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The Journal of Pediatric Academy is the official publication of the Kayseri Child Health Association.

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Journal of Pediatric Academy (JPA) reports on major advances in the diagnosis and treatment of diseases in children. Each issue presents informative original research articles, review articles, case reports, image corners, and letters to the editor from leading clinicians and investigators worldwide.

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Manuscript Types

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Editorial Comment:

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Table 1.
Limitations for each manuscript type

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

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Cite unpublished data—such as papers submitted but not yet accepted for publication and personal communications, including e-mail communications—in parentheses in the text.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

Journal Article:

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

Journal Article published in non-English Languages:

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

Book Chapter:

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

Entire Book:

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

Software:

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

Online Journals:

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

Database:

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

World Wide Web:

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

URL (Uniform Resource Locator)

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

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Journal of Pediatric Academy

Original Article

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Retrospective Evaluation of the Complications and Risk Factors Related to Cardiac Catheterization: Single Center Experience

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Abstract

Cardiac catheterization is an invasive procedure that carries the risk of life-threatening complications. The aim of our study is to evaluate the risk factors and complications of cardiac catheterization procedures performed over a 14-year period at the Department of Pediatric Cardiology, Erciyes University Faculty of Medicine. Complications of 2265 cardiac catheterization procedures in 1880 different patients between September 16, 1995, and December 30, 2009, along with risk factors, were evaluated. Complications occurred in 169 (7.5%) of the 2265 cardiac catheterizations. One hundred and twenty-four (5.5%) were minor and 45 (2%) were major complications. Among 1880 patients, 6 patients (0.31%) died within the first 24 hours. A statistically significant difference was observed between the type of procedure and anesthesia used when comparing minor and major complications. The overall complication rate was 12.9% in patients under one year of age, 11.3% in the cyanotic heart disease group, 8.7% in therapeutic procedures, and 10.9% in patients with a body weight of less than 10 kg. Retrospective studies examining risk factors and complications in cardiac catheterization procedures will provide insights for prospective studies.

Keywords: Cardiac catheterization, complication, risk factors

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Introduction

Cardiac catheterization is a technique in which a catheter is inserted into a peripheral vessel and guided into the heart chambers, and large blood vessels. This allows for the measurement of oxygen saturation in blood samples and the assessment of pressure levels in these regions[1,2]. It is used for determining the heart's anatomy, assessing the presence and size of shunts, measuring pulmonary vascular resistance, evaluating the response to vasodilators and oxygen, monitoring postoperatively, conducting myocardial biopsy and electrophysiological studies, as well as performing transcatheter ablation and therapeutic procedures[1,2].

Highlights

- Increasing number of cardiac catheterizations are being performed today, and complications related to catheterization develops unavoidable.
- The complication rates were found to be higher in therapeutic procedures, cyanotic congenital heart diseases, children under one year of age and weighing less than ten kg in our study.
- Retrospective studies focusing on risk factors will provide guidance for prospective studies.

Cardiac catheterization is an invasive procedure that carries complications, both major and minor, which can occur during or after the procedure. Complications may be related to patient-dependent and/or patient-independent risk factors. Arrhythmias, vascular complications, neurological complications, vasovagal reactions, cardiac perforation, phlebitis, infection, fever, hypertension, and allergic reactions are some of the complications[3-6].

The complication rate after diagnostic catheterization is shown as 4.1-19% in some studies[7-9]. Several studies have demonstrated that the rate of complications is higher in therapeutic procedures than in diagnostic procedures[5,8,10,11].

Low-weight (<2.5 kg) and younger age (≤7 days) at procedure time; prematurity; associated genetic syndromes; univentricular physiology; and high procedure risk category are reported as major risk factors for morbidity and mortality in neonatal age[12].

The aim of this study is to evaluate the risk factors and complications that occurred during and after cardiac catheterization procedures performed over a 14-year period at the Department of Pediatric Cardiology, Erciyes University Faculty of Medicine, and to discuss these findings in the context of the current literature.

Material and Method

Study Design

Risk factors and complications for 2265 cardiac catheterization procedures performed on 1880 different patients at the Department of Pediatric Cardiology, Erciyes University Faculty of Medicine, between September 16, 1995 and December 30, 2009, were evaluated.

The study was approved by the Ethics Committee of Kayseri City Hospital (date: 26.11.2024, approval number: 252/2024).

Definitions of Complications

Complications that are life-threatening, such as respiratory arrest, hemopericardium, hemothorax, cardiac perforation, device migration, and permanent rhythm disturbances were classified as major complications. Complications that do not pose a life-threatening risk, such as circulatory disturbances and temporary rhythm abnormalities, were classified as minor complications.

Deaths that occur during the procedure or within 24 hours after the procedure were considered procedure-related deaths. Complications that were directly related to the procedure, either during or after it, were classified as procedural complications.

Inclusion Criteria

A total of 169 cases that developed complications were included in the study.

Statistical Analysis

Statistical evaluation was conducted using SPSS version 26 (SPSS Inc., Chicago, IL, USA). Histograms, q-q graphs and Shapiro-Wilk normality tests were used to examine whether the data showed a normal distribution. Normally distributed parameters were expressed as mean ± standard deviation; parameters with abnormal distribution were expressed as median minimum-maximum and 25-75p. The chi-square test was used to evaluate non-parametric independent qualitative data in two groups. Mann-Whitney's U-test was used for the difference between two non-parametric quantitative independent groups. A p-value less than 0.05 was considered statistically significant in all statistical analyses.

Results

Among 2265 cardiac catheterizations, 1577 procedures were performed for diagnostic purposes. A total of 294 patients with isolated ventricular septal defect (VSD) and 147 patients with tetralogy of Fallot (TOF) comprised two major groups of the diagnostic study population.

A total of 688 therapeutic procedures were performed. The most frequently performed therapeutic procedures were: 165 valvuloplasty, 123 patent ductus arteriosus (PDA) embolization with coil, 73 PDA closures with amplatzer duct occluder (ADO), 116 atrial septal defect (ASD), and 26 VSD closures with amplatzer septal occluder, 99 angioplasty, 15 aortic coarctation (CoA) correction with stent, and 62 balloon atrial septostomies.

Complications occurred in 169 (7.5%) of the 2265 cardiac catheterizations. 124 (5.5%) were minor and 45 (2%) were major complications. Among 1880 patients 6 patients (0.31%) died within the first 24 hours.

The median age was 6 months (1 day-21 years), and the median weight was 6.6 kg (1.4-76) in patients with complications. Seventy-four (43.8%) of the patients were female and 95 (56.2%) were male. Among the patients, 58 (34.3%) had cyanotic congenital heart disease, and 110 (65.1%) had acyanotic congenital heart disease. One patient (0.6%) had normal cardiac catheterization. One hundred and nine procedures (64.5%) were diagnostic, and 60 procedures (35.5%) were therapeutic. Ninety-seven patients (57.4%) were under 1 year of age, while 72 (42.6%) were over 1 year old.

The total complication rate was 12.9% in cases under one year of age, compared to 5% in cases aged one year and older. The overall complication rate was 11.3% in cyanotic congenital heart disease, compared to 6.7% in acyanotic congenital heart disease.

The overall complication rate was 6.9% in diagnostic cardiac catheterization, while it was 8.7% in therapeutic cardiac catheterization. The total complication rate was 10.9% in cases with a weight less than 10 kg, whereas it was 5.1% in cases weighing 10 kg or more.

Dysrhythmia was detected in 41 (1.8%) cases. Tachycardia developed in 13 cases (0.57%), and complete Atrioventricular (A-V) block in 12 cases (0.52%). Dysrhythmia was most frequently observed in 5 isolated VSD (12.2%), in 4 (9.8%) transposition of great arteries (TGA), and in 4 (9.8%) complex cardiac pathologies.

Respiratory arrest occurred in 16 patients (0.7%) during cardiac catheterization. Respiratory arrest was most frequently observed in TGA (31.3%) and pulmonary stenosis (18.8%).

Cyanotic spells were observed in eight cases. Four of them have tetralogy of Fallot, two have tricuspid atresia, one has complex cardiac pathology, and one has double outlet right ventricle.

Convulsions developed in five cases, cerebral infarct and convulsions in two, transient loss of strength in one case, and hemiparesis in one case. Neurological complications were most frequently observed in cases of isolated CoA or with PDA and VSD (44.4%).

Endocarditis occurred in three patients (1.7%) following the closure of PDA with ADO and after diagnostic cardiac catheterization procedures were performed for conditions such as double outlet right ventricle and CoA.

Chest pain developed in the patient with normal cardiac catheterization (0.6%), who was operated on because of a coronary A-V fistula. Cardiac perforation occurred in one case (0.6%) with pulmonary atresia.

Femoral veins were used for right heart catheterization; femoral arteries were used for left heart catheterization. The most commonly used sheath in patients with complications was 5F (84%). The right femoral vein was the most common used vascular access site in 106 procedures, while the left femoral artery was the fewest vasculer access site with just 30 procedures. Vascular complications were most frequently detected in isolated PDA (18.5%) and TOF (14.8%). Vascular events were found to develop in 32 patients (59.3%) under 1 year of age and in 39 patients (72.2%) weighing under 10 kg. There was no significant difference in the development of vascular complications between patients under and over 1 year of age. Similarly, when patients under 10 kg were compared with patients over 10 kg, the difference was not statistically significant ($p>0.05$).

General anesthesia was applied for ASD and VSD closure procedures. Sedation and superficial anesthesia were applied to all other cases. The most common complication in patients undergoing superficial anesthesia was arrhythmia (23.9%). The most common complication was device migration in patients undergoing general anesthesia (40%).

Statistically significant difference was observed between the type of procedure and anesthesia used when comparing minor and major complications.

The distribution of complications is shown in **Table 1**, and the characteristics of the cases that developed complications and died within the first 24 hours are shown in **Table 2**. Comparison of the variables in patients with complications is shown in **Table 3**.

Management of the Complications

Low molecular weight heparin was given to cases that developed thrombosis. Thrombectomy was performed in one case with TAG. Heparin infusion was administered to patients with circulatory disorders until the clinical vascular symptoms improved. Antiaggregant treatment was given subsequently. The symptoms of cyanotic spells improved with supportive treatment.

