23.06±1724	0.874	34.657±24.469	33.407±72.609	0.936
Creatinine (mg/dL)	1.244±1.756	0.446±0.566	0.149	0.815±1.081	0.448±0.875	0.155
Sodium (meq/L)	139.62±12.28	140.00±6.16	0.818	143.18±8.170	137.24±6.24	0.002*
Urine density	1018.69±8.85	1015.84±8.54	0.432	1018.61±9.27	1014±7.71	0.071

MV: Mechanical ventilation, BE: Base deficit, *: Statistically significant

Table 3. Relationship between physical examination findings and laboratory parameters

	CRT			Pulse rate (according to age)			$Ta_{systolic}$ (according to age)			
	Normal (n=46)	Elongated (n=16)	p	Normal (n=47)	Increased (n=15)	p	Ta normal (n=38)	Ta decreased (n=18)	Ta increased (n=6)	p
Lactate	3.2±1.9	10.1±5.6	<0.001*	4.4±3.9	6.9±5.6	0.058	3.1±2.8	9.1±5.2	4.0±2.6	0.002*
pH	7.40±0.07	7.33±0.07	<0.001*	7.38±0.07	7.35±0.07	0.109	7.39±0.06	7.33±0.06	7.43±0.06	0.002*
CO_2 (mmHg)	41.5±9.7	46.1±12.7	0.148	41.8±9.9	45.4±13.0	0.268	41.1±10.3	47.9±11.0	37.0±7.4	0.032*
HCO_3 (mmol/L)	24.1±4.4	22.5±6.2	0.283	23.8±8.1	23.4±5.4	0.835	23.6±5.0	23.4±5.4	25.1±3.6	0.752
BE (mmol/L)	0.1±4.0	-2.4±5.9	0.125	-0.4±4.7	-0.9±4.6	0.748	-0.1±4.3	-1.7±5.4	0.4±4.0	0.434
Hemoglobin (g/dL)	9.7±1.8	15.4±6.1	0.370	11.9±14.4	9.0±2.6	0.455	12.3±1.6	9.4±2.1	9.5±2.5	0.692
Hematocrit (%)	29.6±5.3	28.4±6.1	0.453	29.7±4.9	28.1±7.2	0.334	29.9±4.7	28.4±6.5	27.8±7.2	0.530
White blood cell (x1/µL)	9388±4524	9175±4782	0.874	9120±4530	10001±4721	0.519	10212±4640	8040±4249	7646±4115	0.150
Urea (mg/dL)	17.9±10.4	80.5±97.1	0.02*	23.0±17.8	68.5±105.2	0.117	17.3±9.8	72.3±94.1	25.2±16.2	0.067
Creatinine (mg/dL)	0.31±0.19	1.50±1.64	0.01*	0.54±0.80	0.85±1.42	0.423	0.28±0.16	1.36±1.59	0.49±0.35	0.032*
Sodium (meq/L)	138.1±5.1	145.2±11.2	0.025*	140.0±7.6	139.7±8.3	0.886	139.2±6.0	142.9±10.8	135.7±3.0	0.030*
Urine density	1012±5.9	1027±5.9	<0.001*	1015±7.8	1020±9.8	0.028*	1013±6.8	1025±6.5	1012±2.2	<0.001*

CRT: Capillary refill time, $Ta_{systolic}$: Systolic blood pressure, BE: Base deficit, *: Statistically significant

Table 4. Evaluation of D_{max}, D_{min}, dIVC/cIVC, PVI, PI parameters of patients according to chronic disease and mechanical ventilator support status

	No chronic disease (n=23)		Chronic illness present (n=39)		p	MV is not available (n=34)		MV is available (n=28)		p
	Min-max	Median (25-75%)	Min-max	Median (25-75%)		Min-max	Median (25-75%)	Min-max	Median (25-75%)	
D_{max} (cm)	0.67-2.90	1.23 (0.92-1.64)	0.56-2.90	0.9 (0.77-1.12)	0.003*	0.62-2.90	1.02 (0.86-1.35)	0.56-2.90	0,91 (0.77-1.57)	0.336
D_{min} (cm)	0.34-2.10	0,67 (0.47-0.82)	0.27-1.90	0.45 (0.38-0.67)	0.012*	0.30-2.10	0.55 (0.41-0.68)	0.27-2.00	0.49 (0.38-0.78)	0.655
dIVC/cIVC (%)**	27.6-133.3	49.2 (44.6-56.9)	34.3-165.0	54.3 (49.2-100.0)	0.070	27.6-59.2	49.2 (44.6-51.6)	34.3-165.0	96.2 (57.8-107.3)	<0.001*
PVI	12-40	26 (21-32)	10-44	21 (15-25)	0.030*	10-40	23.50 (18.00-30.25)	12-44	22.00 (14.00-26.50)	0.181
PI	0.14-8	1.80 (0.58-3.10)	0.12-12	1.4 (0.8-2.3)	0.867	0.12-12	1.20 (0.59-2.45)	0.35-8.00	1.50 (0.92-2.80)	0.151

**: In all analyses, dIVC value was analyzed for patients receiving mechanical ventilator support and cIVC value was analyzed for patients who did not receive mechanical ventilator support but breathed spontaneously.
D_{max}: Vena cava inferior maximum diameter, D_{min}: Vena cava inferior minimum diameter, dIVC: Vena cava inferior distensibility, cIVC: Vena cava inferior collapsibility, PI: Perfusion index, PVI: Pleth variability index, MV: Mechanical ventilator, *: Statistically significant

Table 5. Correlations of vena cava inferior measurements, PI and PVI with each other in patient groups formed according to mechanical ventilator support

			D_{min}	cIVC/dIVC	PVI	p
Mechanical ventilation is not available	D_{max}	r	0.954	-0.363	-0.091	-0.026
		p	<0.001*	0.035*	0.608	0.886
	D_{min}	r		-0.588	0.013	0.081
		p		<0.001*	0.942	0.650
	cIVC	r			-0.404	-0.355
		p			0.018*	0.040*
	PVI	r				0.194
		p				0.271
Mechanical ventilation is available	D_{max}	r	0.961	-0.303	0.048	0.369
		p	<0.001*	0.116	0.809	0.053
	D_{min}	r		-0.520	-0.012	0.449
		p		0.005*	0.953	0.017
	dIVC	r			<0.001	-0.300
		p			0.999	0.121
	PVI	r				0.043
		p				0.828

**: In all analyses, dIVC value was analyzed for patients receiving mechanical ventilator support and cIVC value was analyzed for patients who did not receive mechanical ventilator support but breathed spontaneously.
D_{max}: Vena cava inferior maximum diameter, D_{min}: Vena cava inferior minimum diameter, dIVC: Vena cava inferior distensibility, cIVC: Vena cava inferior collapsibility, PI: Perfusion index, PVI: Pleth variability index, *: Statistically significant

Table 6. Correlations between vena cava inferior measurements, PI, PVI and biochemical parameters

		D_{min} (cm)	cIVC/ dIVC	PVI	PI	Lactate	pH	CO_2 (mmHg)	HCO_3 (mmol/L)	BE (mmol/L)	Hgb (g/dL)	Hct (%)	WBC (x1/ µL)	Urea (mg/ dL)	Creatinine (mg/dL)	Na (mEq /L)	Urine density
D_{max} (cm)	r	0.928	-0.228	0.113	0.037	0.092	0.137	0.047	0.167	0.001	0.042	0.004	0.018	0.028	0.349	-0.001	0.059
	p	<0.001*	0.075	0.381	0.778	0.478	0.287	0.715	0.196	0.993	0.745	0.975	0.889	0.831	0.005*	0.995	0.650
D_{min} (cm)	r		-0.416	0.162	0.115	0.096	0.167	-0.021	0.155	-0.028	0.060	0.010	0.101	0.010	0.326	0.107	0.038
	p		0.001*	0.210	0.375	0.460	0.194	0.874	0.228	0.830	0.644	0.937	0.437	0.941	0.010*	0.408	0.772
cIVC/dIVC**	r			-0.157	-0.136	0.174	-0.309	0.324	-0.056	-0.106	-0.206	-0.152	-0.330	0.269	0.064	0.041	0.190
	p			0.223	0.293	0.176	0.014*	0.010*	0.666	0.413	0.108	0.238	0.009*	0.034*	0.620	0.752	0.139
PVI	r				0.393	-0.272	0.005	-0.003	-0.228	-0.192	0.105	0.040	-0.060	-0.147	-0.139	0.010	-0.127
	p				0.002*	0.033*	0.971	0.979	0.075	0.134	0.415	0.758	0.643	0.254	0.280	0.938	0.326
PI	r					-0.088	0.061	0.078	-0.149	-0.054	-0.035	-0.047	-0.061	-0.056	-0.042	-0.009	-0.032
	p					0.495	0.635	0.546	0.246	0.675	0.785	0.717	0.640	0.665	0.744	0.946	0.805

**: In all analyses, dIVC value was analyzed for patients receiving mechanical ventilator support and cIVC value was analyzed for patients who did not receive mechanical ventilator support but breathed spontaneously.
D_{max}: Vena cava inferior maximum diameter, D_{min}: Vena cava inferior minimum diameter, dIVC: Vena cava inferior distensibility, cIVC: Vena cava inferior collapsibility, PI: Perfusion index, PVI: Pleth variability index, BE: Base deficit, Hgb: Hemoglobin, Hct: Hematocrit, WBC: White blood cell, *: Statistically significant

Unlike creatinine, urea was positively correlated with cIVC or dIVC (r=0.269, p=0.034). There is a positive correlation between PVI and PI, and a negative correlation between lactate and these parameters (r=0.393, p=0.02; r=-0.272, p=0.033). Thus, PVI is directly proportional to PI and inversely proportional to lactate. The study found no statistically significant association between PI and any laboratory parameter (p>0.005).

The study found significant correlations between lactate and pH, urea, creatinine, sodium, and urine density. Lactate and pH correlated negatively (r=-0.38, p=0.002). This is because lactic acidosis is the major component of metabolic acidosis in intravascular volume loss. Additionally, lactate levels are significantly correlated with increases in urea, creatinine, sodium, and urine density (respectively r=0.454, p<0.001; r=0.380, p=0.002; r=0.326, p=0.010; r=0.640, p<0.001). Although there was a significant negative correlation between pH and urea, sodium, and urine density (r was negative for each of them and p<0.05), the correlation with creatinine was not statistically significant, even though creatinine increased as pH decreased (r=-0.223, p=0.081).

Discussion

In PICU patients, fluid status should be determined and appropriate fluid resuscitation initiated without delay. However, inadequate or forceful fluid treatment may cause fatal outcomes. Therefore, assessing patients' fluid status and starting appropriate treatment are vital.[8,9]

To date, IVC diameter and respiratory variability in adult patients have been studied extensively.[9,10] Compared to adult patients, pediatric research is more limited and has more inconsistent outcomes. Age-related changes in IVC diameter may be a major cause of this paradox. Mannarino et al.[11] found that IVC diameters increased with age in healthy Caucasian children, but there was a weak correlation between cIVC and age. In another study involving 63 healthy, normovolemic children, it was shown that the measured IVC diameter increased with age, and this increase was statistically significant (p<0.001) in all pediatric ages.[12] Similar to previous studies in pediatric ages, in our study of 62 pediatric patients hospitalized in the PICU, a linear relationship was found between age and D_{min}, D_{max}. It was observed that these diameters increased with increasing age (r=0.646, p<0.001 for D_{min}; r=0.724, p<0.001 for D_{max}).

Positive pressure ventilation increases intrathoracic pressure during inspiration, decreases systemic venous return, and causes a rise in IVC diameter. Therefore, dIVC is more reflective of preload dependency.[13,14] In contrast, in spontaneously

breathing patients, intrathoracic pressure decreases during inspiration, increasing venous return and causing IVC collapse. Thus, inspiratory IVC diameter is smaller than expiratory IVC diameter, and hypovolaemia may increase respiratory variability. This makes cIVC a more appropriate parameter for spontaneously breathing patients.[13]

In a literature review published by Ciozda et al.[14] in 2016, data from a total of 1430 patients receiving MV support were combined, and the usefulness of IVC diameters for the estimation of central venous pressure (CVP) was evaluated. The results indicated that the reported correlations between IVC size and CVP in patients receiving MV support were weak and inconsistent. In approximately half of the studies in this population of 1430 patients, no statistically significant correlation was found between CVP and IVC diameters; and in those in which significance was found, correlations were mostly weak and moderate in strength. Weber et al.[15] confirmed the low degree of predictability of respiratory variation of IVC diameter in determining fluid sensitivity during MV in a pediatric patient population.

In a prospective study conducted in the PICU of a clinic in which 50 patients aged 5-18 years with a diagnosis of shock were evaluated, a statistically significant correlation was found between IVC diameters measured at the end of expiration and inspiration, and CVP measured at the same stage. In addition, it was observed that respiratory variability of IVC decreased as CVP and IVC diameters increased during effective fluid resuscitation. This study concluded that ultrasonographic evaluation of the IVC is a good guide for the assessment of fluid status in children with shock, contrary to many studies with contradictory results in the literature.[16] However, Zhang et al.[17] suggested in their study that the distensibility of IVC diameter in mechanically ventilated patients can only be used with moderate reliability in patients with low CVP, i.e., hypovolaemia, whereas it is not reliable in estimating CVP in patients with normal or high CVP.

In a study conducted on children with spontaneously breathing sepsis, contrary to many studies in the literature, cIVC had very poor test properties in predicting fluid sensitivity. The authors suggested that this was due to the fact that in sepsis, that is, in the presence of systemic inflammation, fluid outflow from the vein is prominent due to marked endothelial dysfunction, and the effect size and duration of the fluid therapy applied are reduced.[18]

Previous studies evaluating the usefulness of IVC diameters and respiratory variability to assess intravascular volume status have been conducted in either spontaneously breathing patients or mechanically ventilated patients, and most of them have been compared with CVP measurement, which is an invasive method. Unlike these studies, we included patients from both groups in our study without making a distinction between spontaneously breathing and mechanically ventilated patients. Therefore, we had the opportunity to conduct a comparison of these two groups. In order to make these comparisons, we needed data other than IVC diameters.

Indeed, in a study of 100 PICU patients aged 1-12 years, a moderate positive correlation was found between PI and blood pressure, while a strong positive correlation was found with pulse rate. Based on the obtained data analysis, they suggested that a 57% decrease in PI could predict shock in children aged 1-12 years. Therefore, they concluded that PI can detect hypovolemia and/or shock long before cardiovascular deterioration occurs.[19]

Based on this information, we preferred to record non-invasive data, including physical examination findings, biochemical markers, PI and PVI, which we use in clinical practice to assess the fluid status of patients, rather than using an invasive method like CVP measurement, which may have complications. Our main starting point was to predict fluid status and fluid responsiveness without resorting to an invasive method unless patients required it.

In our study, 45.2% of patients were receiving MV support in synchronized intermittent mandatory ventilation/pressure support mode accompanied by sedation, while 54.8% were spontaneously breathing in room air without MV support. We found a strong negative correlation between D_{min} and cIVC or dIVC in both groups (r=-0.588, p<0.001; r=-0.520, p=0.005). Both groups had a negative correlation with D_{max}, but only spontaneously breathing patients without MV support had a statistically significant negative correlation with cIVC (r=-0.363, p=0.035). However, PI and PVI were negatively correlated with cIVC in patients without MV support (r=-0.355, p=0.040; r=-0.404, p=0.018). Patients with low PI and PVI had high cIVC values, which may indicate intravascular volume loss. In the mechanically ventilated group, PI, PVI, IVC ultrasonography, and dIVC did not show a statistically significant correlation. Positive pressure may affect IVC diameter and respiratory variability in mechanically ventilated patients.

Miller et al.[13] found that while cIVC isn't better for diagnosing acute heart failure in spontaneously breathing patients with dyspnea, the IVC/aortic ratio can be used with higher specificity in combination with other physical examination findings and laboratory parameters to assess hemodynamic status. In our study, CRT and blood pressure were statistically significantly different in the group that needed fluid loading before hospitalization, and received it, according to the analyses in which physical examination findings were evaluated by patient groups (p=0.025; p=0.039). Compared to a control group, the blood pressure in the fluid-loaded group was lower, and CRT was longer. In addition to physical examination

results, laboratory measures are used to assess peripheral perfusion, organ hypoperfusion, and intravascular status. The lactate level is the most sensitive of these parameters to perfusion disorder. In the presence of hypovolemia, lactate levels increase because lactate clearance decreases. A study found that reduced lactate clearance is a good indication of shock and resuscitation.[20]

Our study related lactate levels to other parameters. Patients with and without chronic disease showed similar lactate levels. MV-supported patients had significantly higher lactate levels than others. For patients who needed and received fluid loading before hospitalization, the volume administered was higher. Lactate levels were higher in patients with fluid deficit and decreased peripheral perfusion (p=0.022), as previously reported. In patients with prolonged CRT and low blood pressure for age, lactate levels were significantly higher than in patients with normal or high blood pressure (p<0.001; p=0.002). Elevated pulse rate patients showed higher lactate levels than normal patients, although not significantly. In conclusion, decreased intravascular volume status led to lactate levels and physical examination findings being similarly affected. Our investigation found similar results for lactate and urea; creatinine; salt; and urine density, all of which should increase with kidney hypoperfusion. This shows that lactate level and IVC diameter are more sensitive fluid status indicators. Lactate level was positively correlated with D_{min}, D_{max}, dIVC/cIVC and negatively correlated with PI and PVI. Only the PVI-lactate correlation was significant (r=-0.272, p=0.033). D_{min}, D_{max}, and dIVC/cIVC are positively associated with urea, creatinine, sodium, and urine density, although only D_{min} and D_{max} were significantly correlated with creatinine (r=0.326, p=0.010; r=0.349, p=0.005). It is thought that this may be due to the limited number of patients in our study.

Study Limitations

Our study contains flaws. The number of patients was insufficient because the study was conducted at one center over a short period. However, ultrasonographic measurements were often performed throughout the day by a single PICU faculty member specialized in this discipline to ensure reproducibility. Another major drawback is that patients who were under 2 years old, spontaneously breathing, and not sedated were prone to *valsalva* during measurements, which took longer and may have compromised dependability.

Conclusion

In our study, IVC diameters were measured ultrasonographically and respiratory variability was calculated. After analyzing these data, we found that cIVC can predict fluid status in spontaneously breathing pediatric patients because IVC diameters don't have a fixed cut-off value. We found that patients with lower blood pressure; prolonged CRT; higher lactate; or lower PI and PVI had higher cIVC. When these results are considered, spontaneously breathing patients with high cIVC (closer to 100%) may have intravascular volume loss.

In contrast, mechanically ventilated patients had statistically significant but modest relationships with various variables, although none were as robust as those of freely breathing patients. We can conclude that positive pressure may affect IVC diameter and respiratory variability in mechanically ventilated patients.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from Mersin University Clinical Research Ethics Committee, with the board (decision date: 08.01.2020 and decision no: 2020/26).

Informed Consent: Written informed consent was obtained from all the parents before the participants were enrolled in the study.

Footnotes

Authorship Contributions

Concept: A.E.A., Design: A.M.A., A.E.A., M.A., Data Collection or Processing: A.M.A., M.A., Analysis or Interpretation: A.M.A., A.E.A., M.A., S.E., Literature Search: A.M.A., A.E.A., S.E., Writing: A.M.A., A.E.A.

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Clinical Profile of Children and Adolescents Referred for Psychiatric Admission Following Emergency Psychiatric Evaluation

Acil Psikiyatrik Değerlendirme Sonrası Psikiyatri Yatışına Yönlendirilen Çocuk ve Ergenlerin Klinik Profili

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Abstract

Introduction: This study aims to examine the psychiatric profiles and hospitalization-related characteristics of children and adolescents referred for inpatient psychiatric treatment following emergency psychiatric evaluation in Türkiye.

Methods: A retrospective chart review was conducted on 57 adolescents (36 females, 21 males) who were evaluated in the pediatric emergency department and referred for psychiatric hospitalization between October 2022 and September 2024. Socio-demographic variables, psychiatric diagnoses, suicide attempt history, psychotropic medication use, and hospitalization outcomes were analyzed.