After the ASD closing procedure, the device was in the right ventricle in one case, in the aortic arch in one case, and in the pulmonary artery in two cases. The device that migrated to the aorta was captured with a snare catheter

Table 1. *Distribution of complications*

Complication	Major	Minor	Total (%)
Dysrhythmia	9	32	41 (24.3)
Circulatory disturbance	-	24	24 (14.2)
Fever	-	18	18 (10.7)
Respiratory arrest	16	-	16 (9.5)
Bleeding	-	15	15 (8.9)
Neurological complications	4	5	9 (5.3)
Hematoma	-	8	8 (4.7)
Cyanotic spell	-	8	8 (4.7)
Thrombosis	1	6	7 (4.1)
Device migration	6	-	6 (3.5)
Hemopericardium/ hemothorax	4	-	4 (2.4)
Infective endocarditis	3	-	3 (1.7)
Transient hypertension	-	2	2 (1.2)
Pericardial effusion	-	2	2 (1.2)
Flushing	-	2	2 (1.2)
Cardiac perforation	1	-	1 (0.6)
Larynx spasm	-	1	1 (0.6)
Chest pain	-	1	1 (0.6)
Intimal rupture	1	-	1 (0.6)
Total	**45**	**124**	**169 (100)**

and removed from the femoral artery. The devices that migrated to the right ventricle and pulmonary artery were surgically removed. ASDs were also surgically closed.

One patient developed hemiparesis after undergoing correction of CoA with a stent. Monoparesis continued in the left arm during follow-up. Cranial imaging of the patient who developed transient weakness after ASD closure was normal. Strength recovered without sequelae in the follow-up period.

Three patients with complete A-V block were treated with a temporary pacemaker; one patient was treated with a permanent pacemaker.

All of the patients with respiratory arrest were intubated, and among them, six patients died.

The patient who had cardiac perforation underwent surgery but unfortunately died within the first 24 hours.

Discussion

Since cardiac catheterization procedures are invasive, they also carry associated risks. Complications related to cardiac catheterization are influenced by both patient-dependent and independent risk factors. These risk factors include: age, weight, gender, type of procedure, duration of the procedure and fluoroscopy, the severity of the clinical condition, and the experience of the operator[1].

Uysal[3], Vitiello et al.[4], and Bennet et al.[5] reported complication rates of 5.8%, 8.8%, and 9.3%, respectively. The complication rate was 7.5% in our study, and it is consistent with these findings.

The incidence of major complications was found to be 2.3%, 2%, and 1.76% by Yavaş Abalı et al.[10], Vitiello et al.[4], and Mehta et al.[13], respectively. The incidence of major complications in our study, which was 2% is similar to the literature. The frequency of minor complications was found to be 5.5% in our study, which is lower than these three studies. The complication rates were 15.2%, 9.2%, and 7.7%, respectively, in these studies.

Bennett et al.[5] reported the frequency of complications to be 9.3% in diagnostic procedures and 11.6% in therapeutic procedures. The overall frequency of complications was 6.9% in diagnostic procedures and 8.7% in therapeutic procedures in our study.

Uysal[3] reported that the complication rate in patients undergoing catheterization due to cyanotic congenital heart disease was 1.7 times that of the acyanotic group. Similar rates were observed in our study.

Complications such as thrombosis, pseudoaneurysm, dissection, laceration, arteriovenous fistula, bleeding, infection, and distal embolization may occur at the vascular site due to cardiac catheterization[14,15]. The incidence of vascular complications has been shown to be higher in therapeutic procedures, using sheaths larger than 4F in patients weighing less than 4 kg and/or under one month of age[16,17]. Also, longer duration of cardiac catheterization procedures, unplanned access sites, younger age, and smaller body weight are associated with an increased risk of complications[18]. Bansal et al.[19] reported that patients younger than 8 months, and weighing less than 7 kg were found to have a high risk of femoral artery thrombosis due to catheterization.

Table 2. *Characteristics of the cases that developed complications and died within the first 24 hours*

Case	Year	Gender	Diagnosis	Complication
1	9 day-old	M	CoA+VSD	Bradycardia and convulsion
2	20 day-old	F	Pulmonary stenosis	Cardiac arrest
3	7 month-old	F	TGA+PS+VSD+PDA	Respiratory arrest
4	22 day-old	M	TGA	Respiratory arrest
5	16 day-old	M	Pulmonary atresia	Cardiac perforation
6	8 day-old	M	CoA+AS+PDA	A-V block

VSD; Ventricular septal defect, TGA; Transposition of the great arteries, PS; Pulmonary stenosis, PDA; Patent ductus arteriosus, AS; Aortic stenosis, CoA; Coarctation of the aorta, A-V; Atrioventricular

Table 3. *Comparison of the variables in patients with complications*

Variable		Major complication	Minor complication	p
Gender (Female/Male)	**n** **%**	(16/29) (35.5/64.5)	(58/66) (46.8/53.2)	0.194^{x2}
Age	**Median (25-75p)**	5 month (27 day-6.5 years)	6 month (2 month-4years)	0.394^{m}
Weight (kg)	**Median (25-75p)**	5.8 (3.6-17.7)	6.7 (4.6-14.3)	0.502^{m}
Therapeutic/diagnostic	**n** **%**	26/19 (57.8/42.2)	34/90 (27.4/72.6)	**0.000**^{x2}
Cyanotic/acyanotic	**n**	18/27	40/83	0.553^{x2}
Under one year's/over one years	**n** **%**	28/17 (62.2/37.8)	69/55 (55.6/44.4)	0.445^{x2}
Under 10 kg/over 10 kg	**n** **%**	29/16 (64.4/35.6)	82/42 (66.1-33.9)	0.838^{x2}
Superficial/general anesthesia	**n** **%**	39/6 (86.7/13.3)	120/4 (96.8/3.2)	**0.014**^{x2}

χ2; Chi-square test, m; Mann-Whitney U test

50 IU/kg heparin was administered in diagnostic procedures when using venous access; whereas 100 IU/kg heparin was used in therapeutic procedures and administered during arterial access in our study. Despite the use of systemic anticoagulation and the improved techniques and equipment, vascular complications continue to be frequent. In our study, a total of 54 vascular events were observed, including circulatory disorders in 24 patients, bleeding in 15 patients, hematoma in 8 patients, and thrombosis in 7 patients. Vascular events were found to develop in 32 patients (59.3%) under 1 year of age and 39 patients (72.2%) under 10 kg. There was no difference between patients under 1 year of age and over 1 year of age. Similarly, the difference was not statistically significant below and above the 10 kg threshold ($p>0.05$).

Arrhythmias were observed in 41 procedures (1.8%) in our study, which is lower than the studies of Kasar et al.[7] (7%) and Doğan et al.[20] (6.7%). This lower frequency of arrhythmias may be attributed to the fact that transient tachycardia and bradycardia were not included in the reports.

Neurological complications such as convulsions, hemiplegia, intracranial hemorrhage, extrapyramidal side effects, visual and hearing impairments, and brachial plexus injury have been reported[21]. The frequency of neurological complications is reported to be 0.36-6.6%[3,6,10]. Neurological complications, consistent with the literature, were observed in 9 (0.39%) procedures in our study, including convulsions, cerebral infarction, and transient muscle weakness.

Some of the reasons complications develop more frequently in children under 1 year of age and under 10 kg include limited intervention area due to smaller body size, increased hemodynamic instability, complicated heart diseases, and the tendency of critically ill patients to be younger and of lower weight and age.

Yilmazer et al.[22] suggested that younger children (<1 year of age) may experience more complications during cardiac catheterization. Bergersen et al.[23] found that young age (<1 year) is a risk factor for adverse events and is considered independently in the catheterization for congenital heart disease adjustment for risk method. The total complication rate was 12.9% in cases under one year of age, while it was 5% in cases aged one year and older in our study.

Rhodes et al.[24] showed that patient weight <5 kg is a significant risk factor for complications irrespective of the type of procedure performed. Backes et al.[25] reported that the risk of adverse events during cardiac catheterization of infants increases with lower weight. They showed that death occurred more frequently in the subjects weighing less than 2 kg. The total complication rate was 10.9% in cases with a weight less than 10 kg, whereas it was 5.1% in cases weighing 10 kg or more in our study.

Yilmazer and Meşe[26] reported a 10-month-old girl with infective endocarditis who underwent PDA closure with an ADO. She was admitted to the hospital with tachypnoea, fatigue and fever. Fever occurred in our patients after cardiac catheterization; vegetation was detected in the first echocardiographic evaluation. Therefore, catheterization-related infective endocarditis was considered.

Cardiac perforation is a rare complication that can be fatal. McCrossan et al.[27] reported cardiac perforation in 50 out of 36,986 patients (0.14%). They showed that the risk of cardiac perforation is higher in younger patients who undergo emergency and/or interventional procedures. Cardiac perforation occurred in a 16-day-old baby with pulmonary atresia, in our study. Despite surgical intervention, the patient died.

Study Limitations

This study has some limitations. The study was designed as a retrospective, single-center study. This study did not include long-term longitudinal follow-up data on the patients. There is a need for prospective studies in which factors that may reduce the incidence of complications and outcomes of patients are also evaluated. The other limitation of our study is that we do not have any data on the duration of the cardiac catheterization procedure.

Conclusion

The impact of improvements in catheterization techniques, equipment, procedures, patient selection, and preprocedural medical management on catheterization-related morbidity and mortality rates is well known. Retrospective studies focusing on risk factors and complications will provide guidance for prospective studies.

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*This study was prepared using data obtained from a pediatrics thesis in 2010 (Retrospective evaluation of the cases and cardiac catheterization/angiocardiography procedures which were performed in Pediatric Cardiology Department, Medical Faculty of Erciyes University).

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and good clinical practice ethics. The study was approved by the Ethics Committee of Kayseri City Hospital (date: 26.11.2024, approval number: 252/2024).

Footnotes

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

Author Contributions: Soylu Üstkoyuncu P: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Üzüm K: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Literature Search; Narin N: Surgical and Medical Practices, Design; Baykan A: Surgical and Medical Practices, Concept, Design; Onan SH: Surgical and Medical Practices, Data Collection or Processing; Sezer S: Surgical and Medical Practices, Data Collection or Processing.