Results: No significant gender differences were found in age, family structure, or school attendance. However, suicide attempts were significantly more common in females (80.6%) than males (42.9%) (p=0.004). Poisoning was the most frequent method among females (75.9%), whereas males more often used hanging or jumping. Depressive disorder was the most common diagnosis in females (69.4%), while bipolar disorder (23.8%) and psychotic disorder (14.3%) were more prevalent in males. Comorbidity was more frequent in females (44.4%) compared to males (19.0%), (p=0.053). At the time of presentation, 91.7% of females and 95.2% of males were already using psychotropic medication. Overall, 50.9% of the cases were admitted to inpatient care. Treatment refusal was higher among males (42.9%) than females (25%).

Conclusion: Our study underscores significant gender-based differences in psychiatric presentations, suicide attempt characteristics, and hospitalization outcomes. These findings highlight the urgent need, in pediatric emergency settings, to improve access to inpatient psychiatric care and to strengthen early intervention strategies for acute psychiatric conditions, with a specific emphasis on suicide-related presentations.

Keywords: Child and adolescent psychiatry, emergency admissions, suicide attempts

Öz

Giriş: Bu çalışma, Türkiye'de acil psikiyatrik değerlendirme sonrasında psikiyatri yatışına yönlendirilen çocuk ve ergenlerin psikiyatrik profillerini ve yatışla ilişkili özelliklerini incelemeyi amaçlamaktadır.

Yöntemler: Ekim 2022 ile Eylül 2024 tarihleri arasında çocuk acil serviste değerlendirilen ve psikiyatri yatışına yönlendirilen 57 ergenin (36 kız, 21 erkek) dosyaları geriye dönük olarak incelenmiştir. Sosyo-demografik veriler, psikiyatrik tanılar, özkıyım girişimi öyküsü, psikotrop ilaç kullanımı ve yatış sonuçları değerlendirilmiştir.

Bulgular: Yaş, aile yapısı ve okul devam durumu açısından cinsiyetler arasında anlamlı fark bulunmamıştır. Ancak özkıyım girişimi kızlarda (%80,6) erkeklere (%42,9) göre anlamlı düzeyde daha yaygındı (p=0,004). Kızlarda en sık yöntem zehirlenme (%75,9) iken, erkeklerde ası veya yüksekten atlama gibi yöntemler gözlenmiştir. Kızlarda en yaygın tanı depresif bozukluk (%69,4), erkeklerde ise bipolar bozukluk (%23,8) ve psikotik bozukluk (%14,3) idi. Komorbidite kızlarda (%44,4) erkeklere (%19,0) göre daha yüksekti (p=0,053). Başvuru sırasında kızların %91,7'si, erkeklerin %95,2'si psikotrop ilaç kullanmaktaydı. Olguların %50,9'u yatırılarak tedavi altına alınırken, tedavi reddi erkeklerde (%42,9) kızlara (%25) göre daha sık görüldü.

Sonuç: Çalışmamız, psikiyatri başvuru özellikleri ve yatışla ilgili sonuçlarda cinsiyete dayalı belirgin farkları ortaya koymaktadır. Bu bulgular, çocuk acil servislerinde özellikle özkıyımla ilişkili durumlar başta olmak üzere, akut psikiyatrik bozukluklara yönelik erken müdahale stratejilerinin güçlendirilmesi ve psikiyatri yatış hizmetlerine erişimin artırılması gerekliliğini ortaya koymaktadır.

Anahtar Kelimeler: Çocuk ve ergen ruh sağlığı ve hastalıkları, acil başvuru, özkıyım girişimleri

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Introduction

In recent years, a striking increase has been observed in psychiatric-related emergency visits among children and adolescents worldwide.[1] Recent large-scale studies from the United States (US) and Europe confirm a sharp rise in emergency presentations due to mental health concerns among youth, particularly related to suicide risk and mood.[2] This trend indicates a growing prevalence of mental health problems in the younger population and highlights that emergency departments are increasingly encountering such cases. Suicidal behaviors, depressive and anxiety symptoms, behavioral problems, acute psychotic episodes, and adverse effects of psychotropic medications are among the most common reasons for child and adolescent psychiatric presentations to emergency services.[1,3]

Pediatric emergency departments are of critical importance for the prompt and effective management of psychiatric disorders in children and adolescents.[4] In psychiatric emergency presentations, interventions typically involve a comprehensive psychiatric evaluation of the pediatric patient, crisis intervention when indicated, and appropriate triage or referral. In cases involving suicidal behavior, an initial assessment is performed to ensure medical stabilization.[5] Following stabilization, the patient's safety and overall well-being are evaluated, and a formal psychiatric assessment is conducted. A thorough physical examination is essential to exclude potential organic etiologies underlying the psychiatric presentation. Based on the findings of the psychiatric evaluation, clinical decisions may include discharge, short-term observation, admission to an inpatient psychiatric unit, or referral for child psychiatry outpatient clinic follow-up.[6] A study conducted in Türkiye demonstrated that only one-quarter of patients presenting to the emergency department with psychiatric complaints met the criteria for acute psychiatric conditions requiring inpatient admission, while more than half were discharged with pharmacological management.[7] This pattern is consistent with international findings, where many pediatric psychiatric emergencies are managed without inpatient admission due to triage protocols and limited psychiatric bed availability.[8]

While the majority of psychiatric disorders in childhood and adolescence are managed through outpatient follow-up, certain conditions necessitate partial hospitalization or inpatient care. Factors such as risk of self-harm or harm to others, acute psychotic symptoms, substance intoxication, and inadequate family support are among the primary considerations for inpatient admission in children and adolescents.[3,9] In a study conducted in Türkiye examining the indications for hospitalization among 245 patients aged 6 to 18 years, the most common reasons for admission were major depressive disorder (23.3%), bipolar disorder (20%), and disruptive behavior disorder (14.7%).[10,11] Recent data from a pediatric psychiatric emergency unit in Türkiye identified emotional dysregulation, suicidal ideation, and disruptive behaviours as the most frequent reasons for emergency referrals among youth.[12] Similarly, international studies highlight mood and psychotic disorders as the leading diagnoses in pediatric psychiatric hospitalizations.[10,11,13] Additionally, among all psychiatric admissions in the US, the most frequently reported diagnoses included depression (35.9%), substance use disorders (34.0%), and attention-deficit/hyperactivity disorder [(ADHD): 19.4%].[10,13]

Due to the limited number of inpatient child and adolescent mental health clinics in our country, patients may experience prolonged stays in the emergency setting, which can delay timely intervention. The emergency department of the hospital where our study was conducted receives both individual psychiatric admissions and referrals from nearby hospitals. Most patients are referred to outpatient care, while those with severe conditions are hospitalized. This study aims to examine the clinical and referral characteristics of pediatric patients admitted through emergency services, thereby offering evidence-based insights into acute care pathways in child and adolescent psychiatry. By focusing on this specific patient population, the study addresses a critical gap in the literature and contributes to a better understanding of the clinical needs and referral dynamics in acute child and adolescent mental health care.

Materials and Methods

This study included patients who presented with psychiatric complaints to the pediatric emergency department of Marmara University Pendik Training and Research Hospital between October 1, 2022, and September 30, 2024. These patients were referred for psychiatric consultation, and subsequently evaluated by a child and adolescent psychiatrist, resulting in a decision for psychiatric inpatient admission. Marmara University Pendik Training and Research Hospital was a fully equipped tertiary care center located on the Anatolian side of İstanbul. The hospital provides 24/7 child and adolescent psychiatry services, including emergency psychiatric care. The pediatric emergency department receives approximately 150,000-160,000 patient visits annually; during the study period, a total of 302,532 patients were admitted to this unit. All patients admitted to the pediatric emergency department are initially assessed by a pediatrician. Patients requiring psychiatric evaluation are referred to our clinic. Psychiatric evaluations are performed in a designated private interview room within the emergency department to ensure confidentiality and appropriate clinical conditions. Patients are monitored in the high-acuity area of the emergency

department under the supervision of both pediatric and child psychiatry teams, accompanied by their caregivers, while awaiting admission to the appropriate inpatient service. The average length of stay in the emergency department for these patients ranges from 2 to 3 days, although in some cases, this period may be extended depending on bed availability.

Between October 1, 2022; and September 30, 2024, a total of 1,355 patients will be referred to our clinic for emergency psychiatric evaluation. Among these, 62 patients (4.58%) were deemed in need of inpatient psychiatric admission to the child and adolescent psychiatry unit. Inclusion criteria included being between 0 and 18 years of age and having received a formal referral for inpatient care. Patients were excluded if critical clinical or socio-demographic data-such as psychiatric diagnoses, medication history, or basic demographic information-were missing from the hospital information system. As a result, 5 patients were excluded due to incomplete diagnostic records, yielding a final study sample of 57 adolescents (36 females, 21 males).

Data were obtained from the patients' files recorded in the hospital's electronic medical records system, and all data were anonymized. The socio-demographic characteristics of the patients, psychiatric diagnoses, use of psychotropic medication, history of suicide attempts, and outcomes of the inpatient admission process were examined. Psychiatric diagnoses were determined through clinical interviews based on Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, conducted as part of the emergency psychiatric evaluation, along with history obtained from the family.[14] No structured diagnostic tools were used in the evaluation. This limitation has been described in detail in the limitations section.

Psychotropic medication use among patients was categorized into selective serotonin reuptake inhibitors (SSRIs), antipsychotics, ADHD medications (including methylphenidate and atomoxetine), mood stabilizers, benzodiazepines, and acute injectable treatments administered in the emergency department. Injectable antipsychotic medications were administered according to the urgency of symptom control and the patient's clinical profile. Within the scope of this study, the injectable treatments used in our clinical practice were classified based on their duration of action. Haloperidol lactate was categorized as a short-acting injection (SAI). Zuclopenthixol acetate was classified as an intermediate-acting injection (IAI). Zuclopenthixol decanoate and risperidone microsphere extended-release were identified as long-acting injections (LAIs).

The children's global assessment scale (CGAS) was used to assess the functional status of the children and adolescents.[15] CGAS was used to evaluate the overall functional level of the children.[15] In this study, the CGAS was used to assess the individual's overall psychosocial functioning[15]. The validity and reliability of the Turkish version of the scale were established by Gökler et al.[16] The CGAS is a clinician-rated instrument that provides a single score ranging from 1 to 100, based on the assessment of various aspects of a child's psychological functioning. According to the scoring criteria, children who receive a score of 80 or below are referred for psychiatric follow-up; those scoring 60 or below are referred for psychiatric treatment and monitoring; and those scoring 40 or below are considered for inpatient psychiatric care.

Ethical approval for this study was obtained from the Marmara University Faculty of Medicine Clinical Research Ethics Committee (approval no: 09.2025.25-0025, date: 18.04.2025). All participants were informed about the study and written consent was obtained.

Statistical Analysis

Descriptive statistics including frequency, percentage, mean, and standard deviation were used to summarize the data. The distribution of the data was tested using the Kolmogorov-Smirnov test. The Independent Samples t-test was used to analyze parametric continuous variables, while the Mann-Whitney U test was applied for non-parametric data. The chi-square test or Fisher's exact test was used to compare categorical variables. A p-value of <0.05 was considered statistically significant. All analyses were conducted using SPSS version 23.0.

Results

Our study included 36 female adolescents (mean age: 15.20±1.68 years) and 21 male adolescents (mean age: 15.81±1.13 years) who were referred for psychiatric inpatient clinic admission. Among the female participants, 50% (n=18) were attending formal education, compared to 33.3% (n=7) of the males (χ^2=1.496, p=0.221). Both parents were living together in 50% (n=18) of the female group and 52.4% (n=11) of the male group (χ^2=1.872, p=0.392). A family history of psychiatric disorders was reported in 41.7% (n=15) of females and 57.1% (n=12) of males (χ^2=1.274, p=0.259).

The onset of initial psychiatric symptoms occurred 18.48±2.55 months in females and 19.92±4.51 months in males prior. The duration of psychiatric follow-up was 14.19±3.10 months for female patients and 7.37±3.56 months for male patients. Data regarding psychiatric diagnosis and CGAS scores are presented in Table 1. Comorbidity was identified in 20 patients (n=20, 35.1%) within the sample. Of these, 15 patients (n=15, 26.3%) had two psychiatric diagnoses, while 5 patients (n=5, 8.8%) had three co-occurring psychiatric diagnoses. Among patients diagnosed with depressive disorder (n=13; 22.8%),

comorbid psychiatric disorders included conduct disorder (n=6; 10.5%), anxiety disorders (n=5; 8.8%), and ADHD (n=4, 7.0%). In the subgroup with ADHD (n=7, 12.3%), comorbid diagnoses were conduct disorder (n=4, 7.0%), bipolar disorder (n=1, 1.8%), and depressive disorder (n=4, 7.0%). Among those diagnosed with conduct disorder (n=12, 21.1%), comorbid conditions included depressive disorder (n=6, 10.5%), ADHD (n=4, 7.0%), bipolar disorder (n=2, 3.5%), and anxiety disorder (n=1, 1.8%).

The rate of suicide attempts was significantly higher at 80.6% (n=29) among females compared to 42.9% (n=9) among males (p=0.004). Among those who had attempted suicide, 48.3% (n=14) of the female patients and 66.7% (n=6) of the male patients reported it as their first attempt, while the remaining cases had a history of multiple attempts (p=0.763). Data on methods of suicide attempts by gender are presented in Table 2. Among the 19 patients referred for inpatient psychiatric hospitalization without a history of suicide attempt (n=19, 33.3%), the primary reasons for referral were as follows: depressive disorder with suicidal ideation (n=5, 8.8%), conduct disorder with prominent aggression and risk of harm to others (n=5, 8.8%), manic episode (n=4, 7.0%), acute psychotic episode (n=3, 5.3%), and severe obsessive-compulsive disorder (n=2, 3.5%).

In our study, 91.7% of the female patients and 95.2% of the male patients were already on psychotropic medication at the time of emergency department admission. The most commonly used medication classes were atypical antipsychotics and SSRIs. Data on psychotropic medication use are provided in Table 3. None of the patients was receiving injectable treatments at the time of admission; however, the types of antipsychotic medications administered via injection in the emergency department are also listed in Table 3. Among the total sample of 57 patients, 27 (n=27, 47.4%) received at least one form of intramuscular injection during their emergency psychiatric evaluation. Of these, 4 patients (n=4, 7.0%) received all three types of injectable agents: short-, intermediate- and long-acting. In 11 cases (n=11, 19.3%), two types of injectables were used. Additionally, 12 patients (n=12, 21.1%) were treated exclusively with short-acting injectables. SAIs were administered to 20 patients (35.1%). These included patients diagnosed with bipolar disorder (n=6, 10.5%), major depressive disorder (n=5, 8.8%), conduct disorder (n=3, 5.3%), psychotic disorder (n=3, 5.3%), ADHD (n=2, 3.5%), and anxiety disorder (n=1, 1.8%). IAIs were administered to 15 patients (26.3%). These were used in patients with bipolar disorder (n=4, 7.0%), major depressive disorder (n=4, 7.0%), conduct disorder (n=2, 3.5%), psychotic disorder (n=2, 3.5%), ADHD (n=2, 3.5%), and anxiety disorder (n=1, 1.8%). LAIs were used in 6 patients (10.5%), including those with bipolar disorder

Table 1. Psychiatric diagnosis and CGAS scores of the participants

	Female n=36 (%)	Male n=21 (%)	p-value
Depressive disorder	25 (69.4%)	7 (33.3%)	**0.008***
Conduct disorder	14 (38.9%)	6 (28.6%)	0.568*
Anxiety disorder	12 (33.3%)	2 (9.5%)	**0.044***
ADHD	7 (19.4%)	3 (14.3%)	0.624*
Bipolar disorder	4 (11.1%)	5 (23.8%)	0.205*
Psychotic disorder	3 (8.3%)	3 (14.3%)	0.480*
Conversion disorder	2 (5.6%)	3 (14.3%)	0.346*
OCD	1 (2.8%)	1 (4.8%)	0.695*
Comorbidity	16 (44.4%)	4 (19.0%)	**0.053***
	Mean ± SS	**Mean ± SS**	
CGAS score	30.91±1.66	32.85±12.84	0.531**

p<05 was considered statistically significant. Statistical significance is indicated in bold
*: Chi-square test, **: Student's t-test, CGAS: Children's global assessment scale, ADHD: Attention deficit hyperactivity disorder, OCD: Obsessive-compulsive disorder, SS: Statistical significance

Table 2. Methods of suicide attempts

	Female n=36 (%)	Male n=21 (%)	p-value
Suicide attempts	29 (80.6%)	9 (42.9%)	**0.004***
	Female n=29 (%)	**Male n=9 (%)**	
Poisoning	22 (75.9%)	2 (22.2%)	**0.004***
Cutting	3 (10.3%)	2 (22.2%)	0.357*
Hanging	0 (0%)	2 (22.2%)	**0.009***
Jump from high place	3 (10.3%)	2 (22.2%)	0.357*
Other	1 (3.4%)	1 (11.1%)	0.368*

p<05 was considered statistically significant. Statistical significance is indicated in bold
*: Chi-square test

Table 3. Types of psychotropic medications

	Female n=36 (%)	Male n=21 (%)	p-value
Use of at least one medication	33 (91.7%)	20 (95.2%)	0.611*
SSRIs	21 (58.3%)	10 (47.6%)	0.433*
Atypical antipsychotics	30 (83.3%)	19 (90.5%)	0.454*
Methylphenidate	5 (13.9%)	1 (4.8%)	0.279*
Mood stabilizer	8 (22.2%)	3 (14.3%)	0.464*
Benzodiazepine	3 (8.3%)	3 (14.3%)	0.480*
SAIs	12 (33.3%)	8 (38.1%)	0.716*
IAIs	7 (19.4%)	8 (38.1%)	0.123*
LAIs	3 (8.3%)	3 (14.3%)	0.480*

p<05 was considered statistically significant.
Short-acting injection: Haloperidol, Intermediate-acting injection: Zuclopenthixol acetate, Long-acting injection: Zuclopenthixol decanoate
*: Chi-square test, SSRIs: Selective serotonin reuptake inhibitors, SAIs: Short-acting injectable antipsychotics, IAIs: Intermediate-acting injectable antipsychotics, LAIs: Long-acting injectable antipsychotics

(n=3, 5.3%), psychotic disorder (n=2, 3.5%), and conduct disorder (n=1, 1.8%).

Of the patients referred for psychiatric hospitalization, 50.9% (n=29) were successfully admitted to the inpatient clinic unit. The mean waiting time in the emergency department for these patients was 39.07±39.02 (mean ± SD) hours. The outcomes following referral for inpatient clinic admission are presented in Table 4.

Discussion

The present study investigated the psychiatric characteristics and hospitalization referrals of children and adolescents presenting to a pediatric emergency department over a two-year period. Consistent with global trends, our findings reflect a rising demand for emergency psychiatric care and inpatient services in youth populations. Compared to previous national and international research, our study provides updated data on clinical presentations and admission outcomes contributing to the understanding of service needs in acute child psychiatry.

The demographic characteristics of children and adolescents referred for psychiatric hospitalization were examined to explore potential gender-based differences. No statistically significant differences were found between female and male patients in terms of age or family structure. A high prevalence of psychiatric disorders in the families of both female and male patients was noted. While half of the girls were enrolled in formal education, the majority of boys were not attending school. Nonetheless, the relatively small sample size may have limited the ability to detect subtle demographic variations between groups. Previous studies have identified several key risk factors associated with adolescent psychiatric emergencies and suicide attempts, including adverse life events, parental separation, parental psychiatric disorders, low socio-economic status, limited access to education, and poor academic performance.[17]

In our study, the most common diagnoses among female and male adolescents were depressive disorder and conduct disorder, respectively. A high rate of comorbidity was observed in both groups. Bipolar and psychotic disorders were found to be more prevalent in male patients. Acute psychiatric conditions such as severe aggression, explosive anger outbursts, psychosis, or severe anxiety disorders, serious suicide attempts, and toxic-metabolic conditions including neuroleptic malignant syndrome and serotonin syndrome are among the leading causes of emergency psychiatric intervention.[18] Following initial stabilization in the emergency department, some patients are referred for outpatient follow-up, while others are admitted to inpatient units. In our sample, depressive disorder emerged as the most frequent diagnosis, which may be associated with the high rate of suicide attempts. Bipolar and psychotic disorders were less frequently cited as reasons for hospitalization, as these cases were often stabilized with pharmacological treatment and followed up on an outpatient basis. Two previous studies conducted in Türkiye similarly reported that the most common reasons for inpatient child psychiatry admissions were mood disorders, particularly depressive disorders, as well as disruptive behavior disorders and psychotic disorders.[10,19] In our study, depressive disorder was the leading diagnosis among those referred for psychiatric admission, which is consistent with the existing literature. Similarly, a recent study from Türkiye also identified depression as the most common diagnoses in pediatric psychiatric emergency admissions.[12] However, notable variability in diagnostic distribution may occur depending on the characteristics of the psychiatric units. Such variability may stem from differences in the populations served, the clinical approaches employed, and the application of diagnostic criteria.[19]

Table 4. Outcomes of psychiatric hospitalization referrals

	Female n=36 (%)	Male n=21 (%)	p-value
Child psychiatry inpatient admission	17 (47.2%)	8 (38.1%)	0.726*
Psychiatry inpatient admission	3 (8.3%)	1 (4.8%)	
Refusal of treatment	9 (25%)	9 (42.9%)	
Referral canceled and continued with outpatient follow-up	7 (19.5%)	3 (14.3%)	

p<05 was considered statistically significant.
*: Chi-square test

Suicide attempt rates were significantly higher among female adolescents. Approximately 80% of the female patients referred for psychiatric hospitalization had a history of suicide attempt, whereas the rate was notably lower among male patients. When examining the methods of attempt, poisoning was significantly more frequent among females, while hanging was more common among males. These findings are consistent with previous studies indicating that, during adolescence, females are more likely to engage in suicide attempts, whereas males tend to choose more lethal methods and are more often to be involved in fatal outcomes.[20] Similar to our findings, a recent study from a pediatric emergency unit in Türkiye reported that 80% of patients presenting with suicide attempts were female, with drug overdose being the most common method, highlighting the gendered nature of suicidal behavior and supporting the need for differentiated risk assessment and follow-up strategies.[21] While depressive disorders are a strong predictor of suicidal ideation, accompanying symptoms such as anxiety, irritability, and impaired emotional regulation have also been identified as significant contributors to suicide attempts.[22] In our study, the high prevalence of depressive disorder and

comorbid psychiatric disorders may account for the elevated rate of suicide attempts observed in this population. The notably higher standard deviation observed in CGAS scores among male patients may be attributed to greater diagnostic heterogeneity within this group. While a large proportion of female patients, exhibited similar clinical profiles characterized by suicide attempts-resulting in more uniformly impaired functioning-male patients demonstrated a broader range of psychiatric diagnoses and symptom presentations, leading to a wider distribution of functional impairment levels.

Psychotropic medication use was common in both genders, with SSRIs, and atypical antipsychotics frequently prescribed. These medications play a critical role in managing depressive symptoms and other psychopathological conditions.[23] The persistence of severe symptoms at emergency admission suggests limited treatment response and the need for more intensive care. Injectable treatments were also frequently used to ensure rapid symptom control, particularly during extended emergency stays due to limited inpatient bed availability. Global trends reflect these observations as recent reviews report a significant increase in psychotropic prescriptions-including antidepressants, stimulants, and atypical antipsychotics-among children and adolescents between 2013 and 2023. Moreover, long-acting injectable antipsychotics are increasingly utilized in youth populations, particularly for early-onset psychotic disorders.[24,25] These findings underscore the importance of timely pharmacological intervention and the integration of individualized treatment strategies.[26]

The inpatient admission rate to the child psychiatry unit was found to be 47.2% for females and 38.1% for males, with no statistically significant difference between the two groups. However, the rate of treatment refusal was notably higher among male patients (42.9%) compared to female patients (25%). Rates of admission cancellation and outpatient follow-up were similar across both genders. These findings suggest that gender is not a determining factor in referral decisions for inpatient child psychiatry care. The higher treatment refusal rates among male patients may be related to lower help-seeking behavior and concerns about stigma commonly observed in males.[27] A study conducted in Türkiye emphasized that adolescent males may demonstrate lower motivation for help-seeking and treatment adherence compared to females, which may reflect broader socio-cultural influences on psychiatric service utilization.[28] Furthermore, during the study period, it was noted that while there were two inpatient units available for the admission of female patients in İstanbul, only one unit was available for males. This discrepancy likely led to longer waiting times for male patients, which may have contributed to the increased rate of treatment refusal observed in this group. In addition, social and familial factors may have influenced the decision to accept or refuse inpatient care. Variables such as parental attitudes toward psychiatric hospitalization, cultural perceptions of mental illness, and perceived necessity or urgency of treatment can play a crucial role in treatment compliance. Longer waiting times in the emergency department may have exacerbated caregiver fatigue and emotional distress, particularly among families of male patients, and thereby increased resistance to hospitalization.[29] Prior studies have shown that systemic delays in psychiatric care can negatively impact both patient and caregiver cooperation, ultimately contributing to treatment refusal.[8]

Study Limitations

This study provides important insights into the psychiatric profiles of children and adolescents referred for inpatient psychiatric care after presenting to a pediatric emergency unit in Türkiye. Although our hospital lacks a dedicated child and adolescent psychiatry inpatient unit, psychiatric consultations are nonetheless provided 24/7-a practice rarely implemented in other institutions nationwide. Therefore, the data presented here reflect a realistic profile of psychiatric inpatient referral needs in this age group. However, several limitations should be acknowledged. First, the retrospective nature of the study, which relied on clinical records, may have introduced bias due to variability in documentation quality and the absence of standardized data collection protocols. Second, the limited sample size (n=57) may have substantially reduced the statistical power, particularly for subgroup comparisons, thereby limiting the generalizability of the results. Additionally, psychiatric diagnoses were made using unstructured clinical interviews rather than standardized diagnostic tools like structured ones. While all evaluations were conducted by experienced clinicians using DSM-5 criteria, the lack of structured tools may have reduced inter-rater reliability, diagnostic objectivity, and contributed to the underreporting of comorbid conditions. Importantly, given the emergency department setting, the use of structured diagnostic interviews was not feasible under the existing clinical constraints. Moreover, although relevant risk factors such as low socio-economic status, parental separation, and school attendance, were routinely explored during psychiatric evaluations, these variables were not assessed through standardized and systematic methods, which limits the ability to draw firm conclusions regarding their role. In addition, the unequal distribution of inpatient facilities during the study period-with two inpatient units available for girls but only one for boys in İstanbul-may have contributed to disparities in admission and treatment refusal rates. Finally, although this is a single-center study, it was conducted in İstanbul-a city marked

by significant socio-cultural diversity and high population density, drawing patients from many regions of Türkiye. This context may partially enhance the representativeness of the findings.

Conclusion

This study comprehensively examined the inpatient referral process of children and adolescents following emergency psychiatric evaluations, with a particular focus on gender-based clinical differences and key factors influencing admission decisions. Higher rates of depressive and anxiety disorders, psychiatric comorbidity, and suicide attempts were observed among female adolescents; however, outcomes related to psychopharmacological interventions and referral patterns did not differ significantly by gender. These findings underscore the critical importance of early identification, adequate inpatient capacity, and systematic improvements in emergency psychiatric care for youth. Clinically, the results highlight the need to tailor admission procedures to account for gender-specific risk profiles and to address systemic barriers, including treatment refusal. Improving environmental conditions in emergency settings and expediting referral pathways based on clinical urgency may enhance outcomes. Notably, the high proportion of suicidal behavior observed points to an urgent need for specialized inpatient services for at-risk youth, particularly in urban and socio-economically diverse regions. Ultimately, the results advocate for policy reforms aimed at expanding and strengthening child and adolescent psychiatric services to ensure timely and equitable mental health care.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Marmara University Faculty of Medicine Clinical Research Ethics Committee (approval no: 09.2025.25-0025, date: 18.04.2025).

Informed Consent: All participants were informed about the study and written consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ç.D.T., G.Y.A., Concept: Ç.D.T., G.Y.A., Design: Ç.D.T., G.Y.A., Data Collection or Processing: Ç.D.T., K.N., Analysis or Interpretation: Ç.D.T., G.Y.A., Literature Search: Ç.D.T., K.N., G.Y.A., Writing: Ç.D.T., G.Y.A.

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Research Article / Özgün Araştırma

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Risk Modeling for Hospitalization and Mortality in Pediatric Cyanotic Congenital Heart Disease: An 11-year National Emergency Cohort

Siyanotik Konjenital Kalp Hastalığı Olan Çocuklarda Hastane Yatışı ve Mortalite Risk Modellemesi: Ulusal Bir Referans Merkezinden 11 Yıllık Pediyatrik Acil Servis Verisi

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Abstract

Introduction: Although the outcomes and the mortality rates in congenital heart disease have improved dramatically, children with complex cardiac anomalies remain at increased risk for both cardiac and non-cardiac morbidity and mortality. This study aimed to characterize presentations to the pediatric emergency department (PED) by patients with cyanotic congenital heart disease (CCHD) and to identify factors associated with hospitalization and mortality.

Methods: A retrospective review of children with CCHD who were admitted to PED between January 2011 and September 2022 was conducted. Demographic, clinical, and outcome data were collected. Logistic regression was performed to identify predictors of hospitalization and mortality. The Glasgow Coma scale (GCS), Emergency Severity Index, and need for emergency life-saving interventions were also evaluated.

Results: Out of 351 presentations, 56.7% were male. The most common diagnoses were upper respiratory tract infection (49.0%), acute gastroenteritis (13.1%), and lower respiratory tract infection (LRTI) (11.7%). The most common cardiac diagnoses at the time of admission were cyanotic spell (1.7%) and heart failure (1.4%). Hospitalization occurred in 12.5% of admissions, and 6.8% required pediatric intensive care unit (PICU) admission. LRTI was the leading cause of both hospitalization (40.9%) and PICU admission (41.7%). Significant predictors for hospitalization were younger

Öz

Giriş: Konjenital kalp hastalığı olan çocuklarda sağkalım oranları artmış ve mortalite belirgin azalmış olsa da, kompleks kardiyak anomalilere sahip çocuklar hem kardiyak hem de diğer morbidite ve mortalite nedenleri açısından yüksek risk taşımaya devam etmektedir. Bu çalışmanın amacı, siyanotik konjenital kalp hastalığı (SKKH) tanılı hastaların çocuk acil servise (ÇAS) başvuru özelliklerini tanımlamak, hastaneye yatış ve mortalite ile ilişkili faktörleri belirlemektir.

Yöntemler: Ocak 2011 ile Eylül 2022 tarihleri arasında ÇAS'ye başvuran SKKH tanılı çocukların verileri geriye dönük olarak incelendi. Demografik, klinik ve sonuçlara ilişkin veriler toplandı. Hastaneye yatış ve mortaliteyi öngören faktörleri belirlemek amacıyla lojistik regresyon analizi uygulandı. Glasgow Koma skalası (GKS), Aciliyet Önem İndeksi ve acil yaşam kurtarıcı müdahale gereksinimi değerlendirildi.

Bulgular: Toplam 351 başvurunun %56,7'si erkekti. En sık tanılar üst solunum yolu enfeksiyonu (%49,0), akut gastroenterit (%13,1) ve alt solunum yolu enfeksiyonu (ASYE) (%11,7) idi. Başvuru anındaki en yaygın kardiyak tanılar siyanotik spell (%1,7) ve kalp yetersizliği (%1,4) olarak saptandı. Başvuruların %12,5'i hastaneye yatışla, %6,8'i ise çocuk yoğun bakım ünitesine (ÇYBÜ) yatışla

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Abstract

age, urinary tract infection, LRTI, emergency life-saving intervention, and ventilatory support. Mortality was statistically associated with increased cyanosis, dyspnea/respiratory distress, LRTI, heart failure, GCS ≤12, emergency life-saving intervention, significant intravenous fluid resuscitation, ventilation support, and circulatory support death. Mortality was statistically associated with increased cyanosis, dyspnea/respiratory distress, LRTI, heart failure, GCS ≤12, emergency life-saving intervention, significant intravenous fluid resuscitation, ventilation support, and circulatory support.

Conclusion: Emergency physicians should be vigilant for red flags indicating increased risk of hospitalization or mortality in CCHD patients to ensure timely and effective care.

Keywords: Cyanotic congenital heart disease, pediatric emergency department, mortality, hospitalization

Öz

sonuçlandı. ASYE hem hastane (%40,9) hem de ÇYBÜ (%41,7) yatışlarının en sık nedeniydi. Yatış için anlamlı öngörücüler küçük yaş, idrar yolu enfeksiyonu, ASYE, acil yaşam kurtarıcı müdahale ve solunum desteği idi. Artmış siyanoz, dispne/solunum sıkıntısı, ASYE, kalp yetersizliği, GKS ≤12, acil yaşam kurtarıcı müdahale, intravenöz sıvı resüsitasyonu, solunum ve dolaşım desteği ile mortalite arasında istatistiksel olarak anlamlı ilişki vardı.

Sonuç: Acil servis hekimleri, SKKH tanılı hastalarda hastaneye yatış veya mortalite riskini artıran uyarı işaretlerine karşı dikkatli olmalı ve zamanında, etkili müdahale sağlamalıdır.

Anahtar Kelimeler: Siyanotik konjenital kalp hastalığı, çocuk acil servis, mortalite, hastaneye yatış

Introduction

Congenital heart disease (CHD) is the most common major birth defect, with an incidence ranging from 4.6 to 12.2 per 1000 live births.[1,2] CHDs are typically classified as cyanotic and acyanotic.[3,4] Cyanotic CHD (CCHD) encompasses a broad spectrum of more complex pathologies than acyanotic heart diseases and account for approximately 25% of all CHDs, with a mean incidence of 1.4 per 1000 live births.[5]

Although the incidence of CHD has remained relatively stable over time, major advances in prenatal diagnosis, pharmacological management, interventional procedures, and surgical techniques have significantly improved survival into adulthood. Consequently, presentations of CHD patients to the pediatric emergency department (PED) have increased. While some PED visits are directly related to cardiac causes, many are due to common pediatric conditions. The overlap of cardiac and non-cardiac symptoms can pose diagnostic and management challenges.[6,7]

To the best of our knowledge, most of the previous studies of CHD have focused on inpatient populations, with limited data available on the characteristics and outcomes of PED presentations, particularly for CCHD patients.[6-8] This study aims to evaluate the characteristics of PED admissions among CCHD patients and to identify the predictors of hospitalization and mortality.

Materials and Methods

This retrospective study included all patients under 18 years of age who were followed up for CCHD in the pediatric cardiology department, and who presented to the PED of our institution between January 2011 and September 2022. The PED is part of a tertiary referral center with 284 pediatric beds and a comprehensive pediatric heart center, which is one of the leading institutions in our country. It provides care for a wide range of diagnoses and performs advanced interventions including the use of mechanical support devices and heart transplantation.

Patients under 18 years of age who had a prior diagnosis of CCHD or who were newly diagnosed with CCHD at the time of admission were included in the study. The patients with acyanotic CHD or missing data were excluded from the study. Demographic data, presenting complaints, and final diagnoses were evaluated. The Glasgow Coma Scale (GCS) was used to assess the status of the patients at admission to the emergency service, categorized as mild,[9-12] intermediate,[13-15] or severe (≤8). The Emergency Severity Index triage system was used to define emergency life-saving interventions.[9] Life-saving interventions refer to urgent medical procedures and treatments such as airway and breathing support (e.g., positive pressure ventilation, intubation, surgical airway), electrical therapy (defibrillation, cardioversion), emergency procedures (e.g., needle decompression, pericardiocentesis), hemodynamic stabilization [e.g., significant intravenous (IV) fluid resuscitation, blood transfusion], and administration of critical medications (e.g., adenosine, epinephrine, atropine).[9] The durations of PED observation, hospitalization, and pediatric intensive care unit (PICU) stay were evaluated. Additionally, clinical features potentially influencing hospitalization and mortality were evaluated.

The study protocol was approved by the Ethics Committee of Ankara University Faculty of Medicine (approval number: İ03-164-23, approval date: 05.04.2023).

Statistical Analysis

Descriptive statistics were presented as mean ± standard deviation for normally distributed variables, median (Q1- Q3) for non-normally distributed variables, and n (%) for categorical variables. Categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test, as appropriate.

Logistic regression (univariable and multivariable) was performed to identify predictors of hospitalization and mortality. First, univariable logistic regression models were used to examine the independent effects of each variable. Variables found to be significant in univariable analyses were included in a multivariable logistic regression model to assess their adjusted effects.

The performance of the multivariable logistic regression model was evaluated using receiver operating characteristic curve analysis, with model discrimination assessed by calculating the area under the curve (AUC). Additionally, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were computed. The results of the logistic regression analyses were reported as odds ratios with 95% confidence intervals (CI). Statistical significance was defined as $p<0.05$. All statistical analyses were performed using IBM SPSS Statistics version 30.

Results

During the study period, 67 patients with CCHD made a total of 351 visits out of 1,040,393 admissions to the PED. The median number of PED visits per patient was 2.00 [interquartile range (IQR): 1.00-7.00]. Of these patients, 56.7% were male, and the median age at presentation was 20.03 months (IQR: 8.70-67.50). The most common CCHD diagnoses were Tetralogy of Fallot (TOF) (47.8%), pulmonary atresia (PA) (11.9%), Ebstein's anomaly (EA) (6.0%), and hypoplastic left heart syndrome (HLHS) (6.0%). The distribution of CCHD diagnoses is illustrated in Figure 1.

The most common presenting complaints were cough (41.3%), fever (41.0%), and vomiting (13.4%) (Table 1).

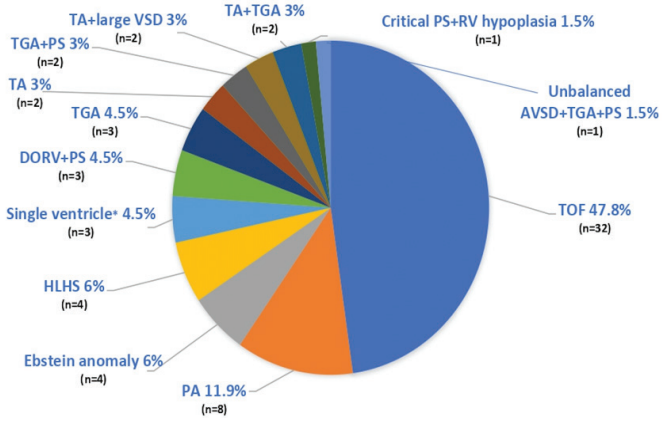

Figure 1. The distribution of diagnoses of patients cyanotic congenital heart diseases
*Single ventricle: Refers to children with anatomically single ventricle and diseases like double inlet left ventricle.
AVSD: Atrioventricular septal defect, DORV: Double outlet right ventricle, HLHS: Hypoplastic left heart syndrome, PA: Pulmonary atresia, PS: Pulmonary stenosis, RV: Right ventricle, TA: Tricuspid atresia, TGA: Transposition of the great arteries, TOF: Tetralogy of Fallot, VSD: Ventricular septal defect

Table 1. Characteristics of patients with cyanotic congenital heart disease presenting to the PED (n=351)

Characteristics	n (%)
Complaints	
Cough	145 (41.3)
Fever	144 (41.0)
Vomiting	47 (13.4)
Dyspnea/respiratory distress	44 (12.5)
Diarrhea	32 (9.1)
Increased cyanosis	30 (8.5)
Uneasiness	24 (6.8)
Sore throat	24 (6.8)
Chest pain	10 (2.8)
Eruption	10 (2.8)
Palpitation	5 (1.4)
Syncope	2 (0.6)
Seizure	2 (0.6)
Others	46 (13.1)
Visit diagnosis	
URTI	172 (49.0)
AGE	46 (13.1)
LRTI	41 (11.7)
Constipation	14 (4.0)
Otitis media	14 (4.0)
Soft tissue trauma	11 (3.1)
Urinary tract infection	7 (2.0)
Cyanotic spell	6 (1.7)
HF	5 (1.4)
Urticaria	5 (1.4)
Gastrointestinal bleeding	3 (0.9)
Cardiopulmonary arrest	2 (0.6)
Brain abscess	1 (0.3)
Seizure	1 (0.3)
Shunt dysfunction	1 (0.3)
Others	28 (8.0)
GCS	
≤8	5 (1.4)
9-12	10 (2.8)
13-15	336 (95.7)
Life-saving intervention	13 (3.7)
Significant IV fluid resuscitation	11 (3.1)
PPV	4 (1.1)
Intubation	4 (1.1)
CPR	2 (0.6)
PED observation unit admission	109 (31.0)
Hospitalization	44 (12.5)
PICU admission	24 (6.8)
Ventilation support	19 (5.4)
Circulatory support	13 (3.7)
Excitus	7 (2.0)

PED: Pediatric emergency department, URTI: Upper respiratory tract infection, AGE: Acute gastroenteritis, LRTI: Lower respiratory tract infection, HF: Heart failure, GCS: Glasgow Coma scale, IV: Intravenous, PPV: Positive pressure ventilation, CPR: Cardiopulmonary resuscitation, PICU: Pediatric intensive care unit

Among patients presenting with cough, the majority were diagnosed with upper respiratory tract infection (URTI) (n=101, 69.7%) or lower respiratory tract infection (LRTI) (n=37, 25.5%). Fever was most frequently associated with URTI (n=99, 68.8%), followed by acute gastroenteritis (AGE) (n=17, 11.8%) and LRTI (n=12, 8.3%). Among the 44 patients who presented with respiratory distress, 23 (52.3%) were diagnosed with LRTI, 14 (31.8%) were diagnosed with URTI, 2 (4.5%) were diagnosed with heart failure (HF), and 2 (4.5%) were diagnosed with a cyanotic spell. Among the thirty patients who presented with complaints of increased cyanosis, nine (30.0%) were diagnosed with URTI, six (20.0%) with LRTI, five (16.7%) with a cyanotic spell, and two (6.7%) with HF.