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References

1. Soylu P. Retrospective evaluation of the cases and cardiac catheterization which were performed in Pediatric Cardiology Department, Medical Faculty of Erciyes University. Pediatric Thesis, 2010. *[CrossRef]*
2. Uçar T, Tutar E. Kalp kateterizasyonunun temel ilkeleri. Çeliker A (editör). Konjenital kalp hastalıklarında girişimsel tanı ve tedavi. Ankara: Erkem Tıbbi Yayıncılık. 2008:9. *[CrossRef]*
3. Uysal Ö. Mayıs 2002-Eylül 2005 tarihleri arasında Dr. Sami ULUS Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi Pediatrik Kardiyoloji bölümünde kardiyak kateterizasyon ve anjiyokardiyografi yapılan hastaların ve komplikasyonların değerlendirilmesi. Uzmanlık tezi, 2006. *[CrossRef]*
4. Vitiello R, McCrindle BW, Nykanen D, Freedom RM, Benson LN. Complications associated with pediatric cardiac catheterization. *J Am Coll Cardiol.* 1998;32:1433-1440. *[CrossRef]*
5. Bennett D, Marcus R, Stokes M. Incidents and complications during pediatric cardiac catheterization. *Paediatr Anaesth.* 2005;15:1083-1088. *[CrossRef]*
6. Ülgen Tekerek N, Aykan HH, Yüksekgönül AÜ, et al. Interventional cardiac catheterization in neonates and premature infants with congenital heart disease: a single center experience. *The Turkish Journal of Pediatrics.* 2023;65:939-948. *[CrossRef]*
7. Kasar T, Tanıdır IC, Öztürk E, et al. Arrhythmia during diagnostic cardiac catheterization in pediatric patients with congenital heart disease. *Turk Kardiyol Dern Ars*. 2018;46:675-682. *[CrossRef]*
8. Mori Y, Nakazawa M, Yagihara T. Complications of pediatric cardiac catheterization and system of catheterization laboratories minimizing complications--a Japanese multicenter survey. *J Cardiol*. 2010;56:183-188. *[CrossRef]*
9. Agnoletti G, Bonnet C, Boudjemline Y, et al. Complications of paediatric interventional catheterisation: an analysis of risk factors. *Cardiol Young.* 2005;15:402-408. *[CrossRef]*
10. Yavaş Abalı Z, Nişli K, Dindar A, Eker R, Aydoğan Ü. Evaluation of complications associated with cardiac catheterization: a single-center experience. *Trends in Pediatrics*. 2022;3:156-162. *[CrossRef]*
11. Bergersen L, Gauvreau K, Jenkins KJ, Lock JE. Adverse event rates in congenital cardiac catheterization: a new understanding of risks. *Congenit Heart Dis.* 2008;3:90-105. *[CrossRef]*
12. Giordano M, Santoro G, Agnoletti G, et al. Interventional cardiac catheterization in neonatal age: results in a multicentre Italian experience. *Int J Cardiol.* 2020;314:36-42. *[CrossRef]*
13. Mehta R, Lee KJ, Chaturvedi R, Benson L. Complications of pediatric cardiac catheterization: a review in the current era. *Catheter Cardiovasc Interv.* 2008;72:278-285. *[CrossRef]*
14. Kaya F, Arslan D, Çimen D, Güvenç O, Oran B. Complications of heart catheterization in children. *Selçuk Tıp Derg.* 2013;29:9-11. *[CrossRef]*
15. Uçar B, Kılıç Z, Karataş Z. Vascular complications belonging to catheter insertion in children who underwent cardiac catheterization. *Turkish J Pediatr Dis.* 2012;6:23-30. *[CrossRef]*
16. Bulbul ZR, Galal MO, Mahmoud E, et al. Arterial complications following cardiac catheterization in children less than 10 kg. *Asian Cardiovasc Thorac Ann.* 2002;10:129-132. *[CrossRef]*
17. Pamukçu Ö, Görkem BS. Femoral vascular complication incidence and possible risk factors of pediatric patients after cardiac catheterization. *J Dr Behcet Uz Child Hosp.* 2017;7:147-151. *[CrossRef]*
18. Roushdy AM, Abdelmonem N, El Fiky AA. Factors affecting vascular access complications in children undergoing congenital cardiac catheterization. *Cardiol Young.* 2012;22:136-144. *[CrossRef]*
19. Bansal N, Misra A, Forbes TJ, Kobayashi D. Femoral artery thrombosis after pediatric cardiac catheterization. *Pediatr Cardiol.* 2021;42:753-761. *[CrossRef]*
20. Doğan E, Gerçeker E, Vuran G, et al. Evaluation of arrhythmia prevalence, management, and risk factors in patients with transcatheter and surgically closed secundum atrial septal defects. *Turk Kardiyol Dern Ars.* 2023;51:50-55. English. *[CrossRef]*
21. Liu XY, Wong V, Leung M. Neurologic complications due to catheterization. *Pediatr Neurol.* 2001;24:270-275. *[CrossRef]*
22. Yilmazer MM, Ustyol A, Güven B, et al. Complications of cardiac catheterization in pediatric patients: a single center experience. *Turk J Pediatr.* 2012;54:478-485. *[CrossRef]*
23. Bergersen L, Gauvreau K, Foerster SR, et al. Catheterization for congenital heart disease adjustment for risk method (CHARM). *JACC Cardiovasc Interv.* 2011;4:1037-1046. *[CrossRef]*
24. Rhodes JF, Asnes JD, Blaufox AD, Sommer RJ. Impact of low body weight on frequency of pediatric cardiac catheterization complications. *Am J Cardiol.* 2000;86:1275-1278, A9. *[CrossRef]*
25. Backes CH, Cua C, Kreutzer J, et al. Low weight as an independent risk factor for adverse events during cardiac catheterization of infants. *Catheter Cardiovasc Interv.* 2013;82:786-794. *[CrossRef]*
26. Yilmazer MM, Meşe T. Infective endocarditis developing early after percutaneous closure of a patent ductus arteriosus in a child using the Amplatzer Duct Occluder II. *Cardiol Young.* 2020;30:591-593. *[CrossRef]*
27. McCrossan BA, Karayiannis S, Shields M, et al. Incidence, predictors, and outcomes of cardiac perforation during pediatric cardiac catheterization: a retrospective observational study from the congenital cardiac interventional study consortium (CCISC). *Pediatr Cardiol.* 2023;44:867-872. *[CrossRef]*

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Effects of a School-based Multicomponent Intervention on the Behavior and Anthropometry of Overweight and Obese Children Aged 10-13 Years-a Randomized Control Trial

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Abstract

Obesity is a growing concern in developing countries and is associated with significant mortality and morbidity in childhood. It is attributed to an interplay of environmental and genetic factors. There is a notable difficulty in addressing the various dimensions of managing obesity and hence a combination of interventions incorporating physical activity, education on healthy lifestyle and family involvement becomes a necessity. We aimed to evaluate the effects of a school-based multicomponent intervention (integrating health education, yoga, and parental involvement) on the anthropometric measures and healthy lifestyle behavior of obese and overweight children aged 10-13 years in Puducherry, India. The study included 120 overweight and obese children aged 10-13 years, in two randomly selected urban schools. The children were then randomized to intervention (60) and control (60) groups. The intervention group received health education classes, Yoga classes by certified yoga trainers and parental counseling for 3 months. The control group received routine counseling. Anthropometric measures such as body mass index (BMI), waist-to-hip ratio (WHR), and healthy lifestyle scoring in three domains (nutrition, physical activity levels, and screen time) were assessed pre- and post-intervention for both groups after 3 months. The intervention group showed significant reduction in BMI ($p=0.017$), WHR ($p=0.003$), and improvement in behavior scores of nutrition ($p<0.001$), physical activity ($p<0.001$), and reduced screen time ($p<0.001$) at 3 months post-intervention. No significant changes were observed in the control group on follow-up after 3 months. Thus, we conclude that a school-based multi-faceted intervention is an effective program in combating childhood obesity. We recommend long-term follow-up studies on these interventions to discern the sustainable results of such interventions.

Keywords: Body mass index, child, health education, pediatric obesity, yoga

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Introduction

Childhood obesity has emerged as a silent epidemic in India and poses significant health risks to the nation's younger population. It is a growing concern necessitating a comprehensive understanding of its prevalence and impact. As per the World Health Organization (WHO), around 390 million children in the age group of 5-18 years were overweight in 2022[1]. Overweight and obesity in childhood occur due to interaction between genetic, behavioral, and environmental factors. Of particular mention include excess calorie intake, especially unhealthy eating behavior and sedentary lifestyle among Indian children. Overweight and obese young children are at an increased risk of developing non-communicable diseases such as insulin resistance, increased blood pressure, deranged lipid profile, obstructive sleep apnea, and various cancers, which can track into adulthood[2]. Additionally, obesity in children and adolescents can lead to liver diseases, early puberty onset, reduced quality of life, psychiatric disorders, asthma, and other respiratory problems[2]. Efforts to combat childhood obesity have been multifaceted, involving policies aimed at promoting healthier environments in schools, homes, and communities. These include initiatives to improve school nutrition, increase physical activity opportunities, and regulate the marketing of unhealthy foods to children. Despite these efforts, challenges persist in addressing childhood obesity comprehensively. The complex interplay of factors contributing to obesity demands holistic interventions involving all levels of childcare. There is a pressing need to promote a healthy lifestyle early and create supportive environments where children can thrive physically and emotionally. Several international studies have focused on varying combinations of behavioral, nutritional, physical activity, and parental interventions on parameters such as body mass index (BMI), waist-to-hip ratio (WHR), eating habits and physical activity[3-5]. A comprehensive strategy that is multilevel, as well as multicomponent, addressing a wide range of issues is a necessity in India. In this setting, we aimed to study the effects of a school-based multicomponent intervention on the anthropometric profile and healthy lifestyle behavior of obese and overweight children aged 10-13 years.

Highlights

- This study examined the effects of a school-based multicomponent intervention encompassing yoga, nutritional education and parental involvement on anthropometry and behavior of children aged 10-13 years with overweight and obesity.
- There was a significant reduction in body mass index (BMI) and waist-to-hip ratio (WHR) in the intervention group at 3 months post-intervention.
- There was also a significant improvement in behavioral scores in the areas of nutrition, physical activity, and screen use in the intervention group at 3 months post-intervention.
- There was no significant change in BMI, WHR and in behavioral scores in the areas of nutrition, physical activity, and screen time in the control group at 3 months follow-up.
- Thus, this study signifies the importance of a multicomponent strategy in managing children with obesity.

Material and Method

Design and Setting

This was an open-label, school based, randomized control trial conducted over a period of 12 months. The study commenced after the Mahatma Gandhi Medical College and Research Institute Institutional Human Ethics Committee approval (no: MGMCRI/Res/01/2021/99/IHEC/135, date: 31.01.2023) and was registered in the Clinical Trials Registry-India (CTRI/2024/07/070695).

Participants

All children aged 10-13 years, with obesity and overweightness (based on the Indian Academy of Pediatrics (IAP) definition)[6], attending urban, private, co-education schools were eligible to participate in the study. Those children with chronic illnesses, dysmorphism, and physical disabilities and those not willing to participate were excluded. Pubertal status assessment was not included in our study protocol, which represents a limitation given the age group studied (10-13 years).

Sample Size Calculation

The sample size was calculated using the formula below, based on observations from a previous RCT[7],

$$n = \frac{2\sigma^2 (Z_{1-\beta} + Z_{1-\alpha/2})^2}{(\mu_1 - \mu_2)^2}$$

Mean and standard deviation (SD) of group 1=22.82 and 1.27, mean and SD of group 2= 23.79 and 1.15, with confidence level of 99%, power of 90%. On applying the formula, n was more than or equal to 47. Adding an attrition of 15%, the sample size in each group was rounded to 60.

Sampling

All the urban private, co-education schools in Puducherry (who do not have yoga classes) were listed down by the investigator in alphabetical order, and amongst these schools two schools were chosen randomly, by lottery method. After getting informed written consent from the concerned school principals, the allocation of these 2 schools to study and control group was done randomly by lottery method. Two chits named study group and control group were put inside a box and the headmistress of one school was asked to pick up a chit and the group allocation was done (study group school and control group school).