The most frequent diagnoses were URTI (49.0%), AGE (13.1%), and LRTI (11.7%) (Table 1). The median age of patients with LRTI was 10.43 months (IQR: 2.00-12.00). The most common underlying CCHDs in LRTI patients were TOF (n=13, 31.7%), EA (n=12, 29.3%), and ventricular septal defect with PA (n=9, 22.0%). Among these patients, 90.2% (n=37) were observed in the PED, 43.9% (n=18) were hospitalized, and 24.4% (n=10) were transferred to the PICU. The rate of PICU admission among hospitalized LRTI cases was 55.6%.

The most common cardiac-related diagnoses were cyanotic spell (1.7%) and HF (1.4%), with median ages at admission of 4.76 months (IQR: 1.36-64.70) and 1.83 months (IQR: 0.76-10.06), respectively. Cyanotic spells occurred in 4 patients with TOF (66.7%) and 2 patients with double outlet right ventricle (DORV) and pulmonary stenosis (PS) (33.3%). HF was observed in 3 (60.0%) HLHS patients, 1 (20.0%) with transposition of the great arteries (TGA), and 1 (20.0%) with tricuspid atresia (TA) and TGA. Among patients with cyanotic spells, presenting symptoms included increased cyanosis (n=5, 83.3%), respiratory distress (n=2, 33.3%), and syncope (n=1, 16.7%). Patients with HF most frequently presented with respiratory distress (n=2, 40.0%), increased cyanosis (n=2, 40.0%), cough (n=1, 20.0%), and uneasiness (n=1, 20.0%).

A total of 109 (31.1%) visits involved observation in the PED. The most common presenting complaints leading to observation were cough (n=53, 48.6%), fever (n=40, 36.7%), respiratory distress (n=30, 27.5%), and increased cyanosis (n=16, 14.7%). The leading diagnoses in this group were LRTI (n=37, 33.9%), URTI (n=30, 27.5%), and AGE (n=17,

Table 2. Risk factors for hospitalization

	Hospitalization			
Characteristics	**Yes (n=44)**	**No (n=307)**	**Total (n=351)**	**p-value**
Complaints				
Dyspnea/respiratory distress	15 (34.1)	29 (9.4)	44 (12.5)	<0.001[b]
Increased cyanosis	12 (27.3)	18 (5.9)	30 (8.5)	<0.001[a]
Syncope	2 (4.5)	0 (0)	2 (0.6)	0.015[a]
Visit diagnosis				
URTI	0 (0)	172 (56.0)	172 (49.0)	<0.001[b]
LRTI	18 (40.9)	23 (7.5)	41 (11.7)	<0.001[b]
Urinary tract infection	3 (6.8)	4 (1.3)	7 (2.0)	0.045[a]
Cyanotic spell	3 (6.8)	3 (1.0)	6 (1.7)	0.028[a]
HF	5 (11.4)	0 (0)	5 (1.4)	<0.001[a]
Cardiopulmonary arrest	2 (4.5)	0 (0)	2 (0.6)	0.015[a]
GCS				
GCS ≤12	13 (29.5)	2 (0.7)	15 (4.3)	<0.001[a]
Life-saving intervention	10 (22.7)	3 (1.0)	13 (3.7)	<0.001[a]
Significant IV fluid resuscitation	8 (18.2)	3 (1.0)	11 (3.1)	<0.001[a]
PPV	4 (9.1)	0 (0)	4 (1.1)	<0.001[a]
Intubation	4 (9.1)	0 (0)	4 (1.1)	<0.001[a]
CPR	2 (4.5)	0 (0)	2 (0.6)	0.015[a]
Ventilation support	18 (40.9)	1 (0.3)	19 (5.4)	<0.001[a]
Circulatory support	13 (29.5)	0 (0)	13 (3.7)	<0.001[a]

All values are presented as n (%).
[a]: Fisher's exact test, [b]: Pearson chi-square test, URTI: Upper respiratory tract infection, LRTI: Lower respiratory tract infection, HF: Heart failure, GCS: Glasgow Coma scale, IV: Intravenous, PPV: Positive pressure ventilation, CPR: Cardiopulmonary resuscitation

15.6%). Observation rates were significantly higher among patients with respiratory distress, increased cyanosis, URTI, LRTI, gastrointestinal bleeding, and HF (p<0.001, p=0.011, p<0.001, p<0.001, p=0.029, p=0.034, respectively). Among patients with LRTI, 90.2% (n=37) were observed in the emergency room.

A total of 44 visits (12.5%) resulted in hospitalization, occurring more frequently among infants with a mean age of 6.75 months (IQR: 1.91-11.49). The median length of hospital stay was 6.0 days (IQR: 4.0-9.75). The leading diagnoses among hospitalized patients were LRTI (40.9%), AGE (18.2%), and HF (11.4%). The hospitalization rate among patients with LRTI was 43.9%. Risk factors associated with hospitalization are presented in Table 2.

Twenty-four (6.8%) of the PED admissions required PICU care. The median PICU stay was 6.0 days (IQR: 3.0-9.5). Among these, the most common presenting symptoms were respiratory distress (n=9, 37.5%), cough (n=9, 37.5%), and increased cyanosis (n=9, 37.5%). The leading diagnoses were LRTI (n=10, 41.7%), HF (n=5, 20.8%), and cardiac arrest (n=2, 8.3%). 24.4% of patients diagnosed with LRTI were transferred to the PICU, and among those hospitalized due to LRTI, the rate of PICU stay was even higher, with a rate of 55.6%.

Additionally, the rate of admission to the PICU was significantly higher in patients with respiratory distress, increased cyanosis, fever, LRTI, cardiopulmonary arrest, and HF (p=0.001, p<0.001, p=0.003, p<0.001, p=0.004, p<0.001, respectively). Circulatory and ventilatory support were provided to 13 (54.2%) and 16 (66.7%) of the patients in the PICU, respectively.

Seven patients, with a median age of 10.13 months (IQR: 2.16-16.83), died. The causes of death were pneumonia (n=4), cardiac arrhythmia (n=2), and HF (n=1). One patient with DORV + PS and one with HLHS died due to arrhythmia. The patient who died from HF also had HLHS. As expected, HLHS had the highest associated mortality rate (50.0%). The mortality rates by underlying CHD were: HLHS (50.0%), DORV + PS (33.3%), EA (25.0%), PA (25.0%), TA with TGA (16.6%), and TOF (3.1%).

The GCS was ≥13 in 95.7% (n=336) of PED visits. Only one patient with a GCS of ≥13 died. GCS ≤12 was significantly associated with mortality (p<0.001). Emergency life-saving procedures were performed in 13 admissions (3.7%), and

Table 3. Risk factors for mortality

	Mortality			
Characteristic	**No (n=344)**	**Yes (n=7)**	**Total (n=351)**	**p-value**
Complaints				
Fever	144 (41.9)	0 (0)	144 (41.0)	0.044
Dyspnea/respiratory distress	40 (11.6)	4 (57.1)	44 (12.5)	0.006
Increased cyanosis	26 (7.6)	4 (57.1)	30 (8.5)	0.001
Visit diagnosis				
URTI	172 (50.0)	0 (0)	172 (49.0)	0.015
LRTI	38 (11.0)	3 (42.9)	41 (11.7)	0.037
HF	3 (0.9)	2 (28.6)	5 (1.4)	0.003
Cardiopulmonary arrest	0 (0)	2 (28.6)	2 (0.6)	<0.001
GCS				
GCS ≤12	9 (2.6)	6 (85.7)	15 (4.3)	<0.001
Life-saving intervention	10 (2.9)	3 (42.9)	13 (3.7)	0.001
Significant IV fluid resuscitation	8 (2.3)	3 (42.9)	11 (3.1)	0.001
PPV	2 (0.6)	2 (28.6)	4 (1.1)	0.002
Intubation	2 (0.6)	2 (28.6)	4 (1.1)	0.002
CPR	0 (0)	2 (28.6)	2 (0.6)	<0.001
PED observation unit admission	103 (29.9)	6 (85.7)	109 (31.1)	0.004
Hospitalization	37 (10.8)	7 (100.0)	44 (12.5)	<0.001
PICU admission	17 (4.9)	7 (100.0)	24 (6.8)	<0.001
Ventilation support	12 (3.5)	7 (100.0)	19 (5.4)	<0.001
Circulatory support	7 (2.0)	6 (85.7)	13 (3.7)	<0.001

All values are presented as n (%), and all comparisons were performed using Fisher's exact test.
URTI: Upper respiratory tract infection, LRTI: Lower respiratory tract infection, HF: Heart failure, GCS: Glasgow Coma scale, IV: Intravenous, PPV: Positive pressure ventilation, CPR: Cardiopulmonary resuscitation, PED: Pediatric emergency department, PICU: Pediatric intensive care unit

3 (23.1%) of these patients died. There was a significant correlation between emergency life-saving interventions and mortality (p=0.001). Specific interventions such as positive pressure ventilation, intubation, cardiopulmonary resuscitation (CPR), and significant IV fluid resuscitation were also significantly associated with mortality. The risk factors for mortality are presented in Table 3.

Logistic regression analysis identified urinary tract infection, LRTI, emergency life-saving intervention, and respiratory support as significant predictors of hospitalization. The model demonstrated excellent discrimination, with an AUC of 0.907 (95% CI: 0.859-0.956, p<0.001), sensitivity of 45.5%, specificity of 99.3%, PPV of 90.9%, and NPV of 92.7%. Significant associations were also found between mortality and increased cyanosis, dyspnea/respiratory distress, LRTI, HF, GCS ≤12, emergency life-saving intervention, significant IV fluid resuscitation, positive pressure ventilation, intubation, and circulatory support (Table 4).

Discussion

The majority of pediatric patients present to the PED with infectious diseases, most frequently with fever, cough, sore throat, earache, abdominal pain, diarrhea, vomiting, respiratory distress, and cyanosis.[10] Children with underlying cardiac disease are exposed to similar factors as the general population, although their clinical course and management may differ significantly due to their underlying cardiac pathology. Special attention is required during differential diagnosis as symptoms of cardiac and non-cardiac conditions often overlap. There are a limited number of studies evaluating the characteristics of CCHD patients presenting to the PED.[6,7] This study aimed to identify the characteristics of PED admissions and determine the predictors of hospitalization and mortality among CCHD patients. To the best of our knowledge, this is the first study addressing this topic in our country.

Table 4. Logistic regression of clinical features for prediction of hospitalization and mortality

	Hospitalization				Mortality	
	Univariable regression model		Multivariable regression model		Univariable regression model	
Characteristic	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Gender, girl	1.862 (0.984-3.524)	0.056			2.554 (0.562-11.599)	0.225
Age	0.972 (0.957-0.988)	<0.001	0.987 (0.973-1.001)	0.077	0.937 (0.865-1.016)	0.114
Fever	0.563 (0.284-1.119)	0.101				
Cough	0.981 (0.516-1.865)	0.954			1.920 (0.423-8.710)	0.398
Increased cyanosis	6.021 (2.661-13.624)	<0.001			16.308 (3.463-76.788)	<0.001
Dyspnea/respiratory distress	4.958 (2.386-10.303)	<0.001			10.133 (2.188-46.929)	0.003
Uneasiness	0.997 (0.285-3.489)	0.996			2.326 (0.269-20.147)	0.443
Diarrhea	2.134 (0.863-5.278)	0.101				
Vomiting	1.263 (0.527-3.025)	0.601				
Urinary tract infection	5.543 (1.198-25.650)	0.028	9.209 (1.591-53.315)	0.013		
AGE	1.573 (0.680-3.637)	0.289				
LRTI	8.548 (4.095-17.846)	<0.001	7.131 (2.701-18.829)	<0.001	6.039 (1.302-28.015)	0.022
Cyanotic spell	7.415 (1.448-37.964)	0.016				
GCS ≤12	63.952 (13.794-296.483)	<0.001			223.333 (24.302-2052.415)	<0.001
Life-saving intervention	29.804 (7.820-113.595)	<0.001	24.822 (3.416-180.347)	0.002	25.050 (4.939-127.053)	<0.001
Significant IV fluid resuscitation	22.519 (5.716-88.719)	<0.001			31.500 (6.031-164.516)	<0.001
Ventilation support	211.846 (27.188-1650.691)	<0.001	117.893 (13.574-1023.951)	<0.001		
PPV					68.400 (7.970-586.997)	<0.001
Circulatory support					288.857 (30.585-2728.057)	<0.001
HF					45.467 (6.183-334.343)	<0.001

OR: Odds ratio, CI: Confidence interval, AGE: Acute gastroenteritis, LRTI: Lower respiratory tract infection, GCS: Glasgow Coma scale, IV: Intravenous, PPV: Positive pressure ventilation, HF: Heart failure

TOF is the most common CCHD (5-10%), followed by TGA.[5] Consistent with previous studies, TOF (47.8%) was the most common CCHD followed by PA (11.9%). Similarly, Masood et al.[11] and Ilyas et al.[6] reported TOF as the most common CCHD among children admitted to PED (17.7% vs. 50%, respectively).

The most frequent presenting symptoms of CHD include respiratory distress, cyanosis, cough, feeding difficulties, fever, inadequate weight gain, and palpitations.[11-13] In our study, the most common reasons for admission were cough and fever; followed by vomiting, respiratory distress, diarrhea, and increased cyanosis, in alignment with the existing literature.

URTI is the most frequent diagnosis in the PED, followed by fever, asthma, otitis media, and viral infections.[10] Similarly, respiratory tract infections have been reported as the predominant diagnoses among children with CHD in previous studies.[14,15] This increased susceptibility, especially in children under 24 months, is attributed to their limited cardiopulmonary reserve.[7,16] Children with CHD have a threefold increased risk of developing LRTIs, which also constitutes the most common reason for hospitalization.[17] Lee et al.[14] reported an earlier onset of respiratory tract infections in patients with CCHD (median age 1.1 years). Similarly, patients with LRTI had a mean age of 10.43 months and it was the most common reason for hospitalization in our study.

The most common cardiac causes of PED admission were cyanotic spells and HF. Cyanotic spells typically occur in infants aged 2 months to 2 years with reduced pulmonary blood flow (PBF), often triggered by a decreased systemic vascular resistance and increased right-to-left shunting. This further reduction in PBF leads to worsening hypoxia and deepening cyanosis.[18] Cyanotic spells are most commonly observed in TOF, PA and DORV with PS. In our study, cyanotic spells were more frequently observed in TOF patients, with a median age of 4.7 months, consistent with expected clinical patterns.

HF results from the heart's inability to meet metabolic demands of the body due to decreased cardiac output.[19] Its incidence is estimated at 0.1-0.2% among all live births and 6-24% among children with CHD.[20-22] CHD is the leading cause of HF in children, often presenting during the first year of life. In the United States, approximately 11,000-14,000 children are hospitalized annually with HF and an overall mortality rate of 7%, compared to 0.4% in children without HF.[20-24] Lee et al.[14] reported HF as the cause of 14.7% of PED admissions among children with congenital CHD.[6,25,26] In our study, HF was the second most common cardiac diagnosis, accounting for 14.3% of cases. The leading presenting complaints were increased cyanosis, respiratory distress, and cough. The reduced incidence of HF in older children may be attributed to the effects of corrective or palliative surgical interventions.

LRTI, AGE, and HF were the most common indications for hospitalization, while LRTI, HF, and cardiac arrest predominated among those requiring PICU care. LRTI accounts for 3-18% of hospitalizations in high-income countries.[17] Pneumonia is more frequent and severe in patients with CHD and is associated with increased mortality.[27-29] PICU admission is required in 3-14% of hospitalized cases with LRTI.[17] In our study, 90.2% of CCHD patients with LRTI were observed in the PED; 43.9% were hospitalized, and 24.4% required PICU admission. Among hospitalized LRTI cases, 55.6% required PICU care, highlighting a higher burden in the CCHD population.

In our study, respiratory distress, increased cyanosis, cyanotic spells, and a GCS score of ≤12 were identified as significant predictors of hospitalization. As with all critically ill patients, timely and effective interventions are essential for children with cyanotic CCHD presenting to the emergency department. Emergency life-saving interventions were also among the most significant parameters associated with hospitalization. PICU management commonly involved both invasive and non-invasive mechanical ventilatory support, circulatory support with vasopressors, IV fluid resuscitation, and blood product transfusions. Our findings showed that 6.8% of CCHD patients required PICU admission, and those admitted frequently needed high levels of support, including mechanical ventilation (66.7%) and circulatory support (54.2%).

CHD accounts for approximately 12.4% of all childhood deaths.[29] Advances in diagnosis and interventional therapies have significantly improved survival; nonetheless, HLHS continues to carry the highest mortality. Recent studies show that 96% of infants with CHD who survive their first year remain alive at age,[16] shifting CHD-related mortality into adulthood.[30,31] Globally, reductions in CHD mortality vary according to socioeconomic status, ranging from 34.5% in low-income settings to 64% in high-income countries.[32] As CHD-related mortality shifts into adulthood, the leading causes of death also evolve, with arrhythmia and HF being the most common.[30] Lee et al.[14] reported respiratory tract infection (5.8%) as the leading cause of mortality in CHD patients. Similarly, in our study, pneumonia was the most common cause of death, followed by arrhythmia and HF. Several clinical parameters—such as increased cyanosis, emergency life-saving interventions, intravenous (IV) fluid resuscitation, respiratory and circulatory support, and GCS score—were significantly associated with mortality. GCS at the time of admission has been reported as a strong predictor of mortality.[33,34] In our study, 40% of patients with a GCS score ≤12 died. Our study showed that patients with CCHD should be managed more carefully than the healthy population, even when they have a higher GCS score, because of the increased risk of sudden deterioration. Additionally, early and effective emergency

life-saving interventions are essential in preventing mortality in patients with CCHD. Health-care access and quality are another important factor for prognosis. In our country, the national health insurance system provides full coverage for all children under the age of 18; however, low family income can still pose a barrier to accessing health care, particularly for those living in rural areas. Furthermore, parental education levels may affect caregivers' ability to recognize early signs and symptoms of illness, leading to delayed medical intervention, more severe clinical presentation at the time of hospitalization, and a poorer prognosis for affected children.

Study Limitations

This study has several limitations. First of all, this study is subject to the usual limitations of a retrospective study. Second, our center is a tertiary referral hospital with a specialized pediatric cardiology unit and PICU, which may introduce selection bias, as more complex or severe cases are preferentially referred. Third, variability in clinical assessment among different physicians may have influenced decisions regarding admission and observation. Lastly, associated genetic syndromes or extracardiac anomalies—which may affect clinical severity and outcomes—were not included in the statistical analysis.