Selection of Children

All the children in all the sections in the sixth to ninth class (10-13 years of age) of both the schools were screened for overweight and obesity. From the children screened in both the schools, boys and girls were listed separately. Children were selected in both study and control group by simple random sampling by computer-generated random numbers. Thus, the study group consisted of 60 children and the control group had 60 children. Each group had 30 boys and 30 girls. After receiving informed consent from their school principal and also from their parent and written assent from the student, a baseline data was collected. They then filled a knowledge, attitude, and practices (KAP) questionnaire on the healthy lifestyle behavior. They were subjected to anthropometric measurements such as weight, height, waist, and hip circumference. BMI was calculated by the formula, BMI=weight in kg/(height in m)^2. The BMI was plotted on IAP BMI charts. Based on revised IAP guidelines, overweight and obesity was defined by an adult cut-off of 23 and 27 respectively[6]. Then the study group was subjected to a multicomponent intervention for a period of 3 months, after which the outcome measures were assessed again. The control group was given routine advice for weight reduction (advice on diet and physical activity, as per IAP guidelines)[6] for 15 minutes, at the beginning, and then they were followed up after 3 months. Post-intervention, assessment of behavioral and anthropometric measures in both the groups was done at 3 months.

Primary Outcome Measures

Anthropometric Measurements

The height, weight, waist circumference, and hip circumference were measured by the principal investigator. The following indices were computed: BMI, WHR and BMI Z-scores. BMI Z-scores were calculated using WHO Anthro Plus software based on WHO 2007 growth references (https://cran.microsoft.com/snapshot/2022-01-01/web/packages/anthroplus/index.html). Height and weight were measured to the nearest 0.1 cm and 0.1 kg respectively. Height was measured using a stadiometer (Cambia India, New Delhi, India) and weight was measured using an electronic weighing machine (Omron HN-289-EBK model, Haryana, India). Waist and hip circumference were measured using a non-stretchable inch tape. The same instruments were used for all study participants. The waist circumference was measured midway between the lowest rib and the iliac crest, in mid-expiration and hip circumference was measured at thewidest part of the hip (midway between the greater trochanter and lower buttock level).

Healthy Lifestyle Behavior

A KAP questionnaire were designed to assess healthy lifestyle behavior. This questionnaire included 3 areas, namely: Nutrition, physical activity and media use.

1.Nutrition related KAP - This included frequency of consumption of healthy and unhealthy food, 24-hour diet recall chart was obtained, total calorie intake per day, and nutrition knowledge was assessed. A cup measuring 250 mL was shown to the student to estimate the amount of food consumed.

2. Physical activity KAP - This section included type and duration of physical activity per day, and knowledge on physical activity types.

3.Screen use KAP - This section included screen time per day, types of devices at home, and knowledge on adverse effects of excess screen time.

The questionnaire was pre-tested and internally validated before being used for data collection. Scoring of behavior was done. There were totally 23 questions, with a score of 0-4 for each question (total score: 0-92). Nutrition, physical activity and screen time domains had 11, 7 and 5 questions respectively, with a maximum score of 44, 28, 20 respectively in each domain. For knowledge score, each correct response was given a score of 4 and wrong response was scored 0. For attitude and practice scoring, a five-point scale was given with a score ranging from 0-4 (A=0, B=1, C=2, D=3, E=4). Higher scores indicated better lifestyle behavior. The content was validated by giving the questionnaire to 8 experts based on their experience and clinical expertise. There was 100% agreement on the appropriateness and relevance of the tool. To ascertain reliability, the questionnaire was administered to 15 children. Test retest was done and reliability was established with a reliability coefficient of 0.91 (pearson product moment correlation).

Multicomponent Intervention

A multicomponent intervention was given to the study group for a period of 3 months, comprising of nutritional and lifestyle education, yoga classes, and parental involvement.

1. Nutritional and Lifestyle Education

This intervention was based on the Dietary Guidelines for Indians[8]. The children were given nutritional and lifestyle education for 3 months. They were given one lecture per month, which lasted a 45-minutes session based on the following areas: The basics of food groups, importance of each food group for health, the difference between complex and simple carbohydrates, the concept of empty calories and its sources, the importance of fiber in the diet, promotion of physical activity, and adverse effects of screen time, the importance of adapting these measures as a lifestyle. The lectures were conducted as direct classes by the investigator and certified nutritionists. There was a group discussion at the end of 3 months. Thus, there were a total of 3 lectures and 1 group discussion.

2. Yoga

Yoga classes were given, three times a week, distributed on alternate days (monday, wednesday and friday). Each session lasted for 30 minutes, conducted by a certified yoga trainer and comprised of the following order (each step for 5 minutes):

- Full body warm up
- Surya Namaskara
- Twisting asanas-Trikonasana, vakrasana, ardha matsyendriyasana, parivritta parsvakonasana
- Lying asanas-sarvangasana, bhujangasana, dhanurasana, navasana, naukasana, sethubandhasana

• Abdominal exercises-paschimuttanasana, pavana mukthasana

• Pranayama-kapalabhati, nadishoda pranayama, bramari pranayama

3. Parental Involvement

Parents of children in the intervention group were counseled for 10 minutes telephonically every month on healthy lifestyle practices. They were also provided with an educational booklet at the beginning of the intervention. They were enquired about their child's eating behavior, screen time and physical activity at home at every phone call.

Results

Baseline Characteristics

The study included 60 children each in the study and control group respectively. Both groups had 30 boys and 30 girls. The recruitment and conduct of the study are shown in **Figure 1**. The anthropometric and behavioral profiles of the children in the study and control group at the beginning of the study are depicted in **Table 1**. The behavioral scores, mean age and weight were comparable between both the groups. The BMI and WHR were higher in the control group as compared to study group. The mean height of study group was found to be higher than the control group.

Outcome Analysis

After 3 months following the intervention, the study group showed a significant decrease in BMI and WHR, along with an increase in the KAP scores in the three areas namely, nutrition, physical activity and screen use (**Table 2**). Thus, the intervention was effective in improving the healthy lifestyle behavior of the children in the study group. However, the mean weight did not change significantly. Amongst the children in the study group, the changes in the behavioral scores were consistently showing an increase in boys as well as girls (**Table 3**). But the BMI and WHR showed a significant increase in boys as compared to girls. This signifies the gender difference in the anthropometric parameters with boys improving better than girls following the intervention.

In the control group, there were no significant changes in the anthropometric parameters and behavioral scores following 3 months after intervention (**Table 2**). Similarly, there was no difference between boys and girls in the outcome parameters compared (**Table 4**). Comparison between the study and control groups post-intervention showed significant improvement in all three KAP scores in the study group as compared to control group (**Table 2**). However, the BMI and WHR of control group continued to be higher than the study group pre- and post-intervention (**Table 2**).

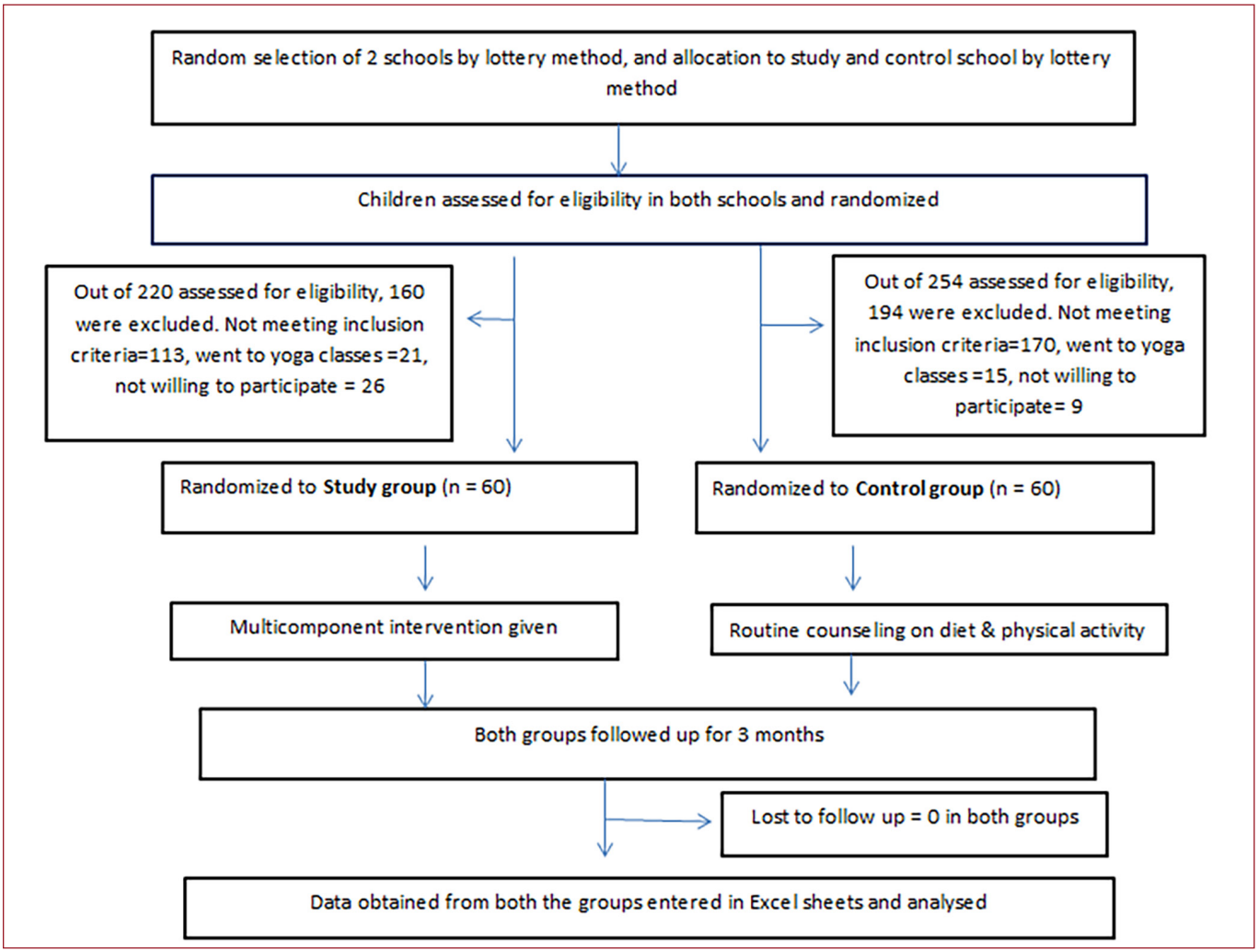

Figure 1. Flow of events in the study

Table 1.
Baseline characteristics of study group & control group

Variable	Study group n=60	Control group n=60	p-value[a]
Age in years, mean (SD)	12.80 (1.20)	12.53 (1.61)	0.614
Males, n (%)	30 (50)	30 (50)	-
Weight in kg, mean (SD)	61.93 (10.06)	60.31 (5.80)	0.284
Height in cm, mean (SD)	159.54 (7.54)	152.16 (7.19)	<0.001
Waist-hip ratio, mean (SD)	0.82 (0.05)	0.89 (0.05)	<0.001
BMI, mean (SD)	24.31 (3.48)	26.02 (1.39)	<0.001
Nutritional KAP score, mean (SD)	23.70 (3.63)	24.62 (3.96)	0.189
Physical activity KAP score, mean (SD)	13.38 (4.88)	13.08 (3.10)	0.689
Screen use KAP score, mean (SD)	10.28 (3.93)	9.40 (3.02)	0.171