Conclusion

Due to the complex nature of CCHD, clinicians must be vigilant regarding risk factors for hospitalization and mortality. Even patients presenting with seemingly mild symptoms may deteriorate rapidly. Early recognition and timely emergency interventions are critical. A better understanding of the demographic characteristics and predictors of poor outcomes will support the development of more effective management strategies for this vulnerable population. Further prospective, multicenter studies are warranted to validate and expand upon our findings. The predictive markers identified in this study may serve as a valuable guide for pediatricians in the emergency management of children with CCHD.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Ankara University Faculty of Medicine (approval number: İ03-164-23, approval date: 05.04.2023), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: G.V., M.G.R., B.G., G.B.Y., S.A., İ.K., T.U., T.K., D.T., Design: G.V., M.G.R., B.G., G.B.Y., U.Ç., T.K., Data Collection or Processing: G.V., M.G.R., B.G., G.B.Y., U.Ç., S.A., İ.K., Analysis or Interpretation: G.V., M.G.R., İ.K., T.U., T.K., D.T., Literature Search: G.V., M.G.R., B.G., G.B.Y., U.Ç., S.A., İ.K., T.U., T.K., D.T., Writing: G.V., M.G.R., B.G., G.B.Y., U.Ç., S.A., İ.K., T.U., T.K., D.T.

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Predictive Factors for Acute and Complicated Appendicitis in Children: A Prospective Study

Çocukluk Yaş Grubunda Akut ve Komplike Apandisit Tanısında Prediktif Faktörlerin Belirlenmesi: Prospektif Bir Çalışma

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Abstract

Introduction: Acute appendicitis is one of the most common surgical emergencies in children, where early diagnosis is crucial to reducing morbidity and mortality. This study aimed to identify predictive factors for appendicitis and evaluate the diagnostic value of serum sodium and blood and urine ketone levels.

Methods: This prospective study included patients under 18 years of age who presented with acute abdominal pain and were clinically suspected of having appendicitis. Patients were divided into two groups: appendicitis and non-appendicitis. The appendicitis group was further categorized into acute and complicated cases. Demographic data, clinical symptoms, physical examination findings, symptom duration, preoperative laboratory values, blood and urine ketone levels, and pathology results were recorded.

Results: A total of 153 patients were included [100 with appendicitis (51 complicated) and 53 non-appendicitis]. In the appendicitis group, leukocyte count, neutrophil count, C-reactive protein (CRP), blood ketones [area under the curve (AUC)=0.618], and urine ketones (AUC=0.627) were significantly higher (p<0.001, p<0.001, p=0.001, p=0.03, and p=0.04, respectively). Among patients presenting within 24 hours of symptom onset, leukocyte count (p=0.013), neutrophil count (p=0.014), and blood ketones (p=0.035) were significantly higher in the appendicitis group. For patients with symptom duration longer than 24 hours, leukocyte count (p=0.005), neutrophil count (p=0.001), and CRP levels (p=0.001) were significantly elevated, while serum sodium levels were significantly lower (p=0.046) in appendicitis cases.

Öz

Giriş: Akut apandisit, çocuklarda en sık görülen cerrahi acil durumlardan biridir. Morbidite ve mortaliteyi azaltmak için erken tanı kritik öneme sahiptir. Bu çalışmanın amacı, apandisit için öngörücü faktörleri belirlemek ve serum sodyum ile kan ve idrar keton düzeylerinin tanı değerini değerlendirmektir.

Yöntemler: Çalışmaya, akut karın ağrısı ile başvuran ve fizik muayenede apandisit şüphesi olan 18 yaş altı hastalar ileriye dönük olarak dahil edildi. Hastalar apandisit olanlar ve olmayanlar olarak gruplandırıldı; apandisit olanlar da kendi içinde akut ve komplike apandisit olarak ayrıldı. Demografik veriler, semptomlar, fizik muayene bulguları, semptom süresi, ameliyat öncesi laboratuvar sonuçları, kan ve idrar keton düzeyleri ve patoloji raporları kaydedildi.

Bulgular: Çalışmaya toplam 153 hasta dahil edildi [100 apandisit (51 komplike) ve 53 apandisit olmayan]. Apandisit grubunda lökosit, nötrofil, C-reaktif protein (CRP), kan ketonları [eğri altında kalan alan (AUC)=0,618] ve idrar ketonları (AUC=0,627) düzeyleri anlamlı derecede yüksekti (sırasıyla p<0,001, p<0,001, p=0,001, p=0,03, p=0,04). Semptom süresi <24 saat olan hastalarda apandisit grubunda lökosit (p=0,013), nötrofil (p=0,014) ve kan ketonu (p=0,035) anlamlı olarak yüksek bulundu. Semptom süresi >24 saat olan hastalarda ise apandisit grubunda lökosit (p=0,005), nötrofil (p=0,001), CRP (p=0,001) anlamlı olarak yüksek, sodyum (p=0,046) anlamlı olarak düşük bulundu.

Sonuç: Çalışmamızda apandisitli çocuklarda kan ve idrar keton düzeyleri anlamlı olarak yüksek bulundu. Kan keton düzeyi özellikle

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Abstract

Conclusion: In our study, blood and urine ketone levels were significantly elevated in children with appendicitis. Blood ketones appeared particularly useful in early-stage presentations, whereas CRP elevation and decreased serum sodium were more prominent in delayed cases.

Keywords: Appendicitis, children, emergency, sodium, ketones

Öz

erken başvurularda faydalı olurken CRP artışı ve serum sodyum düşüklüğü hastaneye başvuru süresi uzadıkça daha anlamlı hale geldi.

Anahtar Kelimeler: Apandisit, çocuklar, acil, sodyum, keton

Introduction

Acute appendicitis (AA) is the most common non-traumatic surgical emergency in children.[1] However, diagnosing AA in pediatric patients can be particularly challenging due to non-specific clinical signs, a broad differential diagnosis of abdominal pain, and young children's limited ability to communicate symptoms or cooperate during physical examinations. Despite advancements in laboratory tests, imaging modalities, and clinical scoring systems, diagnostic delays, misdiagnoses, and unnecessary appendectomies still occur.

As a result, there is ongoing research to identify alternative biomarkers that may improve diagnostic accuracy for pediatric appendicitis. Recent studies suggest that, in addition to commonly used markers such as C-reactive protein (CRP), white blood cell (WBC) count, and absolute neutrophil count (ANC), hematological indices like the neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) may serve as valuable diagnostic tools.[2,3] With the growing interest in conservative management approaches, there is an increasing need to distinguish complicated appendicitis (CA) from AA cases early in the clinical course.

Several studies examining hematological parameters in appendicitis have highlighted immune response patterns, particularly elevated neutrophil and monocyte counts in CA. Monocytes, as part of the innate immune system, tend to increase in inflammatory states, while lymphocyte counts-associated with adaptive immunity-often decline during infections. A decrease in lymphocytes has been linked to appendicitis and appears more pronounced in complicated cases.[4,5] These findings help explain the frequent observation of elevated NLR and decreased LMR in patients with appendicitis.

Hyponatremia has also been identified as a potential marker for CA.[2,6,7] Although the exact mechanism remains unclear, it is thought to involve systemic inflammation and the release of proinflammatory cytokines such as interleukin (IL)-1β and IL-6, which stimulate the secretion of antidiuretic hormone (ADH). These cytokines may cross the blood-brain barrier and activate neurons in the supraoptic and paraventricular nuclei, leading to non-osmotic ADH release, increased water reabsorption in renal tubules, and subsequent dilutional hyponatremia.[8]

During acute stress, when glucose reserves are rapidly depleted, ketone bodies become an alternative energy source for the brain and other tissues.[9] In children with appendicitis, elevated ketone levels may result from increased catabolism, vomiting, fasting, and dehydration. While urinary ketones correlate with serum levels, renal function may influence ketone excretion, potentially limiting their diagnostic reliability. Thus, evaluating both serum and urine ketone levels is necessary; however, only a few studies have investigated the association between ketosis and appendicitis in children.[10-12]

The aim of this study was to evaluate the diagnostic value of leukocyte, neutrophil, lymphocyte, and monocyte counts; CRP and procalcitonin (PCT) levels; NLR and LMR; and, in particular, serum sodium and blood/urine ketone levels in predicting appendicitis in pediatric patients.

Materials and Methods

Study Population

This single-center, prospective case-control study was conducted between April 2022 and October 2023. Pediatric patients under 18 years of age who presented to the Aydın Adnan Menderes University Faculty of Medicine, Department of Pediatric Emergency with an annual patient volume of approximately 30.000-were evaluated for inclusion. Eligible patients had acute abdominal pain and a clinical suspicion of appendicitis based on physical examination findings and a pediatric appendicitis score (PAS) greater than 3.[13] The following data were collected for each patient: socio-demographic characteristics, vital signs, physical examination findings, symptom duration, PAS value, serum sodium levels, WBC, ANC, absolute lymphocyte and monocyte counts, NLR, LMR, CRP, PCT, serum and urine ketone levels, surgical notes, pathology reports, length of hospital stay, and postoperative complications.

While some patients underwent surgical intervention, others were observed and subsequently discharged. For discharged patients, families were contacted within one month to

confirm whether surgery had been performed at another facility. The "non-appendicitis" group included patients who were discharged without surgery or underwent negative appendectomy. Patients with histopathologically confirmed appendicitis were further categorized into either AA or CA. CA was defined as cases involving perforation, gangrenous appendix, intra-abdominal abscess, or peritonitis.

Exclusion criteria included: prior appendectomy, abdominal trauma, malignancy, inflammatory bowel disease, Familial Mediterranean Fever, chronic systemic illness, long-term medication use, or administration of intravenous fluids containing dextrose and/or saline prior to laboratory evaluation.

Biochemical Analysis

Routine laboratory assessments at our institution included complete blood count, serum sodium, and CRP levels. Diagnostic thresholds were defined as follows: leukocytosis >10.000/mm^3, neutrophilia >7.500/mm^3, and hyponatremia <135 mEq/L. Blood samples for ketone [β-hydroxybutyrate (β-OHB)] and PCT analyses were centrifuged at 4.500 rpm for 10 minutes. Serum and urine samples were stored at -80 °C until analysis. Ketone levels were measured using the Cayman β-OHB (ketone body) colorimetric assay kit (item no: 700190). PCT levels were measured using the Abbott Alinity autoanalyzer, based on the chemiluminescent microparticle immunoassay principle.

Statistical Analysis

Sample size estimation was performed using G*Power software. Based on the association between appendicitis and serum sodium levels, a minimum of 128 patients was required to achieve a statistical power of 95% with a 5% significance level.

Statistical analyses were conducted using SPSS version 21.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as frequencies and percentages. Continuous variables with normal distribution were presented as mean ± standard deviation (SD), while non-normally distributed variables were reported as median and interquartile range (25th-75th percentiles). Comparisons between groups were made using the chi-square test for categorical variables, Student's t-test for normally distributed continuous variables, and the Mann-Whitney U test for non-normally distributed variables. Pearson's correlation test was used for parametric data, while Spearman's rank correlation was applied for non-parametric data. A p-value <0.05 was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic and exclusionary performance of numerical variables, including sensitivity, specificity, and cut-off values.

Ethical Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from parents or legal guardians prior to participation. Ethical approval was obtained from the Ethics Committee of Aydın Adnan Menderes University Faculty of Medicine (approval no: 2022/62, date: 07.04.2022).

Results

Of the 169 eligible patients who presented with acute abdominal pain, physical examination findings suggestive of appendicitis, and a PAS greater than 3, a total of 153 patients were included in the final analysis (Figure 1). One patient in the observation group underwent surgery for ovarian torsion at our institution, and another was operated for AA at a different hospital one week later.

In the appendicitis group, the male-to-female ratio was 1.9:1, and the mean ± SD age of the patients was 132.3±45.5 months. No statistically significant difference was observed between the appendicitis and non-appendicitis groups (p=0.336 and p=0.111, respectively) and the AA and CA groups (p=0.536 and p=0.158, respectively) in terms of age or gender. The median PAS was significantly higher in patients with appendicitis compared to those non-appendicitis (p<0.001), and also significantly higher in patients with CA compared to those with AA (p=0.006).

Serum sodium, CRP, and hemogram parameters were studied for all 153 patients. However, additional serum samples were obtained from 115 patients (66 from the appendicitis group and 49 from the non-appendicitis group) for serum ketone and PCT analysis. β-OHB levels were measured in all 115 samples, and PCT levels were analyzed in 106 of them. Additionally, urine samples for β-OHB analysis were obtained from 83 patients (42 appendicitis and 41 non-appendicitis).

The laboratory findings are presented in Table 1. Patients in the appendicitis group had significantly higher values for WBC, ANC, monocyte count, leukocytosis, neutrophilia, NLR, CRP, and both serum and urine ketone levels, while LMR was significantly lower. The corresponding p-values were: p<0.001, p<0.001, p=0.028, p=0.003, p<0.001, p<0.001, p=0.001, p=0.032, p=0.047, and p=0.010, respectively. When comparing AA and CA subgroups, LMR was significantly higher in the AA group (p=0.006), whereas leukocytosis and CRP were significantly elevated in the CA group (p=0.011 and p<0.001, respectively).

ROC curve analysis demonstrated that a blood ketone level ≥0.205 mmol/L predicted appendicitis with a sensitivity of 63.6% and specificity of 58.3% [area under the curve (AUC: 0.618); 95% confidence interval (CI: 0.512-0.723); p=0.032].

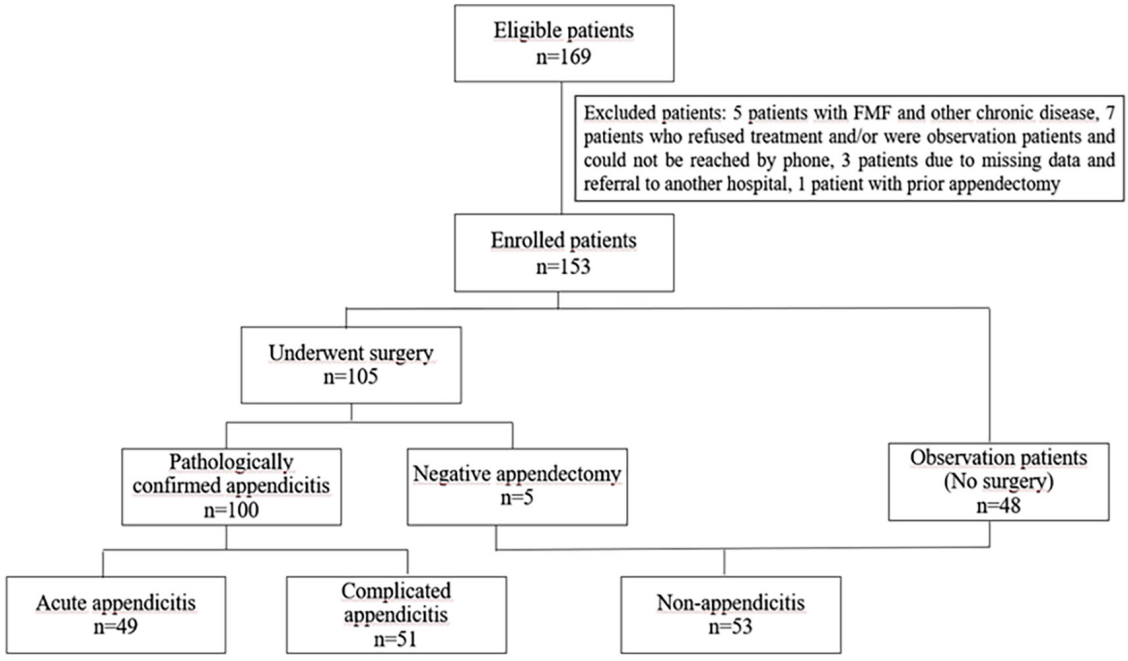

Figure 1. Flowchart of patients
FMF: Familial Mediterranean Fever

Table 1. Laboratory characteristics of the cases

	Appendicitis (n=100)	Non-appendicitis (n=53)	p-value	AA patients (n=49)	CA patients (n=51)	p-value
WBC (cells/mm³)	15510.00 (12790.00-19650.00)	12340.00 (8960.00-16180.00)	**<0.001***	15057.76±5113.43	16900.98±5006.49	0.072
ANC (cells/mm³)	12500.00 (9885.00-16380.00)	9300.00 (5220.00-12210.00)	**<0.001***	12204.49±5031.06	13849.22±4675.36	0.093
Leukocytosis (>10.000/mm³)	88 (88.0)	36 (67.9)	**0.003***	39 (79.6)	49 (96.1)	**0.011***
Neutrophilia (>7.500/mm³)	88 (88.0)	33 (62.3)	**<0.001***	40 (81.6)	48 (94.1)	0.055
Lymphocytes (cells/mm³)	1700.00 (1050.00-2225.00)	1770.00 (1340.00-2510.00)	0.073	1788.37±800.56	1680.39±838.98	0.512
Monocytes (cells/mm³)	1025.00 (775.00-1335.00)	860.00 (680.00-1100.00)	**0.028***	910.00 (740.00-1140.00)	1200.00 (850.00-1520.00)	0.005
NLR	7.53 (5.22-12.72)	4.79 (2.30-7.96)	**<0.001***	6.64 (4.11-12.03)	8.36 (5.65-14.22)	0.106
LMR	1.61 (1.04-2.28)	1.98 (1.29-3.22)	**0.010***	1.94 (1.11-2.55)	1.47 (0.76-1.96)	**0.006***
CRP (mg/L)	34.65 (8.55-89.50)	8.00 (2.00-68.10)	**0.001***	17.10 (4.60-37.60)	63.80 (24.90-144.60)	**<0.001***
PCT (ng/mL)	0.06 (0.02-0.18)	0.07 (0.02-0.20)	0.976	0.04 (0.02-0.17)	0.09 (0.03-0.19)	0.173
Serum sodium (mEq/L)	137.00 (135.00-138.50)	137.00 (136.00-139.00)	0.063	136.70±2.50	135.89±3.56	0.187
Hyponatremia (<135 mEq/L)	24 (24.0)	8 (15.1)	0.197	8 (16.3)	16 (31.4)	0.078
Blood ketone (mmol/L)	0.27 (0.18-0.38)	0.18 (0.15-0.28)	**0.032***	0.24 (0.18-0.35)	0.36 (0.19-0.38)	0.173
Urine ketone (mmol/L)	0.36 (0.13-0.45)	0.20 (0.09-0.39)	**0.047***	0.37 (0.12-0.49)	0.35 (0.15-0.44)	0.879

Categorical data is summarized as n (%), and numerical data is summarized as mean ± SD or median (25^{th}-75^{th} percentiles)
*: p<0.05, AA: Acute appendicitis, CA: Complicated appendicitis, WBC: White blood cell, ANC: Absolute neutrophil count, NLR: Neutrophil-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, CRP: C-reactive protein, PCT: Procalcitonin, SD: Standard deviation

Similarly, a urine ketone level ≥0.280 mmol/L predicted appendicitis with 59.5% sensitivity and 55.0% specificity (AUC: 0.627; 95% CI: 0.506-0.749; p=0.032) (Figure 2).

Blood ketone positivity was observed in 63.6% (n=42) of appendicitis patients compared to 41.7% (n=20) of non-appendicitis patients, and this difference was statistically significant (p=0.020; Table 2). Furthermore, in the AA subgroup, blood ketone levels showed a significant positive correlation with the length of hospital stay (r=0.428, p=0.013).

When patients were grouped based on symptom duration, those presenting within 24 hours and diagnosed with appendicitis had significantly higher WBC (p=0.013), ANC (p=0.014), and blood ketone levels (p=0.035). Among patients with symptoms lasting more than 24 hours, WBC (p=0.005), ANC (p=0.001), and CRP (p=0.001) levels were significantly higher in the appendicitis group, while serum sodium levels were significantly lower (p=0.046) (Table 3).

Regarding pre-hospital medication use, there was no significant difference in antibiotic or analgesic use between the appendicitis and non-appendicitis groups. However, analgesic use prior to admission was significantly more common in the CA group compared to the AA group (p=0.016).

Discussion

AA is one of the most common surgical emergencies in pediatric emergency departments. Clinicians rely on a combination of history, physical examination, laboratory tests, and imaging to assess the likelihood of appendicitis. However, ongoing diagnostic challenges underscore the need for reliable, objective biomarkers. This study aimed to evaluate the predictive value of leukocyte, neutrophil, lymphocyte, and monocyte counts; CRP, PCT; NLR, LMR; serum sodium; and blood/urine ketone levels in pediatric appendicitis.

Delayed hospital presentation, diagnostic uncertainty, and anatomical variability contribute to an increased incidence of CA in children. While previous studies have reported CA rates ranging from 18.7% to 45.6%,[2,7,12,14,15] we observed a higher rate of 51%. This may be attributable to our hospital's status as a tertiary referral center, where more complex or delayed cases are commonly managed.

Consistent with prior literature, we found that symptom duration significantly influenced disease severity. In our cohort, patients presenting more than 24 hours after symptom onset had a 3.2-fold increased risk of CA. Furthermore, our findings suggest that pre-hospital analgesic use may contribute to diagnostic delay and an increased risk of complications.

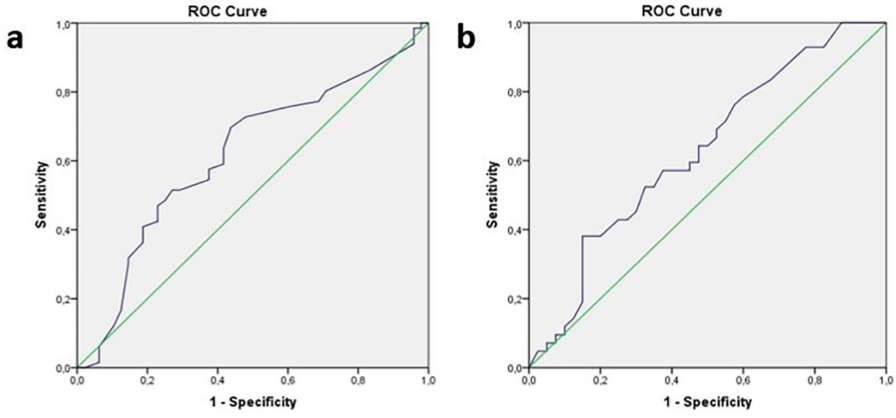

Figure 2. ROC analysis graph of ketone levels between patients with and without appendicitis
a: Blood ketone levels, b: Urine ketone levels, ROC: Receiver operating characteristic

Table 2. Comparison of blood and urine ketone elevation between patients with and without appendicitis according to the cut-off values determined by ROC analysis

		Appendicitis	Non-appendicitis	p-value
Blood ketone n (%)	**Absent**	24 (36.4)	28 (58.3)	**0.020***
	Present	42 (63.6)	20 (41.7)	
Urine ketone n (%)	**Absent**	17 (40.5)	22 (55.0)	0.188
	Present	25 (59.5)	18 (45.0)	

Categorical data is summarized as n (%)
*: p<0.05, ROC: Receiver operating characteristic

Table 3. Comparison of laboratory data between patients with and without appendicitis based on symptom onset time

	First 24 hours			After 24 hours		
	Appendicitis (n=43)	**Non-appendicitis (n=24)**	**p-value**	**Appendicitis (n=57)**	**Non-appendicitis (n=29)**	**p-value**
PAS	7.00 (6.00-8.00)	4.00 (4.00-5.00)	**<0.001***	8.00 (7.00-9.00)	5.00 (4.00-6.00)	**<0.001***
WBC (cells/mm³)	16190.00±4914.05	13233.75±5326.42	**0.025***	15852.81±5305.34	12439.31±5699.12	**0.007***
ANC (cells/mm³)	13516.74±4862.80	10250.42±5443.24	**0.014***	12060.00 (9930.00-15840.00)	9300.00 (4870.00-10590.00)	**0.001***
Lymphocytes (cells/mm³)	1460.00 (980.00-2090.00)	1575.00 (1120.00-2305.00)	0.460	1827.54±818.10	2169.66±812.42	0.070
Monocytes (cells/mm³)	870.00 (740.00-1090.00)	850.00 (695.00-1025.00)	0.628	1220.00 (870.00-1450.00)	940.00 (620.00-1170.00)	**0.014***
Platelets (cells/mm³)	286255.81±74682.53	311750.00±85580.50	0.208	284000.00 (249000.00-340000.00)	260000.00 (210000.00-313000.00)	**0.014***
NLR	8.41 (5.67-15.62)	7.60 (2.07-11.48)	0.082	6.86 (5.21-10.22)	3.65 (2.30-6.33)	**<0.001***
LMR	1.96 (1.09-2.48)	1.95 (1.04-3.12)	0.628	1.47 (1.00-2.04)	2.04 (1.41-3.43)	**0.002***
CRP (mg/L)	11.70 (3.80-32.50)	3.85 (2.00-27.70)	0.092	81.20 (33.60-146.50)	23.30 (2.30-72.80)	**0.001***
PCT (ng/mL)	0.03 (0.02-0.09)	0.05 (0.02-0.14)	0.299	0.11 (0.04-0.43)	0.08 (0.03-0.27)	0.351
Sodium (mEq/L)	137.00 (135.00-139.00)	137.00 (136.00-139.00)	0.640	137.00 (133.00-138.00)	137.00 (136.00-139.00)	**0.046***
Blood ketone (mmol/L)	0.24 (0.18-0.37)	0.18 (0.15-0.25)	**0.035***	0.31 (0.15-0.38)	0.20 (0.17-0.36)	0.233
Urine ketone (mmol/L)	0.36 (0.14-0.48)	0.23 (0.08-0.41)	0.180	0.33 (0.11-0.44)	0.17 (0.10-0.37)	0.173

Categorical data is summarized as n (%), and numerical data is summarized as mean ± SD or median (IQR: 25-75)
*: p<0.05, PAS: Pediatric appendicitis score, WBC: White blood cell, ANC: Absolute neutrophil count, NLR: Neutrophil-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, CRP: C-reactive protein, PCT: Procalcitonin, SD: Standard deviation, IQR: Interquartile range

WBC, ANC, CRP, and PCT

Leukocytosis and a left shift are classical laboratory findings in appendicitis, with elevated WBC and ANC observed in approximately 96% of pediatric cases.[16,17] Numerous studies have demonstrated significantly higher WBC, ANC, and CRP levels in patients with appendicitis, supporting their diagnostic value.[12,14,15] Our results are consistent with these findings, showing elevated levels of WBC, ANC, and CRP, along with pronounced leukocytosis and neutrophilia.

Although PCT is considered a sensitive and specific marker for bacterial infections, its utility in appendicitis remains debated. While some studies report significantly elevated PCT levels in appendicitis,[12,14] our findings-similar to those of Ulusoy et al.[15] did not demonstrate a significant difference between the appendicitis and non-appendicitis groups.

One of the key clinical challenges is predicting complications such as perforation and abscess formation preoperatively. Some studies have shown higher WBC and ANC levels in CA compared to AA,[2,7,12,15] whereas others have not found statistically significant differences.[6,14,18] In our study, while WBC and ANC values did not differ significantly between AA and CA, the prevalence of leukocytosis (WBC >10.000/mm³) was significantly higher in the CA group. According to a meta-analysis by Yu et al.[19], CRP and PCT are better suited to predict CA than AA. In our cohort, CRP was significantly higher in the CA group, whereas PCT showed no significant variation. These findings support the notion that while PCT may have some value in identifying CA, it is less reliable than CRP or WBC in diagnosing appendicitis in general. Thus, routine use of PCT for diagnosis in pediatric appendicitis may not be justified.

We also evaluated biomarker dynamics based on symptom duration. As expected, WBC and ANC were useful for early AA diagnosis. Since CRP is a late-phase reactant, increasing 8-12 hours after symptom onset and peaking between 24-48 hours,[20] it has limited utility early on. However, its sensitivity improves significantly after 24 hours.[21] Our findings confirm that CRP levels were markedly elevated after 24 hours, while PCT levels did not show such time-based variation.

Hematologic Subparameters

Recent research has identified hematologic indices such as NLR and LMR as potential diagnostic tools for appendicitis.[18] Similar to the findings of Tuncer et al.[22], our study showed significantly elevated NLR and monocyte counts, along with lower LMR in patients with appendicitis. Nissen and Tröbs[4] also reported higher NLR and monocyte counts, and reduced LMR in CA cases. However, a recent meta-analysis found insufficient evidence to support the use of LMR specifically in differentiating CA from AA.[23] While NLR and LMR are inexpensive and easily accessible, further prospective studies are needed to establish their diagnostic and prognostic value.

Serum Sodium

Hyponatremia has recently been proposed as a potential biomarker for CA.[2,6,7,18,24] Although Duman et al.[18] found significantly lower sodium levels in patients with appendicitis compared to controls, they observed no difference between AA and CA. In our study, we similarly found no significant difference in sodium levels between appendicitis and non-appendicitis groups or between AA and CA. However, sodium levels tended to decrease with longer symptom duration. This trend may suggest an association with disease severity, although the lack of statistical significance weakens its reliability. Nonetheless, due to its routine availability and low cost, the utility of serum sodium as a predictor of CA warrants further investigation.

Blood and Urine Ketones

The pathophysiology of ketosis in appendicitis likely results from enhanced catabolism, vomiting, fasting, and dehydration. Few studies have explored the diagnostic role of ketone bodies in this context. Song et al.[10] reported that ketonuria may help differentiate AA from right-sided colonic diverticulitis in adults. Chen et al.[11] found a higher frequency of urinary ketone positivity in children with perforated appendicitis compared to those with uncomplicated disease. In a recent study, Arredondo Montero et al.[12] found significantly higher capillary β-OHB levels in children with appendicitis patients compared to those without appendicitis, and also in patients with CA compared to those with uncomplicated appendicitis.

In our study, we measured β-OHB from venous blood and found significantly elevated blood and urine ketone levels in the appendicitis group. However, there was no significant difference between AA and CA groups. Interestingly, elevated blood ketone levels were more prominent in the first 24 hours after symptom onset, possibly reflecting the early metabolic response in pediatric patients. A significant negative correlation between ketone levels and age (r=-0.282, p=0.022) further supports this interpretation.

In children, glycogen stores are depleted more rapidly than in adults-within 8-12 hours (and as little as 4 hours in infants)-resulting in faster onset of ketosis during fasting. Additionally, children have higher metabolic rates and energy requirements. These physiological characteristics may explain the early appearance of ketosis and the inverse correlation between age and ketone levels.[25-27]

To our knowledge, this is the first study to concurrently evaluate both venous blood and urine ketone levels in relation to pediatric appendicitis.

Study Limitations

The strengths of this study include its prospective design and sufficient overall sample size. However, the single-center setting may limit the generalizability of our findings.

The sample size was calculated based on the association between serum sodium and appendicitis, requiring a minimum of 128 patients. With 153 patients enrolled, the study met this threshold. Nonetheless, because ketone measurements were only available for 115 patients, analyses involving ketone levels may have been underpowered.

Another limitation is that ketosis can be seen in various conditions related to fasting, vomiting, dehydration (ketoacidosis, gastroenteritis, etc.) other than appendicitis. Despite this, given that appendicitis is the most common surgical emergency in pediatric emergency departments, we believe that the assessment of ketone levels in this population provides clinically valuable insights.

Further large-scale, prospective, multicenter studies are needed to validate the diagnostic utility of ketone levels and other emerging biomarkers in pediatric appendicitis.

Conclusion

In this study, pediatric patients with appendicitis exhibited significantly elevated levels of CRP, WBC, ANC, and both blood and urine ketones. Notably, blood ketone levels were particularly useful in early presentations, suggesting their potential role as an early diagnostic biomarker. As the time from symptom onset increased, CRP levels rose significantly, and serum sodium levels decreased, highlighting their relevance in later stages of disease progression.

Given the high prevalence and potential morbidity of appendicitis in children, further research is warranted to identify reliable biomarkers that support timely and accurate diagnosis.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of Aydın Adnan Menderes University Faculty of Medicine (approval no: 2022/62, date: 07.04.2022).

Informed Consent: Informed consent was obtained from parents or legal guardians prior to participation.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.O.E., A.A., A.T., İ.M., Concept: E.T.B., A.O.E., A.A., A.Ç., Design: E.T.B., A.O.E., Ş.D., A.T., A.Ç., Data Collection or Processing: E.T.B., Ş.D., A.Ç., Analysis or Interpretation: E.T.B., A.A., A.T., A.Ç., Literature Search: E.T.B., A.A., A.Ç., Writing: E.T.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report / Olgu Sunumu

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Toxic Encephalopathy Developing After High-dose Cytarabine in a Child with Burkitt Lymphoma: A Successful Treatment Case

Burkitt Lenfomalı Bir Çocuk Hastada Yüksek Doz Sitarabin Sonrası Gelişen Toksik Ensefalopati: Başarılı Bir Tedavi Olgusu

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Abstract

Chemotherapy drugs used in the treatment of leukemia and lymphoma can occasionally cause side effects. We present here a rare case of neurotoxicity that occurred after high-dose cytarabine (HiDAC) administration. A 13-year-old girl presented with right eye diplopia while receiving the high-risk non-Hodgkin lymphoma (NHL)-Berlin-Frankfurt-Münster 95 chemotherapy protocol. Magnetic resonance imaging (MRI) screening revealed four new parenchymal lesions, none of which showed contrast enhancement. The patient underwent a detailed evaluation for diplopia. Neurotoxicity occurred after the first HiDAC administration in our 13-year-old patient. Cytarabine is one of the key agents in the treatment of NHL, but complications of cytarabine toxicity include seizures, ataxia, and even death. The patient was treated with pulsed methylprednisolone for three days, which was then tapered and discontinued. A follow-up brain MRI performed at the end of the month showed that the lesions had reduced by more than 90%. This case highlights the importance of recognizing cytarabine-induced neurotoxicity, especially in pediatric patients undergoing intensive chemotherapy. Early diagnosis and prompt management can lead to significant clinical improvement and radiological resolution.

Keywords: High-dose cytarabine, magnetic resonance imaging, non-Hodgkin lymphoma, neurotoxicity, cytarabine

Öz

Lösemi ve lenfoma tedavisinde kullanılan kemoterapi ilaçları zaman zaman yan etkilere yol açabilir. Bu yazıda, yüksek doz sitarabin (YDS) uygulamasından sonra gelişen nadir bir nörotoksisite olgusunu sunuyoruz. On üç yaşında, non-Hodgkin lenfoma (NHL) tanısıyla izlenen kız hasta, yüksek riskli NHL-Berlin-Frankfurt-Münster 95 kemoterapi protokolü sırasında sağ gözünde çift görme (diplopi) şikayetiyle başvurdu. Manyetik rezonans görüntülemesinde (MRG), kontrast tutmayan dört yeni parankimal lezyon saptandı. Hasta diplopi açısından ayrıntılı olarak değerlendirildi. Nörotoksisite, 13 yaşındaki hastamızda ilk YDS uygulamasından sonra gelişti. Sitarabin, NHL tedavisinde önemli kemoterapi ajanlarından biridir. Literatürde, sitarabin toksisitesine bağlı olarak nöbet, ataksi ve ölüm gibi ciddi tablolar bildirilmektedir. Hastaya üç gün süreyle intravenöz pulse metilprednizolon tedavisi verildi ve ardından tedavi kademeli olarak azaltılarak sonlandırıldı. Bir aylık tedavi sonunda çekilen beyin MRG'de lezyonların %90'dan fazla gerilediği görüldü. Bu olgu, özellikle yoğun kemoterapi alan pediatrik hastalarda sitarabin kaynaklı nörotoksisitenin tanınmasının önemini vurgulamaktadır. Erken tanı ve hızlı tedavi, belirgin klinik iyileşme ve radyolojik düzelme sağlayabilir.

Anahtar Kelimeler: Yüksek doz sitarabin, manyetik rezonans görüntüleme, non-Hodgkin lenfoma, nörotoksisite, sitarabin

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Introduction

Lymphoma treatment is a process that involves the use of multiple chemotherapeutic agents, and various toxicities may occur due to these drugs. Cytarabine, a chemotherapeutic agent commonly used in the treatment of leukemia and lymphoma, is a pyrimidine analogue that can cause neurological side effects in up to 14% of cases when administered at high-doses.[1] Neurotoxicity usually begins 6 to 8 days after high-dose cytarabine (HiDAC) administration and may manifest as acute cerebellar toxicity or cerebral dysfunction. These effects can last for 3 to 14 days.[2] It has been suggested that the accumulation of cytarabine metabolites in the central nervous system (CNS) is responsible for the neurotoxicity observed following HiDAC administration.[3] In this report, we present the case of a 13-year-old patient who developed neurotoxicity after receiving HiDAC. The patient showed significant improvement, with more than a 90% reduction in symptoms, following steroid treatment.

Case Report

A 13-year-old girl diagnosed with common disease phase-3 Burkitt's lymphoma, presented with a complaint of diplopia in her right eye while receiving treatment according to the high-risk non-Hodgkin lymphoma (NHL)-Berlin-Frankfurt-Münster 95 chemotherapy protocol. Informed verbal and written consent was obtained from the patient's family for the presentation of this case.

On physical examination, her body weight was 43 kg (10^{th}-25^{th} percentile), her height was 163 cm (75^{th}-90^{th} percentile), her blood pressure was 100/60 mmHg, and her pulse rate was 98 beats per minute. The visual field of the left eye was normal, whereas the right eye exhibited inferior field limitation. Systemic examination was unremarkable, with no pathological findings detected.

Laboratory tests showed hemoglobin 10.6 g/dL, hematocrit 31.5%, white blood cell count 3,090/mm³, absolute neutrophil count 1,130/mm³, C-reactive protein 3 mg/L, and platelet count 224,000/mm³. Biochemical parameters were within normal limits.

Visual acuity was found to be normal in both eyes. However, visual field testing revealed a defect in the upper temporal quadrant of the left eye. Diplopia was present only in upward gaze. Fundus examination and ocular motility were normal. No signs of papilledema were observed.

Given the presence of diplopia, CNS involvement was initially suspected. Cerebrospinal fluid (CSF) analysis following lumbar puncture revealed no malignant cells on cytology; however, elevated protein levels were observed on CSF biochemistry.

Cranial magnetic resonance imaging (MRI) revealed four new parenchymal lesions: one in the left anterior frontal subcortical area, one adjacent to the left genu of the corpus callosum, one in the right posterior parietal white matter, and another in the left temporal periventricular white matter (Figure 1). Visual evoked potentials were within normal limits. Chest and abdominal computed tomography scans showed no evidence of metastasis, instead, some regression of previously detected lesions was observed. The patient's diplopia developed shortly after the first HiDAC administration (16 g) within the chemotherapy protocol, five days following subsequent treatment with 3x9 mg dexamethasone, vincristine, etoposide, HiDAC, and intrathecal methotrexate-cytarabine-prednisolone. Consequently, the sporadic white matter lesions were attributed to cytarabine-induced toxic leukoencephalopathy. Although high-dose methotrexate was also part of the chemotherapy regimen, the patient did not experience diplopia or any neurological symptoms after methotrexate administration. Therefore, methotrexate was excluded as the likely cause of neurotoxicity. Due to suspected cytarabine-related neurotoxicity, a one-month corticosteroid

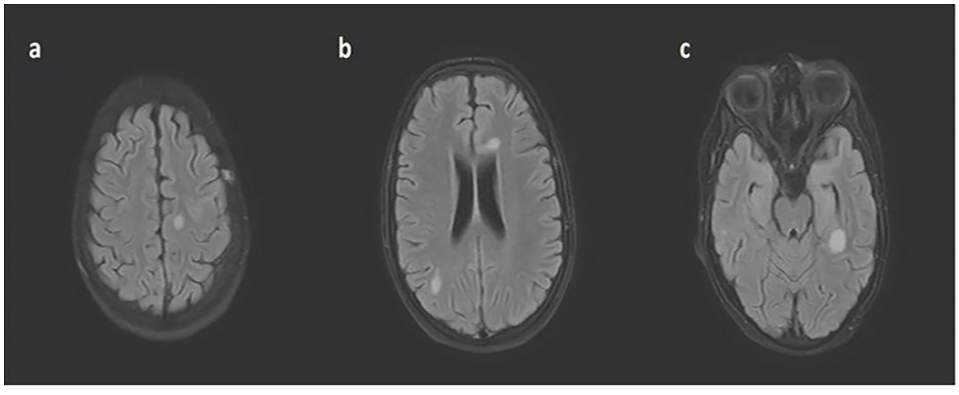

Figure 1. The 13-year-old treated patient diagnosed with Burkitt lymphoma had following lesions present: in the leftparaceptal subcortical area (a), next to the left segment of thecorpus callosum genus (b), in the right posterior parietal area (b) and in the left temporal periventricular white matter (c). The hyperintense lesions detected at FLAIR sequence werefound without significant round shaped edema rings. Thepresence of a corpus callosum lesion firstly raised suspicionfor chemotoxic leukoencephalopathy. The lesions had nopathologic contrast enhancement after the applicated IV contrast material

therapy was initiated. The patient was treated with one gram intravenous methylprednisolone daily for three days, followed by 24 milligrams oral methylprednisolone twice daily, for one week. The steroid dose was gradually tapered each week. During follow-up, the visual field defect in the left eye resolved completely. Cranial MRI at the end of treatment showed near-complete resolution of the lesions (Figure 2).