[a]; Independent t-test was used, SD; Standard deviation, KAP; Knowledge, attitude, and practices, BMI; Body mass index

Table 2.
Comparison of outcome variables pre-post-intervention, within and between study and control groups

Variable	Study group (n=60)			Control group (n=60)			Post-Intervention comparison between study and control group
	Pre-intervention	Post-intervention	p-value[b]	Pre-intervention	Post-intervention	p-value[c]	p-value[d]
Weight (kg)	61.93 (10.06)	61.90 (9.91)	0.784	60.31 (5.80)	60.60 (5.95)	0.037	0.385
BMI	24.31 (3.48)	24.17 (3.44)	0.017	26.02 (1.39)	26.02 (1.56)	0.957	0.0002
BMI Z-score	2.31 (0.42)	2.28 (0.41)	0.015	2.52 (0.38)	2.53 (0.39)	0.945	0.0009
WHR	0.82 (0.05)	0.81 (0.04)	0.003	0.89 (0.05)	0.89 (0.05)	0.083	0.0001
Nutritional KAP score	23.70 (3.63)	26.45 (3.59)	<0.001	24.61 (3.96)	24.75 (3.41)	0.568	0.0089
Physical activity KAP score	13.38 (4.88)	17.43 (4.76)	<0.001	13.08 (3.10)	13.38 (2.82)	0.293	0.0001
Screen use KAP score	10.28 (3.93)	12.91 (3.44)	<0.001	9.40 (3.02)	9.80 (3.39)	0.172	0.0001

[b,c]; Paired t-test was used, [d]; Independent t-test was used, values are presented as mean (standard deviation), BMI; Body mass index, WHR; Waist-to-hip ratio, KAP; Knowledge, attitude, and practices

Table 3.
Gender-specific comparison of outcome variables pre-post-intervention in study group (n=60)

Variable	Boys (n=30)			Girls (n=30)		
	Pre-intervention	Post-intervention	p-value[e]	Pre-intervention	Post-intervention	p-value[f]
Weight (kg)	59.57 (6.82)	59.53 (6.61)	0.762	64.30 (12.21)	63.63 (11.92)	0.124
BMI	24.77 (2.48)	24.59 (2.46)	0.008	23.87 (3.26)	23.60 (3.31)	0.05
BMI Z-score	2.35 (0.39)	2.31 (0.38)	0.007	2.27 (0.45)	2.25 (0.44)	0.06
WHR	0.81 (0.05)	0.80 (0.05)	0.01	0.84 (0.04)	0.84 (0.04)	0.05
Nutritional KAP score	23.75 (3.45)	26.45 (2.96)	<0.001	23.50 (3.55)	25.26 (3.19)	<0.001
Physical activity KAP score	11.86 (3.52)	15.03 (3.42)	<0.001	15.10 (4.95)	18.17 (4.45)	<0.001
Screen use KAP score	9.68 (4.15)	12.65 (4.24)	<0.001	10.23 (3.97)	13.26 (3.06)	<0.001

[e,f]; Paired t-test was used, values are presented as mean (standard deviation), BMI; Body mass index, WHR; Waist-to-hip ratio, KAP; Knowledge, attitude, and practices

Discussion

The prevalence of childhood obesity is on the rise in India, which is on par with the global trends.[9] It becomes a necessity to devise effective interventions for the same. Overweight and obesity in young people are attributable to a combination of factors such as genetics, nutritional, metabolic, behavioral, environmental, and socioeconomic influences. This study investigated the effects of a school-based multifaceted intervention on the anthropometry and healthy lifestyle behavior of obese and overweight children aged 10-13 years. The findings revealed a significant decrease in BMI (p=0.017) and WHR (p=0.003) in the study group at 3 months post-intervention. The study group also revealed a significant increase in the scores in the KAP areas of nutrition, physical activity, and screen use. There was no significant change in BMI, WHR, or KAP scores of nutrition, physical activity, and screen use in the control

Table 4.
Gender-specific comparison of outcome variables pre- & post-intervention in control group

Control group (n=60)						
Variable	Boys (n=30)			Girls (n=30)		
	Pre-intervention	Post-intervention	p-value[g]	Pre-intervention	Post-intervention	p-value[h]
Weight (kg)	60.61 (5.88)	60.94 (5.73)	0.035	59.65 (6.45)	59.85 (6.36)	0.164
BMI	26.17 (1.37)	26.12 (1.32)	0.82	26.06 (1.48)	25.94 (1.38)	0.275
BMI Z-score	2.54 (0.36)	2.53 (0.35)	0.81	2.50 (0.40)	2.48 (0.38)	0.268
WHR	0.89 (0.04)	0.89 (0.04)	0.79	0.88 (0.04)	0.88 (0.04)	1.00
Nutritional KAP score	24.85 (4.17)	24.91 (3.82)	0.654	26.83 (3.38)	26.74 (3.20)	0.475
Physical activity KAP score	13.15 (2.96)	13.38 (3.03)	0.641	13.11 (3.03)	13.22 (3.29)	0.758
Screen use KAP score	9.40 (2.96)	9.71 (3.11)	0.234	9.80 (3.03)	9.91 (3.04)	0.422

[g,h]; Paired t-test was used, values are presented as mean (standard deviation), BMI; Body mass index, WHR; Waist-to-hip ratio, KAP; Knowledge, attitude, and practices

group on 3 months follow-up. These results project the positive impact of the school-based intervention on children with obesity and overweightness.

In alignment with our study results, a study done in India found that a multicomponent intervention comprising of increased physical activity, nutritional education, and parental involvement effectively reduced BMI and fat percentage, and improved lifestyle practices score at 6 months of follow-up in the study group[10]. Another study consisting of 487 adolescents in the age group of 11-15 years also showed a significant decrease in BMI and WHR after a program that included educational tools and changes in the school[11]. Similar such healthy effects have been proved in other school-based studies[12-14]. Thus, we find combining different strategies such as physical activity, educational reinforcement, parental and school involvement is very effective in reducing BMI. Yoga is the physical activity intervention chosen in our study as it is common in Indian setting. A recent systematic review of nine studies found yoga has a little but meaningful effect on weight loss in children[15]. Also, Jain et al found that in a randomised controlled intervention, yoga combined with dietary modification and lifestyle counselling, was useful in reducing BMI and promoting healthy eating[16].

We found in our study that the nutritional score significantly increased following the intervention. A multi-level community based randomized intervention showed that parental involvement (parent monitoring) was effective in increasing the consumption of fruits and vegetables in obese children[17]. But the study found no change in the BMI of these children[17]. In line with our study results, another quasi-experimental study by Prelip et al.[18] found that a multicomponent intervention improved the knowledge and attitude on healthy eating in obese children. However, the study also found that the intervention did not increase the actual consumption of fruit and vegetables, thus pointing to the need of new strategies in the area of school/home food environment[18]. Our study found that a school-based intervention improved the KAP scores of physical activity. A 70% reduction in sedentary time (which included watching TV, video games, and phone) was observed in a school-based intervention by Cong et al.[19]. Similarly, a parent-related quasi experimental study found the benefits of reducing screen time in children following the change in specific parenting practices[20].

In contrast to our study, an Indian study which was a five-year multicomponent intervention combining education, yoga, with involvement of teachers and families, found no significant change in BMI[21]. This study had no control group which could be a possible limitation[21]. Accordingly, no significant change in BMI was observed in a cluster randomized controlled trial of an intervention targeting education and teacher-parent dyad involvement[22]. However, the intervention was fruitful in improving the healthy eating behavior[22]. So, we find conflicting results with school-based interventions comprising education and family involvement. This could be because of the different study methods, follow-up times, and cultural backgrounds in these studies. These contrasting findings imply the need for further studies with uniform interventional methods and larger sample sizes.

This kind of multicomponent involving the school and family is more feasible in the Indian setting which we find as a strength of our study. Further we have done randomisation at two levels (both selection of schools and selection of children were randomised) which adds more validity to the results. A notable limitation of our study was the significant baseline differences in BMI and WHR between the study and control groups, despite randomization. While this could potentially influence the interpretation of results, the significant within-group changes observed in the intervention group suggest the effectiveness of the multicomponent intervention. Future studies should employ stratified randomization to ensure better baseline comparability.

As highlighted by Kurtoğlu et al.[23]., BMI has limitations in accurately reflecting body composition and fat distribution. While BMI is the primary outcome measured, it is a measure of general adiposity and does not give information on body fat distribution, which is related to cardiovascular disease risks in children as well as in adults. Future studies should incorporate more precise measures of body composition such as bioelectrical impedance analysis to better evaluate intervention effects on body fat percentage and distribution. It is important to note that the follow-up duration in our study was relatively short (3 months), and long-term follow-up is necessary to determine if these positive changes

are sustained over time. The lack of pubertal status assessment is another limitation, as pubertal stage can significantly influence anthropometric measurements and their changes over time. A key limitation of our study design is the inability to determine the individual effectiveness of each intervention component (yoga, nutritional education, and parental involvement). Henceforth we suggest that studies should employ a factorial design with separate intervention arms to evaluate the independent and combined effects of these components.

Conclusion

In conclusion, this study provides valuable evidence supporting the effectiveness of a school-based, multicomponent intervention in addressing childhood obesity in areas such as reduction of BMI, WHR, and improvement in healthy lifestyle behavior. These findings are useful in the short-term period. Howsoever, we suggest future studies which delve into the long-term effects of such interventions and also studies comparing individual strategies with multi-faceted ones.

Ethics

Ethical Approval: The study commenced after the Mahatma Gandhi Medical College and Research Institute Institutional Human Ethics Committee approval (no: MGMCRI/Res/01/2021/99/IHEC/135, date: 31.01.2023) and was registered in the Clinical Trials Registry-India (CTRI/2024/07/070695).

Informed Consent: After receiving informed consent from their school principal and also from their parent and written assent from the student, a baseline data was collected.

Footnotes

Author Contributions: Manogna T: Surgical and Medical Practices, Design, Data Collection or Processing, Analysis or Interpretation, Writing; Serane VK: Surgical and Medical Practices, Concept, Data Collection or Processing, Analysis or Interpretation, Writing; Chandramoha A: Surgical and Medical Practices, Design, Analysis or Interpretation, Literature Search, Writing; Bhavanani AB: Surgical and Medical Practices, Concept, Data Collection or Processing, Literature Search, Writing; Palanisamy S: Surgical and Medical Practices, Concept, Analysis or Interpretation, Writing.