Discussion

Neuroimaging findings in cases without CNS metastasis during the treatment of extracranial tumors may result from direct chemotherapeutic toxicity, radiation exposure to tissues near the brain, or paraneoplastic effects of the primary tumor. Among these, direct toxicity can particularly manifest as white matter involvement.[4,5]

Several chemotherapeutic agents have been implicated in the development of leukoencephalopathy, including methotrexate, 5-fluorouracil, topotecan, cisplatin, cytarabine, carmustine, and thiotepa.[6-8] Cytarabine is one of the key agents used in the treatment of NHL and acute myeloid leukemia. Neurotoxic side effects such as seizures, ataxia, and in rare cases, death, have been reported following cytarabine administration.[9]

In high-risk NHL treatment protocols, HiDAC is commonly used at a dose of 3 g/m². Neurotoxicity, although rare, is a potentially devastating adverse effect that may present as acute cerebellar toxicity or cerebral dysfunction.[2] In a small cohort study, cases of cerebral toxicity and paraplegia were reported following intravenous HiDAC and intrathecal cytarabine administration.[10] Neurotoxicity typically begins 6 to 8 days after administration of HiDAC and may persist for 3 to 14 days.[2] It is believed that increased levels of cytarabine metabolites in the CNS are responsible for this toxicity.[3]

Pathologically, the loss of Purkinje cells in the cerebellar hemispheres and vermis has been identified as a hallmark of cytarabine-induced neurotoxicity. Additionally, peripheral neuropathy may result from direct cytotoxic effects on axonal and myelin metabolism.[3,11,12] Several cases in the literature describe successful treatment of cytarabine-induced neurotoxicity either through discontinuation of the drug, plasmapheresis, or corticosteroid therapy alone.[13] In a case series published by Dotson and Jamil[14], two patients who developed neurotoxicity after HiDAC were successfully treated with corticosteroids.

In our case, CNS metastasis was initially considered, as the patient developed diplopia five days after receiving a chemotherapy regimen including HiDAC. However, CSF cytology obtained via intrathecal therapy revealed no malignant cells. Given this, cerebral diffusion MRI was performed, which revealed leukoencephalomalacic lesions suggestive of chemotherapy-related toxicity rather than metastatic disease.

When evaluating the chemotherapy protocol for drug-induced neurotoxicity, cytarabine was identified as the causative agent, as the patient developed diplopia only after receiving HiDAC. The patient was treated with pulsed intravenous methylprednisolone for three days, followed by gradual tapering. A follow-up cerebral MRI at the end of one month showed more than 90% regression of the lesions, and the normalization of the visual field. The resolution of diplopia and imaging findings strongly supports the efficacy of corticosteroid therapy in treating cytarabine-induced neurotoxicity.

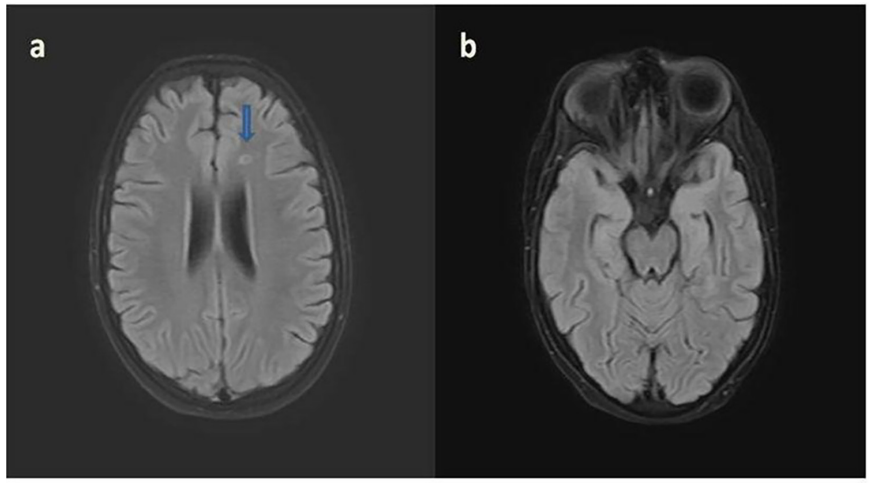

Figure 2. The lesion at the left frontal anterior periventricular white tissue with a cystic encephalomalasy at the center (arrow) had retrieved greatly after the application (a). Other white tissue lesions could not be elected apart at the current examinations (b)

To the best of our knowledge, this case has no direct equivalent in the current literature. It represents the first pediatric case of drug-induced neurotoxicity from cytarabine successfully treated with corticosteroids. Previously reported cases involved only minor white matter lesions.[14] In contrast, our patient exhibited multiple, widespread MRI-documented lesions, with complete clinical and radiological recovery.

Conclusion

In conclusion, this case highlights a rare but critical complication of HiDAC and demonstrates the potential of corticosteroids as an effective treatment option for cytarabine-induced neurotoxicity in pediatric patients. As such, it adds valuable insight to the existing literature and may serve as a reference for managing similar complications in future cases.

Ethics

Informed Consent: Written informed consent was obtained from the patient's legal guardian for the publication of this case report.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.K.K.G., C.A., T.K.G., N.Y., S.K., Concept: M.K.K.G., N.Y., Design: M.K.K.G., T.K.G., N.Y., Data Collection or Processing: M.K.K.G., N.Y., Analysis or Interpretation: M.K.K.G., T.K.G., N.Y., Literature Search: M.K.K.G., T.K.G., N.Y., Writing: M.K.K.G., T.K.G., N.Y.

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Case Report / Olgu Sunumu

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Serotonin Syndrome in a Toddler from Sibutramine Adulterant

Sibutramin Adulteran Nedeniyle Bir Çocukta Serotonin Sendromu

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Abstract

Serotonin syndrome (SS) is a rare yet potentially life-threatening condition resulting from excessive serotonin activity in the nervous system. This case report describes a 3-year-old girl who developed severe agitation and chorea following the accidental ingestion of three tablets of slymochoco, an unregulated dietary supplement containing sibutramine—a banned serotonin-norepinephrine reuptake inhibitor. The child presented with agitation, hypertonia, and generalized involuntary movements eight hours post-ingestion. Emergency treatment included intravenous diazepam, followed by oral chloral hydrate, leading to gradual symptom resolution within 48 hours. Sibutramine toxicity in children is uncommon, but can present SS with neuromuscular abnormalities, autonomic dysregulation, and altered mental status. Pediatric SS presents diagnostic challenges due to variability in symptoms, requiring vigilant assessment for neuromuscular findings such as clonus and hyperreflexia. Supportive care, including benzodiazepines for agitation, forms the cornerstone of management, whereas cyproheptadine may be used in severe cases. This case underscores the diagnostic challenges of SS in children, exacerbated by the continued presence of sibutramine in unregulated slimming agents. Clinicians should inquire about herbal and unregulated weight loss products when evaluating pediatric patients with unexplained autonomic or neuromuscular symptoms.

Keywords: Serotonin syndrome, pediatric, chorea, sibutramine toxicity

Öz

Serotonin sendromu (SS), sinir sisteminde aşırı serotonin aktivitesinden kaynaklanan nadir ancak potansiyel olarak yaşamı tehdit eden bir durumdur. Bu olgu raporu, yasaklanmış bir serotonin-norepinefrin geri alım inhibitörü olan sibutramin içeren, düzenlenmemiş bir besin takviyesi olan slymochoconun üç tabletini kazara yuttuktan sonra şiddetli ajitasyon ve kore gelişen 3 yaşındaki bir kız çocuğunu tanımlamaktadır. Çocuk, ilacı yuttuktan sekiz saat sonra ajitasyon, hipertoni ve genel istemsiz hareketler sergilemiştir. Acil tedavi, intravenöz diazepam ve ardından oral kloral hidrat uygulanmasını içermekteydi ve 48 saat içinde semptomların kademeli olarak düzeldiği görüldü. Sibutramin toksisitesi çocuklarda nadir görülür, ancak nöromüsküler anormallikler, otonomik düzensizlik ve değişmiş zihinsel durum ile birlikte serotonin sendromuna yol açabilir. Pediyatrik serotonin sendromu, semptomların değişkenliği nedeniyle tanı koymada zorluklar yaratır ve klonus ve hiperrefleksi gibi nöromüsküler bulguların dikkatli bir şekilde değerlendirilmesini gerektirir. Ajitasyon için benzodiazepinler içeren destekleyici bakım, tedavinin temelini oluştururken, şiddetli olgularda siproheptadin kullanılabilir. Bu olgu, kontrolsüz zayıflama ajanlarında sibutraminin varlığının devam etmesiyle daha da kötüleşen, çocuklarda SS'nin tanı zorluklarını vurgulamaktadır. Klinisyenler, açıklanamayan otonomik veya nöromüsküler semptomları olan pediatrik hastaları değerlendirirken, bitkisel ve düzenlenmemiş kilo verme ürünleri hakkında araştırma yapmalıdırlar.

Anahtar Kelimeler: Serotonin sendromu, pediatrik, korea, sibutramin toksisitesi

Introduction

Sibutramine, a serotonin-norepinephrine reuptake inhibitor, was once widely prescribed for managing obesity. However, its use has been discontinued globally because of significant cardiovascular risks. Despite this, sibutramine is often found as an adulterant in many counterfeit weight-loss products, leading to potential toxic exposures, particularly to vulnerable populations such as children. This report describes a case of

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a 3-year-old child who developed severe agitation and chorea after accidentally ingesting three tablets of the product. This case highlights the critical need for stringent regulatory enforcement, heightened public awareness, and early recognition of serotonin syndrome (SS) to prevent adverse health outcomes.

Case Report

A 3-year-old girl, previously well, was brought to the emergency department by her mother after accidentally ingesting an unregulated dietary supplement (slymochoco) that belonged to the mother. The child consumed three tablets approximately eight hours before presentation. Two hours post-ingestion, the mother noted involuntary movements involving the upper and lower limbs, and smacking of the lips. As the symptoms worsened, the mother immediately sought medical attention. There was no history of fever, vomiting, diarrhea, or seizures. The child was unable to control abnormal movements and had no history of falls or trauma.

On examination, the child was conscious, pink, and not tachypneic, but appeared agitated. Her vital signs were stable, with a blood pressure of 86/56 mmHg, heart rate of 128 bpm, and SpO of 100% on room air. She was afebrile. Neurological examination revealed chorea-like movements of the bilateral upper and lower limbs with hypertonia and normal reflexes. We didn't observe any specific type of rigidity or tremor in this child. Neither ocular clonus nor clonus of the extremities was observed. Other systemic examinations were unremarkable.

Initial blood work revealed no evidence of infection. The full blood count, renal profile, liver function test results, and electrolytes were within normal ranges. Her electrocardiography shows sinus tachycardia. Intravenous diazepam 2.5 mg (0.2 mg/kg) was administered 9 hours post-ingestion in the emergency department to reduce involuntary movements as the child became increasingly restless and agitated. The involuntary movements persisted but decreased in intensity.

While admitted to the ward, the child was initiated on chloral hydrate syrup (regular) 130 mg, TDS (10 mg/kg) to manage her agitation. She was treated conservatively, and the abnormal movements gradually resolved over 48 hours. A urine sample was taken on the day of admission and stored at the hospital laboratory for 48 hours before being sent to the state chemical laboratory for testing. The results of the urine sibutramine tests were negative on day three after admission. By day three, the child was completely symptom-free and able to sleep throughout the night. She was discharged in good condition. The child's parents permission was obtained for publication of this case.

Discussion

SS is a potentially life-threatening condition caused by excess serotonin in the nervous system, often due to drug ingestion. It presents with a triad of symptoms: Altered mental status, autonomic dysregulation, and neuromuscular abnormalities. While SS is well documented in adults, cases in children are rare. However, a recent literature review revealed that the prescription of selective serotonin reuptake inhibitors is on the rise due to an increase in pediatric mental health issues.[1]

Symptoms of SS can vary widely among pediatric patients, with some children exhibiting mild symptoms such as restlessness and others presenting with severe complications such as rhabdomyolysis and seizures. The most common presenting symptoms are confusion, agitation, tachycardia, hypertension, hyperreflexia, rigidity, and tremor.[1] None of the patients presented with involuntary movement. In a case described by Phan et al.,[2] a single 50 mg dose of sertraline triggered SS in a child, underscoring the heightened sensitivity of pediatric populations to serotonergic agents.

Sibutramine overdose is rare but potentially severe, especially in children. Its clinical presentation often mimics SS, with symptoms such as tachycardia, hypertension, agitation, and hyperthermia. In a report by Bucaretchi et al.,[3] a 4-year-old girl exhibited severe agitation, hallucinations, and autonomic dysfunction after ingesting a significant amount of sibutramine. Another case highlighted psychomotor disturbances and chorea-like movements following sibutramine ingestion in a 26-year-old woman. She responded well to haloperidol therapy.[4] Although this case did not meet the Hunter Criteria due to the absence of clonus or hyperreflexia, the clinical picture remained highly suggestive of SS, particularly in the pediatric population where atypical presentations are documented. The presence of chorea-like movements further complicated the assessment, as it may obscure or mimic classic neuromuscular findings such as clonus or tremor, which are key components of diagnostic criteria like the Hunter Criteria.

The management of sibutramine toxicity focuses on supportive care and symptom control. The initial steps include stabilizing the airway, breathing, and circulation, followed by interventions to manage agitation and autonomic symptoms. Benzodiazepines are commonly used to control agitation and seizures, whereas cyproheptadine, a serotonin antagonist, can be effective in cases of SS. In cases described by Bucaretchi et al.,[3] symptomatic treatment included sedation to manage severe agitation and hypertension. Our patient was managed with benzodiazepines to alleviate her agitation. In this case, while benzodiazepines are the standard first-line agents for managing agitation in SS, chloral hydrate was used to manage the child's persistent restlessness. This decision was influenced by several contextual factors. Firstly, SS is rare

in the pediatric population, contributing to limited clinical familiarity among treating physicians. Additionally, local practice in our setting commonly advocates the use of chloral hydrate as an oral sedative in pediatric patients, particularly when intravenous sedation is not immediately necessary. Given the child's stable cardiorespiratory status and the need for a sedative with a predictable oral administration profile in a non-intensive care unit setting, chloral hydrate was deemed a practical and safe interim measure.[5] The patient's favorable clinical course and resolution of symptoms within 48 hours further supported the appropriateness of this individualized, context-specific management approach. Cyproheptadine is indeed recognized as a safe and effective oral serotonin antagonist in managing mild-to-moderate SS. However, in our setting, cyproheptadine is not readily available in the state hospital formulary, limiting its accessibility for acute use. Additionally, given the child's stable vital signs and progressive improvement following benzodiazepine administration and supportive care, we opted for close clinical observation rather than escalation to cyproheptadine. The decision was based on the mild-to-moderate severity of symptoms, the absence of complications such as hyperthermia or severe autonomic instability, and the child's favorable trajectory within 48 hours. While cyproheptadine may have been a therapeutic consideration under different circumstances, our conservative approach was guided by resource availability and clinical response.

The long-term effects of sibutramine ingestion in children are not well documented. Waszkiewicz et al.[6] reported that sibutramine exposure could trigger manic episodes in predisposed individuals, highlighting the need for careful psychiatric evaluation in affected children.

Diagnostic confirmation often involves urine toxicology testing for sibutramine and its active metabolites, mono-desmethylsibutramine and di-desmethylsibutramine. Sibutramine has a short half-life of approximately 4 hours. Active components such as desmethylsibutramine are metabolized within 24-48 hours of ingestion.[7] Some urine tests for sibutramine levels are designed to detect only certain metabolites and have lower limits of detection. A study utilizing gas chromatography/mass spectrometry reported limits of detection for sibutramine metabolites in the range of 10 to 50 ng/mL, indicating that concentrations below this threshold might not be reliably identified.[7] Another reason for obtaining negative results is improper handling of samples. Delays in testing or improper storage can also lead to the degradation of detectable substances, resulting in false-negative findings. Gastric decontamination with activated charcoal may be considered if ingestion occurs within a short timeframe, although its efficacy diminishes over time.[8]

The recurrent adulteration of unregulated weight loss products with sibutramine presents a critical public health threat, necessitating urgent intervention. Raising awareness among both the public and healthcare professionals about the associated cardiovascular and neurological risks is imperative. Strengthening regulatory frameworks and enforcement mechanisms is essential to curtail the distribution of counterfeit slimming agents. Clinicians should maintain a high index of suspicion for the use of herbal or unregulated weight loss products when assessing pediatric patients with unexplained autonomic or neuromuscular dysfunction, ensuring timely diagnosis and intervention.

Conclusion

This case highlights the ongoing public health risk posed by counterfeit weight loss products adulterated with sibutramine, a serotonin-norepinephrine reuptake inhibitor which was withdrawn due to its cardiovascular risk. Despite SS's rare occurrence in children, it should be considered in cases of unexplained neurologic and autonomic symptoms, with early recognition and supportive management being crucial. This case underscores the limitations of toxicology testing, the need for thorough clinical evaluation, and the importance of strengthening regulatory measures to prevent the distribution of such harmful products.

Ethics

Informed Consent: Informed consent was obtained from the patient's parents.

Footnotes

Authorship Contributions

Concept: S.M., D.G.B., M.K., K.A.B., Design: S.M., D.G.B., M.K., K.A.B., Data Collection or Processing: S.M., D.G.B., M.K., K.A.B., Analysis or Interpretation: S.M., D.G.B., M.K., K.A.B., Literature Search: S.M., D.G.B., M.K., K.A.B., Writing: S.M., D.G.B., M.K., K.A.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report / Olgu Sunumu

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Recognizing and Managing Life-threatening Toxicity in Pediatric Baclofen Poisoning: A Case Report

Pediyatrik Baklofen Zehirlenmesinde Hayati Tehlike Arz Eden Toksisitenin Tanınması ve Yönetimi: Bir Olgu Sunumu

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Abstract

Baclofen is a GABA-β receptor agonist used to treat spasticity, and its rising recreational use has led to increased reports of intoxication. Overdose may cause central nervous system depression, coma, seizures, and respiratory depression. This case report describes a case of accidental baclofen intoxication in a 2-year-old boy with a history of neonatal encephalopathy. A 2-year-old boy presented to the emergency department with sudden-onset drowsiness one hour after his sister suspected accidental ingestion of baclofen syrup (10 mg/mL) prescribed to his bedridden mother. The child was found holding the bottle, which was missing approximately 25% of its contents, suggesting an estimated ingestion of 300 mg, nearly 66 times the maximal daily pediatric dose. Upon arrival at the hospital, three hours post-ingestion, the patient was unresponsive with a Glasgow Coma score of 6, requiring emergency intubation. He was also noted to be bradypneic, bradycardic, hypotensive, and hypothermic with constricted and unreactive pupils, generalized hypotonia, and areflexia. Laboratory tests were largely unremarkable except for hypokalemia. An electrocardiogram showed bradycardia with a prolonged QTc interval. The patient's treatment was primarily supportive. After 19 hours of ventilation, he showed significant improvement, regained consciousness, and was successfully weaned off ventilation. He was later discharged without neurological sequelae. This case highlights the importance of considering baclofen overdose in pediatric patients presenting with coma, hypotonia, bradypnea, bradycardia, and hypotension, even with normal kidney function. Diagnosing baclofen toxicity can be challenging as it is not routinely detected in urine toxicology screenings. The case emphasizes the need for caregiver education regarding medication safety and proper storage to prevent unintentional poisoning. Although treatment is

Öz

Baklofen, spastisite tedavisinde kullanılan bir GABA-β reseptör agonistidir ve eğlence amaçlı kullanımının artması, zehirlenme olgularının da artmasına neden olmuştur. Aşırı doz, merkezi sinir sistemi depresyonu, koma, nöbetler ve solunum depresyonuna neden olabilir. Bu olgu raporu, yenidoğan ensefalopatisi öyküsü olan 2 yaşındaki bir erkek çocukta kazara baklofen zehirlenmesi olgusunu anlatmaktadır. İki yaşındaki bir erkek çocuk, yatağa bağımlı annesine reçete edilen baklofen şurubu (10 mg/mL) kazara içtiğinden şüphelenildikten bir saat sonra ani uyuşukluk şikayetiyle acil servise getirildi. Çocuk, içeriğinin yaklaşık %25'i eksik olan şişeyi elinde tutarken bulundu. Bu da tahmini 300 mg'lik bir alım olduğunu ve bu miktarın pediyatrik maksimum günlük dozun yaklaşık 66 katı olduğunu gösteriyordu. Hastaneye vardığında, ilacı aldıktan üç saat sonra, hasta Glasgow Koma skoru 6 ile tepkisizdi ve acil entübasyon gerektiriyordu. Ayrıca bradipneik, bradikardik, hipotansif ve hipotermi ile birlikte daralmış ve tepkisiz göz bebekleri, genel hipotoni ve arefleksi olduğu da kaydedildi. Laboratuvar testleri, hipokalemi dışında büyük ölçüde normaldi. Elektrokardiyogramda QTc aralığı uzamış bradikardi saptandı. Hastanın tedavisi öncelikle destekleyiciydi. On dokuz saatlik ventilasyonun ardından, hasta önemli ölçüde iyileşme gösterdi, bilincini geri kazandı ve ventilatörden başarıyla çıkarıldı. Daha sonra nörolojik sekeli olmaksızın taburcu edildi. Bu olgu, böbrek fonksiyonu normal olsa bile koma, hipotoni, bradipne, bradikardi ve hipotansiyon ile başvuran pediyatrik hastalarda baklofen doz aşımının göz önünde bulundurulmasının önemini vurgulamaktadır. Baklofen toksisitesinin teşhisi, idrar toksikoloji taramalarında rutin olarak tespit edilmediği için zor olabilir. Bu olgu, kaza sonucu zehirlenmeleri önlemek için ilaç güvenliği ve uygun saklama koşulları konusunda bakım verenlerin eğitilmesinin

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mainly supportive, this case adds to the growing body of literature on pediatric baclofen toxicity and the potential for good outcomes with timely intervention.