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References

1. Obesity and overweight [Internet]. [cited 2024 Jul 23]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight *[CrossRef]*
2. Caprio S, Santoro N, Weiss R. Childhood obesity and the associated rise in cardiometabolic complications. *Nat Metab.* 2020;2:223-232. *[CrossRef]*
3. De Miguel-Etayo P, Bueno G, Garagorri JM, Moreno LA. Interventions for treating obesity in children. *World Rev Nutr Diet.* 2013;108:98-106. *[CrossRef]*
4. Cao ZJ, Wang SM, Chen Y. A randomized trial of multiple interventions for childhood obesity in China. Am *J Prev Med.* 2015;48:552-560. *[CrossRef]*
5. Effectiveness of school-based physical activity and nutrition interventions with direct parental involvement on children's BMI and energy balance-related behaviors – A systematic review | PLOS ONE [Internet]. [cited 2024 Jul 16]. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0204560 *[CrossRef]*
6. Khadilkar V, Shah N, Harish R, et al. Indian Academy of Pediatrics Revised Guidelines on evaluation, prevention and management of childhood obesity. *Indian Pediatr.* 2023;60:1013-1031. *[CrossRef]*
7. Ponnambalam S, Palanisamy S, Singaravelu R, Janardhanan HA. Effectiveness of after-school physical activity intervention on body mass index and waist circumference/height ratio among overweight adolescents in selected schools at puducherry, India: a randomized controlled trial. *Indian J Community Med.* 2022;47:72-75. *[CrossRef]*
8. Manual A. Dietary guidelines for Indians. Nat Inst Nutrition. 2011;2:89-117. *[CrossRef]*
9. Singh S, Awasthi S, Kapoor V, Mishra P. Childhood obesity in India: A two-decade meta-analysis of prevalence and socioeconomic correlates. *Clinical Epidemiology and Global Health.* 2023;23:101390. *[CrossRef]*
10. Nayak BS, Bhat VH. School based multicomponent intervention for obese children in udupi district, South India - a randomized controlled Trial. *J Clin Diagn Res.* 2016;10:SC24-SC28. *[CrossRef]*
11. Tomayko EJ, Tovar A, Fitzgerald N, et al. Parent involvement in diet or physical activity interventions to treat or prevent childhood obesity: an umbrella review. *Nutrients.* 2021;13:3227. *[CrossRef]*
12. Bogart LM, Elliott MN, Cowgill BO, et al. Two-year BMI outcomes from a school-based intervention for nutrition and exercise: a randomized trial. *Pediatrics.* 2016;137:e20152493. *[CrossRef]*
13. Ermetici F, Zelaschi RF, Briganti S, et al. Association between a school-based intervention and adiposity outcomes in adolescents: The Italian "EAT" project. *Obesity (Silver Spring).* 2016;24:687-695. *[CrossRef]*
14. Ardic A, Erdogan S. The effectiveness of the COPE healthy lifestyles TEEN program: a school-based intervention in middle school adolescents with 12-month follow-up. *J Adv Nurs.* 2017;73:1377-1389. *[CrossRef]*
15. (PDF) Yoga as an alternative therapy for weight management in child and adolescent obesity: a systematic review and implications for research [Internet]. [cited 2024 Mar 29]. Available from: https://www.researchgate.net/publication/342958158_Yoga_as_an_Alternative_Therapy_for_Weight_Management_in_Child_and_Adolescent_Obesity_A_Systematic_Review_and_Implications_for_Research
16. Jain V, Kumar B, Sharma A, et al. A comprehensive yoga programme for weight reduction in children & adolescents with obesity: A randomized controlled trial. Indian J Med Res. 2022;155:387-396. *[CrossRef]*
17. Crespo NC, Elder JP, Ayala GX, et al. Results of a multi-level intervention to prevent and control childhood obesity among Latino children: the Aventuras Para Niños Study. *Ann Behav Med.* 2012;43:84-100. *[CrossRef]*
18. Prelip M, Kinsler J, Thai CL, Erausquin JT, Slusser W. Evaluation of a school-based multicomponent nutrition education program to improve young children's fruit and vegetable consumption. *J Nutr Educ Behav.* 2012;44:310-318. *[CrossRef]*
19. Cong Z, Feng D, Liu Y, Esperat MC. Sedentary behaviors among hispanic children: influences of parental support in a school intervention program. Am J Health Promot. 2012;26:270-280. *[CrossRef]*
20. De Lepeleere S, De Bourdeaudhuij I, Cardon G, Verloigne M. The effect of an online video intervention 'movie models' on specific parenting practices and parental self-efficacy related to

children's physical activity, screen-time and healthy diet: a quasi experimental study. *BMC Public Health.* 2017;17:366. *[CrossRef]*

21. Bhave S, Pandit A, Yeravdekar R, Madkaikar V, Chinchwade T, Shaikh N, et al. Effectiveness of a 5-year school-based intervention programme to reduce adiposity and improve fitness and lifestyle in Indian children; the SYM-KEM study. *Archives of Disease in Childhood.* 2016;101:33-41. *[CrossRef]*

22. Cunha DB, Souza BDSND, Pereira RA, Sichieri R. Effectiveness of a randomized school-based intervention involving families and teachers to prevent excessive weight gain among adolescents in Brazil. Hernandez AV, editor. *PLoS One.* 2013;8:e57498. *[CrossRef]*

23. Kurtoğlu S, Mazıcıoğlu MM, Öztürk A, Hatipoğlu N, Çiçek B, Zararsız G. Fat and fat free mass index reference percentiles of healthy Turkish children and adolescent in Turkey. *J Pediatr Acad.* 2020;1:8-15. *[CrossRef]*

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Acute Kidney Injury As A Consequence of Perinatal Asphyxia

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Abstract

Perinatal asphyxia (PNA) results in multiorgan damage including the kidney. The severity of kidney damage is related to the extent of central nervous system damage. This study aimed to determine the prevalence of acute kidney injury (AKI) in neonates with PNA and its association with hypoxic ischemic encephalopathy (HIE) staging. This cross-sectional study was conducted in the neonatal intensive care unit of the Institute of Child and Mother Health, Dhaka, from July 2020 to June 2021. A total of 100 neonates with PNA were included in this study. After careful history taking, examination, and appropriate investigations, HIE staging was done in each subject using the Sarnat and Sarnat method. Data were analyzed by statistical package for the social sciences, version 23. In this study, 45 (45.0%) neonates belonged to the postnatal age group ≤24 hours, and male patients were predominant (57.0%). Out of 100 neonates, 89.0% had HIE stage II and 11.0% had stage III. Among stage II HIE neonates, 9 (10.1%) had AKI and 80 (89.9%) did not have AKI. Among stage III HIE neonates, 5 (45.5%) had AKI and 6 (54.5%) did not have AKI. The difference was statistically significant ($p<0.05$). When HIE stage was higher in PNA patients, there was a higher possibility of developing AKI. Renal function alterations correlated with HIE severity. Therefore, AKI should be evaluated and properly managed among neonates with PNA.

Keywords: Acute kidney injury, hypoxic ischemic encephalopathy, perinatal asphyxia

Introduction

Perinatal asphyxia (PNA), an important cause of neonatal morbidity and mortality, has been a global concern. Its incidence ranges from 1 to 10 per 1,000 live births (McGuire)[1]. Approximately 90% of asphyxial events occur during the antepartum or intrapartum period as a result of placental insufficiency with an inability to provide oxygen and remove CO_2 and hydrogen ions from the fetus. The remaining 10% are postpartum, usually secondary to

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pulmonary, cardiovascular, or neurologic insufficiency (Hansen and Soul[2]).

Rena hypoperfusion as a consequence of PNA acts as pre-renal acute kidney injury (AKI) trigger. Abundance of mitochondria in tubular cells makes the kidney highly oxygen dependent as well as susceptible to oxidative stress. Generation of various reactive oxygen species (e.g., hydroxyl radical, peroxynitrite, hyperchlorous acid) and depletion of some antioxidants (superoxide dismutase, catalase, and glutathione reductase) adversely affect renal tissue, leading to AKI (Gyurászová et al.[3]). The incidence of neonatal AKI ranges from 8% to 20%. The mortality in neonates with AKI is very high as well (Srivastava and Bagga[4].)

Highlights

- Perinatal asphyxia (PNA) is an established cause of multiorgan damage,
- Kidney involvement in PNA ensues significant morbidity and mortality,
- Our study was aimed at determining the percentage of acute kidney injury in PNA, as well as to investigate its association with various stages of hypoxic ischemic encephalopathy.

The present study is aimed to determine the percentage of AKI in PNA and its association with hypoxic ischemic encephalopathy (HIE) staging.

Material and Method

This was a cross-sectional study carried out at neonatal intensive care unit (NICU), Institute of Child and Mother Health (ICMH), and Dhaka Medical College Hospital, Dhaka. The duration of the study was one year, from July 2020 to June 2021. Both in-born and out-born neonates diagnosed with PNA and HIE stage II or III, born at 37-42 weeks of gestation and admitted to the NICU within 72 hours of life, were enrolled. Neonates with any congenital anomaly, PNA, and or antenatal diagnosis of any kidney disease were excluded.

As it was a cross-sectional study, the sample size was calculated using the following formula.

$$n=z^2p(1-p)/d^2$$

$$= \frac{(1.96)^2 x\ 0.12(1-0.12)}{(0.05)^2}$$

$$= \frac{3.8416x0.12x0.88}{0.0025}$$

$$= 162$$

[Where n: sample size, z: 1.96 (standard normal deviate), p means prevalence: 0.12 (Alaro et al.[5]). The degree of accuracy or precision level is d which is considered at 5%] .

By using the above formula, the expected sample was 162, but due to time limitations, 100 subjects were enrolled.

Newborns with PNA admitted to the NICU of ICMH were included in this study irrespective of their gender, race, and ethnic group. After enrollment, a detailed history was taken and a thorough clinical examination was performed. HIE staging was performed on these patients by Modified Sarnat and Sarnat staging (Gomella et al.[6]).

AKI was diagnosed using the kidney disease: improving global outcomes criteria. With all aseptic precautions, a blood sample (3 mL of venous blood) was collected using a disposable syringe from each neonate. The collected blood sample was taken into a sterile test tube and labeled with the identification number, date, and sent to the laboratory of ICMH for investigation. For the complete blood count, a collected blood sample was taken in an ethylenediaminetetraacetic acid sterile tube, and the test was performed using the Sysmex XN-550 machine made in India. Capillary blood glucose was measured by a glucometer from a heel prick, and serum electrolytes were analyzed using the EasyLyte PLUS Electrolyte analyzer made in India. Blood urea and serum creatinine measurements were conducted with the HumanStar 600 autoanalyser machine made in India.