Keywords: Drug overdose, central nervous system, GABA agonists, baclofen

önemini vurgulamaktadır. Tedavi esas olarak destekleyici olsa da, bu olgu pediyatrik baklofen toksisitesi ve zamanında müdahale ile iyi sonuçlar elde edilme olasılığı konusunda giderek artan literatüre katkıda bulunmaktadır.

Anahtar Kelimeler: İlaç aşırı dozu, merkezi sinir sistemi, GABA agonistleri, baklofen

Introduction

Baclofen is a GABA-β receptor agonist that reduces excitatory neurotransmitter release, causing muscle relaxation and central nervous system (CNS) depression. It is used to treat spasticity in multiple sclerosis, spinal cord injuries, cerebral palsy, and stroke; with additional off-label uses, for alcohol withdrawal, chronic hiccups, and cocaine dependence.[1,2] Rising recreational use has led to increased reports of intoxication.[1] Diagnosing baclofen toxicity in children is challenging due to its rarity, non-specific symptoms, absence from routine toxicology screens, and often unreliable history. These factors leading to potential delays or misdiagnosis. An baclofen overdose may cause coma, seizures, respiratory depression, bradycardia, hypotension, and rhabdomyolysis with severe cases leading to cerebral edema.[1] Treatment is mainly supportive, with hemodialysis, effective, in severe toxicity or renal impairment.[3] We report a case of baclofen toxicity due to accidental ingestion in a 2-year-old boy with normal kidney function presenting with reduced consciousness, respiratory depression, and autonomic dysfunction.

Case Report

A 2-year-old boy with a history of neonatal encephalopathy presented to the emergency department with sudden-onset drowsiness an hour prior to presentation. His eldest sister suspected accidental baclofen ingestion after discovering the medication, which had been prescribed to their bed-bound mother, in his possession. His mother had a postpartum amniotic embolism after delivering him, and had been bedridden ever since. The baclofen syrup (10 mg/mL) was in a 100 mL bottle, which had initially been about half full but was later found to contain only 25% of the syrup. The child was playing alone in the living room when his sister found him sitting on the floor, holding a bottle of baclofen syrup. She observed yellowish residue, consistent with the medication's color, around his mouth. She immediately washed his mouth and gave him water. Two hours post-ingestion, he became drowsy and less active, prompting urgent hospital transport.

During transport, he had two episodes of vomiting. Otherwise, he had no seizures, abnormal movements, cyanosis, breathing difficulty, diarrhea, abdominal pain, haematemesis, melaena, sweating, rashes, and bowel or urinary incontinence. Prior to the incident, there was no recent or preceding head trauma or clinical signs and symptoms suggestive of meningitis.

The patient was born at 38 weeks via a perimortem cesarean section following a maternal cardiac arrest due to an amniotic embolism. He had a poor Apgar score and required resuscitation at birth. Consequently, he was diagnosed with neonatal encephalopathy and underwent therapeutic hypothermia. He was discharged on day 8 of life with normal neurology. Serial magnetic resonance imaging (MRI) of the brain showed a small subdural collection with no evidence of hypoxic-ischaemic encephalopathy. His mother had been bedridden since the postpartum period. The patient has had no further admissions to the hospital after that incident. This was his first accidental medication ingestion. His immunisations were up to date for his age.

At his latest follow-up, the main developmental concern was delayed expressive speech, as he could only say one meaningful word, "*baba*." However, his receptive language was appropriate; he could follow commands, identify six body parts, and use gestures to communicate needs. A hearing test two months ago showed normal bilateral hearing, and the audiologist referred him to speech therapy. His gross and fine motor skills were age-appropriate; he could walk, run, climb stairs with support, kick and catch a ball, scribble in circles, and turn book pages. Socially, he could put on slippers, eat with his hands, drink from a cup, pull off his pants, but not put them back on, stay dry during the day, and play with his cousin. No other developmental concerns were noted, and he was otherwise thriving well.

There was no significant family medical or psychiatric history, and no history of self-harm or prior accidental ingestion. Medications were usually stored safely, but the baclofen syrup was unintentionally left in the living room. There was no risk of exposure to illicit drugs, alcohol, or household poisons, and no recent family stressors. His eldest sister, aged 18 years, was his primary caretaker. The father was the sole breadwinner for the family.

Upon arrival at the hospital, three hours post-ingestion, the patient was unresponsive with a Glasgow Coma score of 6 (E1V1M4) and required emergency intubation. He was noted to be bradypnoeic, bradycardic, hypotensive and hypothermic. There were no peculiar breath odor, perioral burns, or drooling. His pupils were constricted and unreactive to light.

Neurological assessment showed generalized hypotonia and areflexia, with no focal deficits or meningeal signs. Fundoscopy was normal with no papilledema or hemorrhages. The rest of the systemic examination was unremarkable.

Laboratory tests, including full blood count, renal profile, and liver function tests were largely unremarkable except for hypokalemia. A venous blood gas was performed on arrival to the emergency department to evaluate respiratory depression, metabolic acidosis, and electrolyte and lactate levels, with results within the normal range (pH: 7.34, HCO_3: 24.8 mmol/L, lactate: 1.8 mmol/L). This suggests a compensated or borderline acid-base status, likely normal or mildly compensated respiratory acidosis. Routine urine toxicology screening was negative, and serum baclofen levels were not available in our setting. A summary of his initial laboratory investigations is shown in Table 1. An electrocardiogram (ECG) showed bradycardia with a prolonged QTc interval.

The patient was transferred to the general ward and gradually recovered. After 19 hours of mechanical ventilation, the patient showed significant improvement and was hemodynamically stable. He regained consciousness rapidly and was successfully weaned off ventilation. While reflexes remained suppressed, muscle tone normalized, and power was normal in all limbs. He was later discharged without neurological sequelae.

Discussion

Baclofen is rapidly absorbed, reaching peak serum levels within 2 hours.[4,5] Approximately 69-85% is excreted unchanged in urine, while 15% is metabolized by the liver.[4] Its moderate lipophilicity allows it to cross the blood-brain barrier, leading to CNS depression at high doses.[5] The half-life ranges from 2-6 hours for oral baclofen and 5-6.8 hours for intrathecal administration.[1] It appears in urine within 2 hours and remains detectable for up to 48 hours in individuals with normal kidney function.[1]

Therapeutic serum levels range from 80 to 400 mg/mL, with severe toxicity in adults usually occurring above 200 mg/mL.[1] However, in children, there is no clear correlation between the dose and the severity of symptoms and the requirement for ventilation.[1] The typical adult dose starts at 5 mg three times daily, with a maximum of 80 mg/day, while pediatric dosing is weight-based (0.3 mg/kg/day for neurological disorders) with a maximum of 1.5-2 mg/kg per day or 80 mg.[6] In this case, the patient was estimated to have ingested a maximum of 300 mg of baclofen, assuming consumption of about 30 mL, or a quarter of a 100 mL bottle (10 mg/mL). The patient's weight was around 15 kg, which meant that the estimated ingested dose was 20 mg/kg, nearly 66 times the maximal daily dose. The upper limit of the dose was considered due to uncertainty about the initial volume, as reported by the caretaker.

This patient presented with coma, hypotonia, areflexia, bradypnea, bradycardia, and hypotension, consistent with baclofen toxicity, which typically manifests within 2-6 hours of ingestion.[1-3,7] Symptoms include respiratory depression, flaccidity, hyporeflexia, hypothermia, seizures, and autonomic disturbances. Autonomic dysfunction may manifest as bradycardia or tachycardia, hypo- or hypertension, and miosis or mydriasis.[7,8]

Cardiac abnormalities like arrhythmias, prolonged QTc, and conduction defects may occur, along with hallucinations (mostly in chronic users) and rhabdomyolysis.[2] Due to baclofen's proconvulsant nature, seizures often occur, but they

Table 1: Summary of initial blood results

Test	Parameter	Result	Normal range	Interpretation
Full blood count	Hb	12 g/dL	11.5-17.0 g/dL	Normal
	WBC	12.2 K/uL	6.0-17.5 K/uL	Normal
	HCT	35.4%	35-54%	Normal
	PLT	215 K/uL	150-400 K/uL	Normal
Renal profile	Na^+	142 mmol/L	135-148 mmol/L	Normal
	K^+	2.9 mmol/L	3.5-5.2 mmol/L	Hypokalemia
Liver function	Total serum bilirubin	0.9 µmol/L	<21 µmol/L	Normal
	AST	18 u/L	5-50 u/L	Normal
	ALT	16 u/L	10-49 u/L	Normal
	ALP	268 u/L	150-420 u/L	Normal
VBG	pH	7.34	7.35–7.45	Slightly acidic
	HCO_3-	24.8 mmol/L	22–26 mmol/L	Normal
	Lactate	1.8 mmol/L	0.5–2.2 mmol/L	Normal

VBG: Venous blood gas, Hb: Hemoglobin, WBC: White blood cell, Hct: Hematocrit, Plt: Platelet count, Na^+: Sodium, K^+: Potassium, AST: Aspartat aminotransferaz, ALT: Alanin aminotransferaz, ALP: Alkalen fosfataz, HCO_3-: Bicarbonate

are generally brief and responsive to treatment.[2] Severe cases can lead to prolonged coma and absent brainstem reflexes, mimicking brain death.[1] Thus, baclofen overdose should be considered in patients with acute unexplained CNS depression, reduced reflexes, seizures, and autonomic instability.

de Marcellus et al.[1] compared 10 reported cases of pediatric baclofen overdose, involving patients aged 1 to 17 years who ingested doses ranging from 20 mg to 2250 mg. The most commonly reported symptoms included coma, hypotonia, hyporeflexia, bradycardia, seizures, hypotension, and hypothermia; however, baclofen blood concentrations varied widely, from undetectable levels to 2009 ng/mL.[1] Electroencephalogram (EEG) findings, when reported, frequently showed suppressed brain activity or seizure patterns, while computed tomography (CT) scans of the brain were mostly normal, though some revealed cerebral edema.[7]

Treatment predominantly involved ventilatory support, with some cases also receiving activated charcoal, gastric lavage, mannitol, or noradrenaline. Clinical outcomes were generally favorable, with most patients recovering and being discharged within 1 to 12 days, although several required prolonged ventilation support.

The patient in this case had risk factors, including a history of neonatal encephalopathy and speech developmental delay. Some literature suggests baclofen intoxication may lead to cerebral edema due to neurotoxicity, blood-brain barrier disruption, increased vascular permeability, respiratory depression, hypoxia-induced cerebral vasodilation, and autonomic dysregulation, all contributing to elevated intracranial pressure and potential ischemic injury.[2,3] However, cerebral edema remains a rare finding.[1]

Baclofen-induced encephalopathy is more common in patients with end-stage kidney disease or acute kidney failure due to impaired renal excretion, leading to drug accumulation and toxicity.[3,4] Therefore, assessing kidney and liver function is crucial in such cases. In this case, a CT scan or MRI may be considered in view of the severity of neurological complications, which could impact the patient's development. An EEG can aid in diagnosis by revealing reversible slow-wave activity and periodic epileptic discharges, while an ECG helps detect cardiac conduction abnormalities such as prolonged QTc, first-degree heart block, premature atrial contractions, and supraventricular tachycardia.[7]

The management of baclofen toxicity is primarily supportive, with gastric lavage and activated charcoal recommended for ingestions exceeding 5 mg/kg.[1,2] Stabilization focuses on airway, breathing, and circulation, with intubation and respiratory support as needed.[1,2] While no specific antidote exists, physostigmine may help with central side effects like somnolence and respiratory depression, though its effectiveness varies.[2] Intravenous atropine may improve cardiac output, bradycardia, ventilation, and temperature regulation.[2,7]

Patients with renal impairment may benefit from hemodialysis, a form of extracorporeal removal, but this effect was not previously documented in children with normal kidney function.[1-3] However, in a reported case of a 6-year-old boy suspected of ingesting 1300 mg of baclofen-one of the highest recorded pediatric doses-despite normal kidney function, hemodialysis was performed because of worsening clinical status and high serum baclofen levels (4 µg/mL, therapeutic range: 0.08-0.4 µg/mL).[3] The treatment proved effective, suggesting hemodialysis may be considered in severe cases, though further research is needed.[3] Overall, supportive care typically results in good outcomes if no hypoxic or ischemic injury occurs. Additionally, no pediatric deaths from baclofen overdose have been reported.[1,2]

This case emphasizes the need to consider baclofen overdose in patients with coma, hypotonia, bradypnea, bradycardia, and hypotension, especially when caregiver history is unavailable. Diagnosing baclofen toxicity is challenging due to its rarity and absence in routine toxicology tests. Clinicians should suspect drug overdose in pediatric cases, particularly in suspected child abuse or neglect. Recognizing its clinical presentation is essential for timely diagnosis, effective management, and better patient outcomes. A notable limitation in this case is the absence of neuroimaging and EEG, which may have provided further diagnostic clarity. Beyond clinical management, this case underscores the need for broader preventive strategies. These include establishing a centralized poison control center to support healthcare providers in toxicology-related cases and implementing structured caregiver education on medication safety-emphasizing the risks of accidental ingestion, adverse effects, and the importance of secure storage.

Ethics

Informed Consent: Informed consent for the publication of this case report was obtained from the patient's father.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.D.H.S., A.M.K., Concept: A.M.K., Design: N.D.H.S., A.M.K., Data Collection or Processing: N.D.H.S., A.M.K., Analysis or Interpretation: N.D.H.S., A.M.K., Literature Search: N.D.H.S., A.M.K., Writing: N.D.H.S., A.M.K.

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Robert H. Bartlett (1939-2025): The Visionary who Gave Critically Ill Children a Second Chance

Robert H. Bartlett (1939-2025): Kritik Hasta Çocuklara İkinci Bir Şans Veren Vizyoner

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With great sadness, the global critical-care community mourns the loss of Dr. Robert H. Bartlett, who died October 20, 2025, at age 86.[1,2] Long hailed as "the father of extracorporeal membrane oxygenation (ECMO)", Dr. Bartlett revolutionized modern intensive care when he successfully used technology to keep patients alive long enough to recover from injuries and diseases that in the past would have been beyond hope. His work has saved tens of thousands of newborns, children, and adults worldwide who could otherwise have been considered beyond salvation.[3]

Pioneer who Redefined the Boundaries of Life Support

Born in Oklahoma City in 1939, Robert H. Bartlett received training as a surgeon at the University of Michigan, where he would spend much of his professional life. In the 1970s he began to explore the concept of prolonged extracorporeal oxygenation as a bridge to recovery in patients suffering from reversible respiratory failure. His success in 1975 with "Baby Esperanza" the first long-term neonatal ECMO survivor, marked a historic turning point in critical care.[4,5] When survival from severe respiratory failure was all but unimaginable, Bartlett's work inspired a generation of clinicians to reimagine what could be accomplished through perseverance and compassion.

The publication of his early clinical series in the Journal of Thoracic and Cardiovascular Surgery laid the scientific foundation for what would later evolve into a global therapeutic movement. In 1989, he founded the Extracorporeal Life Support Organization (ELSO), which provided an international framework for data collection, quality improvement, and training that continues to guide ECMO practice today.[3,4]

Impact on Pediatric and Neonatal Intensive Care

Of all his vast contributions, perhaps the most significant single contribution of Dr. Bartlett has been in the field of pediatric and neonatal critical care. Prior to ECMO, mortality from neonatal respiratory failure or congenital diaphragmatic hernia exceeded 80 percent. After the introduction of Bartlett's technique, survival rates improved dramatically, first in specialized centers in the United States and later across Europe and Asia.[5] He insisted that ECMO should not replace clinical judgment but instead extend the window for recovery when conventional ventilation had failed.

In children, ECMO has since become an integral part of rescue therapy in severe acute respiratory distress syndrome, sepsis, myocarditis, and cardiac arrest, and its use has rapidly increased in developing countries, including Türkiye. Many pediatric intensivists remember encountering Dr. Bartlett at ELSO courses or international congresses where his curiosity and humility were as striking as his intellect.[6] He had a unique way of making even the most complex physiology understandable, underlining teamwork, ethics, and compassion as core elements of life-support medicine.

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Mentorship, Philosophy, and Humanism

Beyond the science, Dr. Bartlett represented a philosophy that technology has to be in service of humanity. He would often tell trainees, "Machines don't save lives-people do." Many of his students went on to be leaders in critical-care medicine, establishing ECMO programs across continents. Even in retirement, he continued to teach, write, and advise, never losing the curiosity that had defined his early research.

He authored over 500 scientific papers, 20 book chapters, and his seminal monograph Extracorporeal Life Support: The ELSO Red Book, the cornerstone reference for practitioners worldwide. In 2020, he received the American College of Surgeons' Jacobson Innovation Award for a lifetime of achievements. Yet colleagues will remember him most for his humility: he said repeatedly that the credit should go to the teams standing beside the bedside, not the machines he helped build. A legacy that lives in every circuit.

The passing of Dr. Bartlett reminds us that medical innovation is not just a matter of invention but also one of faith in recovery. Lives saved by ECMO stand as living testaments to his vision that no patient can be considered beyond hope until every avenue has been tried. Hundreds of pediatric intensive care units today prime their ECMO circuits based on direct principles leading from his research laboratory in Ann Arbor.[1,3,6]

For physicians, nurses, and researchers in pediatric critical care, his legacy lives on with every improvement in a child's oxygenation after cannulation, with every chance a family gets to hold their baby. His influence knows no borders or generation.

As we remember Robert H. Bartlett, we recognize not only the pioneer of extracorporeal life support, but the mentor, the humanist, and the teacher who believed that science serves compassion. His vision will continue to breathe through every circuit primed to save a life-and through every clinician who dares to believe that the impossible is worth attempting.

Keywords: Robert H. Bartlett, extracorporeal membrane oxygenation, intensive care

Anahtar Kelimeler: Robert H. Bartlett, ekstrakorporeal membran oksijenasyonu, yoğun bakım

Footnotes

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