The protocol was submitted and approval was obtained from the Institutional Review Board (IRB) (respective ethics committee) of the ICMH, Dhaka, Bangladesh (approval no.: ICMH/IRB-07SEP2020/17). Informed written consent was obtained before starting the interview. This research activity would not cause any harm to patients.

Statistical Analysis

Checked and cleaned data were analyzed using statistical package for the social sciences version 23. The chi-square test and Fisher's were used for qualitative variables. Unpaired Student's t-test was used for quantitative variables. The p-value <0.05 was considered significant.

Results

The majority of the neonates (45%) belonged to age group ≤24 hours, while 26.0% belonged to age group 25-48 hours and 29.0% belonged to age group 49-72 hours (**Figure 1**). The study found a male predominance (57%) over females (43%) (**Figure 2**). The majority of the mothers (73%) had irregular antenatal visits. Regarding risk factors, 30% had premature rupture of membrane (PROM), 18% had prolonged/obstructed labor, 11% had hypertension (HTN), 8% had diabetes

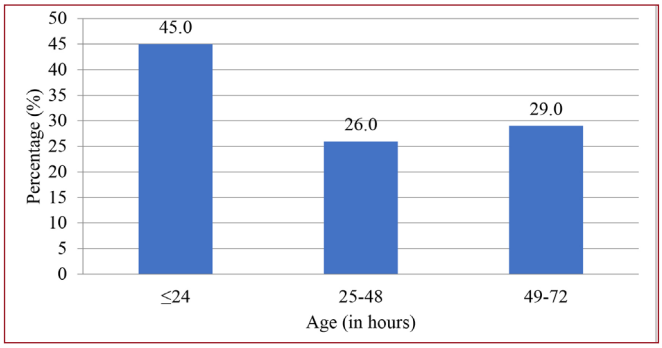

Figure 1. Bar diagram showing age distribution of the neonates (n=100)

mellitus (DM). Most of the mothers (59.0%) had normal vaginal delivery, and 53.0% of the mothers had home delivery (**Table 1**).

About 78.0% of patients had a lethargic appearance; almost 67.0% of patients showed pale color; the majority (67.0%) of patients had a capillary refill time of less than 3 seconds. The majority (64.0%) had a moderately low score (4-6) at 1 minute, and (59.0%) had a moderately low score (4-6) at 5 minutes (**Table 2**).

The majority of cases (89.0%) were classified as HIE stage II, while 11% were classified as HIE stage III (**Figure 3**). Out of 100 cases of PNA, 86 (86%) were found without AKI, and the remaining 14 (14%) had AKI (**Figure 4**). Among the 89 cases with HIE stage II, 9 cases (10.1%) developed AKI, while AKI developed in 5 cases (45.5%) out of 11 HIE stage II cases (**Table 3**). This finding was statistically significant. Differences in serum creatinine and blood urea levels were statistically significant between AKI and without AKI groups, while the differences between blood cell counts, C-reactive protein, serum electrolytes, and calcium levels were not statistically significant (**Table 4**).

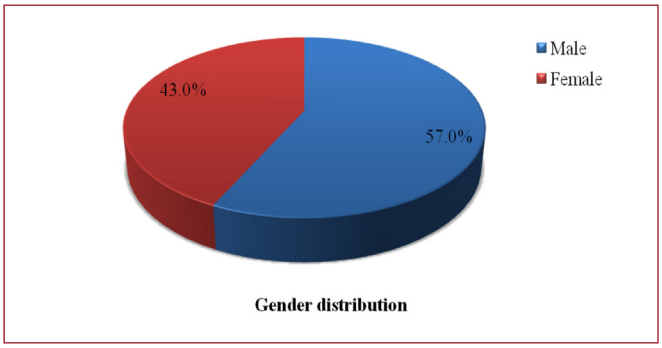

Figure 2. Pie chart showing gender distribution of the study neonates (n=100)

Table 1.
Factors influencing neonatal outcome (n=100)

Related factors	Frequency	Percentage
Antenatal visit		
Regular	12	12.0
Irregular	73	73.0
None	15	15.0
Risk factors		
PROM	30	30.0
Prolong/obstructed labor	18	18.0
HTN	11	11.0
DM	8	8.0
Bronchial asthma	3	3.0
PV bleeding	5	5.0
Meconium-stained liquor	3	3.0
None	22	22.0
Gestation		
Single	100	100.0
Twin	0	0.0
Mode of delivery		
NVD	59	59.0
LUCS	41	41.0
Place of delivery		
Home	53	53.0
Hospital	32	32.0
Clinic	15	15.0

PROM; Premature rupture of membrane, HTN; Hypertension, DM; Diabetes mellitus, PV; Per vaginal, NVD; Normal vaginal delivery, LUCS; Lower uterine cesarean section

Discussion

The pathology of PNA lies in defective blood gas exchange and eventual progression to hypoxemia, along with hypercapnia. It also causes HIE, a significant etiology of neonatal death.

Table 2.
Clinical profile of study neonates (n=100)

Presenting signs	Frequency	Percentage
Appearance		
Lethergic	78	78.0
Active/alert	22	22.0
Colour		
Pink	25	25.0
Pale	67	67.0
Cyanosis	8	8.0
Capillary refill time		
<3 second	67	67.0
≥3 second	33	33.0
APGAR score at 1 minute		
Normal 7-10 score	36	36.0
Moderately depressed 4-6 score	64	64.0
APGAR score at 5 minute		
Normal 7-10 score	41	41.0
Moderately depressed 4-6 score	59	59.0

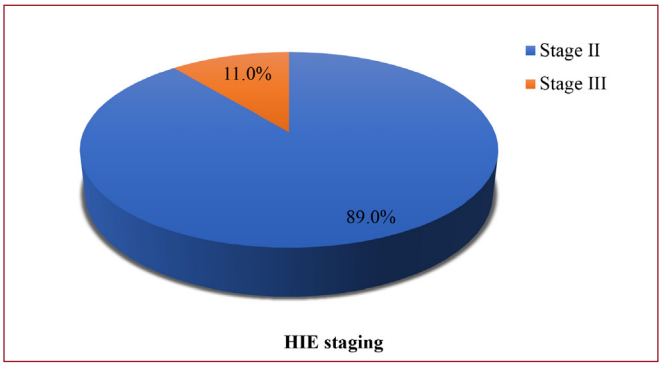

Figure 3. Pie chart showing distribution of cases according to HIE staging (n=100)
HIE; Hypoxic ischemic encephalopathy

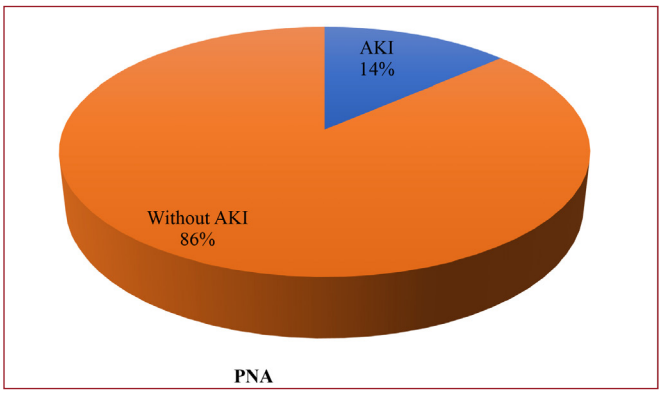

Figure 4. Pie chart showing AKI and without AKI in PNA (n=100)
PNA; Perinatal asphyxia, AKI; Acute kidney injury

Table 3.
Association of HIE staging of AKI and without AKI neonates (n=100)

HIE staging	AKI (n=14)		Without AKI (n=86)		p-value
	n	%	n	%	
Stage II (n=89)	9	10.1	80	89.9	0.001*
Stage III (11)	5	45.5	6	54.5	

*p-value <0.05 was considered as significant, HIE; Hypoxic ischemic encephalopathy, AKI; Acute kidney injury

Table 4.
Laboratory parameters of the study neonates (n=100)

Investigations	AKI (n=14)		Without AKI (n=86)		p-value
	mean	± SD	mean	± SD	
CBC					
Hb% (gm/dL)	18.82	±1.75	17.73	±2.62	0.136
TC-WBC (mm^3)	16710.62	±8941.70	17962.71	±23607.21	0.845
CRP (mg/dL)	33.95	±18.71	26.77	±17.42	0.160
Serum calcium (mg/dL)	9.17	±0.12	8.97	±1.11	0.504
Na (mmol/L)	142.31	±6.53	140.17	±6.01	0.225
K (mmol/L)	6.03	±2.17	5.52	±0.57	0.066
Cl (mmol/L)	106.32	±7.01	108.17	±3.95	0.154
Serum creatinine (mg/dL)	1.67	±0.29	0.85	±0.57	0.001*
Blood urea (mg/dL)	37.87	±13.68	27.53	±9.35	0.001*

Results were expressed as mean ± standard deviation. An unpaired Student's t-test was done as a test of significance.
*p-value <0.05 was considered as significant, AKI; Acute kidney injury, CBC; Complete blood count, Hb; Hemoglobin, TC-WBC; Total count of white blood cells, CRP; C-reactive protein, Na; Sodium, K; Potassium, Cl; Chloride, SD; Standard deviation

The disease process adversely affects various organs, notably the kidneys. A thorough and optimized kidney function evaluation is warranted in these patients (Gopal[7]).

The present study observed 45.0% of neonates aged ≤24 hours, 26.0% aged 25-48 hours and 29.0% beyond 48 hours. Medani et al.[8] in their study reported majority (58.8%) of neonates <7 days of age followed by 36.5% between 8-15 days and 4.7% between 16-28 days.

The present study showed that the majority of neonates were male (57.0%), while the remaining 43.0% were female. Phuljhele et al.[9] studied 241 (58.1%) males and 174 (41.9%) females. Shrestha et al.[10] observed a 1.45/1 male-female ratio in their study.

In the present study, the majority (73.0%) of mothers had irregular antenatal visits. Regarding risk factors, the majority (30%) had PROM; 18.0% had prolonged/obstructed labour; 11.0% had HTN; 8.0% had DM. Alaro et al.[5] observed nearly all mothers (90%) received ANC visit. Gopal[7] observed meconium stained amniotic fluid with prolonged labour as leading pathology (40%) of PNA. Medani et al.[8] reported about two thirds (67.3%) of neonates with PNA and AKI were born to mothers with due antenatal care (ANC) and the remaining one third (32.7%) were devoid of ANC.

In this study, the majority of participants (59, 59.0%) had normal vaginal delivery. More than half (53.0% of) patients had home delivery. Medani et al.[8] reported vaginal delivery (either normally or assisted) as modes of birth in 72.9% of the cases. Eighteen (39.2%) neonates were born at home and 28 (60.8%) were born at clinics.

The current study, showed that the majority (64.0%) had moderately low scores (4-6 scores at 1 minute) and (59.0%) had moderately low scores (4-6 scores at 5 minutes). Shrestha et al.[10] reported in their study that, 71% had an APGAR score of ≤3 at 1 minute, while the APGAR score at 5 minutes was found to be ≤3 in 17% and 4-6 in 77% of cases, respectively. Gopal[7] observed 50 neonates with asphyxia, where 20 (40%) had APGAR score 4-5 at 5 minutes, 18 (36%) had score 6-7, and 12 (24%) had score 0-3.

In the current study, 89.0% cases had HIE stage II and 11.0% cases had HIE stage III. Gopal[7] also found in their study, HIE stage II (25/50) outnumbered stage I (20/50) and stage III (5/50). Phuljhele et al.[9] also reported a majority (242, 58.3%) of HIE-II cases, followed by 121 (29.1%) HIE-III cases and 52 (12.5%) HIE-I cases.

This study found that among 89 patients with HIE stage II, 10.1% developed AKI, while 89.9% did not. Stage III was found in 11 patients, out of which, 45.5% were in the AKI group and 54.5% were in the non-AKI group. The difference was statistically significant (p<0.05) between the two groups. In a study comprising 415 subjects, Phuljhele et al.[9] reported a majority (58.3%) having HIE-II, followed by HIE-III (29.1%) and HIE-I (12.5%). They documented no AKI case from the HIE-I group. Although, 20 (8.2%) subjects having HIE II and 50 (41.3%) subjects having HIE-III developed AKI. Another prospective cohort study in Kenya accounted 15 times higher risk of AKI in HIE III than HIE I (Alaro et al.[5]).

A Tunisian study revealed that among the 15 AKI cases, 10 were in the HIE-II stage according to Sarnat staging (Nouri et al.[11]). In their study, Karlowicz and Adelman[12] found non-oliguric AKI to be predominant

(60%) in asphyxiated newborns, while Jayashree et al.[13] documented oliguric AKI to be predominant in comparable subjects. Few studies also described non-oliguric AKI as being predominant in PNA. Few other studies described non-oliguric AKI as predominant in[14-16].

In this study, higher serum creatinine and blood urea were significantly different between the two groups ($p<0.05$), but there was no difference in electrolyte levels in both groups.

Blood urea and creatinine levels were found to be significantly higher in PNA cases in the study by Chaudhary et al.[17] and by Agrawal et al.[18] respectively. Gopal observed significant differences in the levels of urea and creatinine in asphyxiated neonates with AKI.

We have conducted the study at a limited resource center as well as financial constraint. Traditional creatinine-based criteria were used to diagnose AKI. Many centers are using newer biomarkers, like neutrophil gelatinase-associated lipocalin, cystin C, and kidney injury molecule-1, etc., for early detection of AKI (Canney et al.[19]).

Study Limitations

Due to time constraints, the sample size could not be achieved. Other modern biomarkers of AKI should be checked in conducting further research on this topic. A long-term follow-up is also missing in this study. A further study with a larger sample size in multiple centers, with follow-up, is recommended.

Conclusion

This study showed that 14% of neonates with PNA had developed AKI. Patients with HIE stage II and stage III had developed 10.1% and 45.5% AKI, respectively. A significant association between AKI and HIE staging was observed. When HIE stage was higher, there was a greater likelihood of developing AKI.

Ethics

Ethical Approval: The protocol was submitted and approval was obtained from the Institutional Review Board (IRB) (respective ethics committee) of the ICMH, Dhaka, Bangladesh (approval no.: ICMH/IRB-07SEP2020/17).

Informed Consent: Informed written consent was obtained before starting the interview.

Footnotes

Author Contributions: Rahman O, Adnan MA: Surgical and Medical Practices; Rahman O, Rahman M, Adnan MA: Consept; Rahman O, Rahman M, Adnan MA: Design; Rahman O, Adnan MA, Hye A: Data Collection or Processing; Rahman O, Rahman M, Adnan MA: Analysis or Interpretation; Rahman O, Rahman M, Adnan MA, Hye A: Literature Search; Rahman O, Rahman M, Adnan MA, Hye A: Writing.

Conflict of Interest: The authors declare no conflicts of interest.

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References

1. McGuire W. Perinatal asphyxia. *BMJ Clin Evid.* 2007;2007:0320. *[CrossRef]*
2. Hansen AR, Soul JS. Perinatal asphyxia and hypoxic-ischemic encephalopathy. Manual of Neonatal Care. 2012:711. *[CrossRef]* https://repository.stikesbcm.ac.id/id/eprint/344/1/Manual%20of%20Neonatal%20Care%207th.pdf#page=733
3. Gyurászová M, Gurecká R, Bábíčková J, et al. Oxidative stress in the pathophysiology of kidney disease: implications for noninvasive monitoring and identification of biomarkers. *Oxid Med Cell Longev*. 2020;2020:5478708. *[CrossRef]*
4. Srivastava RN, Bagga A. Paediatric Nephrology. 6th edition. The Health Science Publisher, New Delhi, London, Philadelphia, Panama; 2016:538. *[CrossRef]*
5. Alaro D, Bashir A, Musoke R, et al. Prevalence and outcomes of acute kidney injury in term neonates with perinatal asphyxia. *Afr Health Sci*. 2014;14:682-688. *[CrossRef]*
6. Gomella TL, Eyal F, Bany-Mohammad F. Gomella's Neonatology, Management, procedure, on-call problems, disease and drugs. 8th edition. Mc Graw Hill, Lange; 2020:803-1000. *[CrossRef]*
7. Gopal G. Acute kidney injury (AKI) in perinatal asphyxia. Indian J.Pharm.*Biol.Res.* 2014;2:60-65. *[CrossRef]*
8. Medani SA, Kheir AE, Mohamed MB. Acute kidney injury in asphyxiated neonates admitted to a tertiary neonatal unit in Sudan. *Sudan J Paediatr.* 2014;14:29-34. *[CrossRef]*
9. Phuljhele S, Dewangan S, Rathi Y. Incidence of acute kidney injury in birth asphyxia and its correlation with severity of hypoxic ischemic encephalopathy (HIE) in newborns with perinatal asphyxia in SNCU at Dr. Bram Hospital, Raipur (CG). *Int J Pediatr Res.* 2019;6:304-309. *[CrossRef]*
10. Shrestha NJ, Subedi KU, Shakya S, et al. Prevalence of acute kidney injury in patients with perinatal asphyxia in tertiary hospital. *Journal of Nepal Paediatric Society.* 2019;39:109-115. *[CrossRef]*
11. Nouri S, Mahdhaoui N, Beizig S, et al. L'insuffisance rénale aiguë au cours de l'asphyxie périnatale du nouveau-né à terme. Etude prospective de 87 cas [Acute renal failure in full term neonates with perinatal asphyxia. Prospective study of 87 cases]. *Arch Pediatr.* 2008;15:229-235. *[CrossRef]*
12. Karlowicz MG, Adelman RD. Nonoliguric and oliguric acute renal failure in asphyxiated term neonates. *Pediatr Nephrol.* 1995;9:718-722. *[CrossRef]*
13. Jayashree G, Dutta AK, Sarna MS, et al. Acute renal failure in asphyxiated newborns. *Indian Pediatr.* 1991;28:19-23. *[CrossRef]*
14. Gupta BD, Sharma P, Bagla J, et al. Renal failure in asphyxiated neonates. *Indian Pediatr.* 2005;42:928-934. *[CrossRef]*
15. Evaluation of renal functions in asphyxiated newborns. *J Trop Pediatr.* 2005;51:295-299. *[CrossRef]*
16. Mohan PV, Pai PM. Renal insult in asphyxia neonatorum. Indian Pediatr. 2000;37:1102-6. Erratum in: *Indian Pediatr.* 2000;37:1327. *[CrossRef]*
17. Chaudhary R, Tiwari AK, Usmani F. Study of incidence of acute kidney injury in asphyxiated neonates with hypoxic ischemic encephalopathy. *Int J Contemp Pediatr.* 2020;7:2205-2209. *[CrossRef]*
18. Agrawal S, Chaudhuri PK, Chaudhary AK, et al. Acute kidney injury in asphyxiated neonates and its correlation to hypoxic ischemic encephalopathy staging. *Indian Journal of Child Health*. 2016;3:254-257. *[CrossRef]*
19. Canney M, Clark EG, Hiremath S. Biomarkers in acute kidney injury: n the cusp of a new era? *J Clin Invest.* 2023;133:e171431. *[CrossRef]*

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Predictive Value of Maternal Systemic Inflammatory Markers in Treatment-Requiring Retinopathy of Prematurity

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Abstract

The aim of the study was to investigate the predictive value of maternal systemic inflammatory markers such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), systemic immune-inflammatory index (SII), platelet mass index (PMI) and mean platelet volume (mPV) in treatment-requiring retinopathy of prematurity (TR-ROP). In this retrospective study, 19 mothers whose preterm infants required treatment (intravitreal injection) for ROP were included in the TR-ROP group. Twenty-one mothers whose preterm infants did not require treatment for ROP were included in the control group. Birth weights (BWs) and gestational age (GA) were recorded. Maternal complete blood count samples obtained within 3 days before delivery were analyzed. Maternal NLR, PLR, LMR, SII, PMI and mPV data were calculated and statistically compared. All data were analyzed using statistical package for the social sciences, version 22.0 (SPSS, Chicago, IL, USA). There was no significant difference between the groups in terms of BW (p=0.108). The GA was significantly lower in the TR-ROP group compared to the control group [28 (24-33), 30 (27-32), p=0.04, respectively]. NLR, PLR, LMR and SII values were 5.9/4.2 (p=0.02), 143.8±26.3/123.1±36.2 (p=0.02), 2.06/3.01 (p=0.001), 1279/1040 (p=0.05) between the TR-ROP and control groups, respectively. In the TR-ROP group, when these values were corrected according to the GA in logistic regression analysis, the NLR, PLR, and SII were not statistically significant (p=0.11, p=0.83 and p=0.13), but there was an increase in the LMR [p=0.02, odds ratio=0.38 95% confidence interval (0.16-0.88)]. The relationship of maternal SII, PMI and mPV parameters with TR-ROP was shown for the first time in this study. Maternal LMR in the prenatal period may be helpful in predicting TR-ROP. Additional studies are needed before these conclusions can be applied to daily clinical practice.

Keywords: Inflammatory markers, maternal lymphocyte/monocyte ratio, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, retinopathy of prematurity

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Introduction

Retinopathy of prematurity (ROP) is a sight-threatening disease that affects premature infants with arrested retinal vascularization. It is a leading cause of childhood blindness worldwide. The two most well-known risk factors in the pathophysiology of ROP are premature birth and low birth weight (BW). Numerous studies have shown that retinal ischemia, neovascularization and fibrosis are important factors in the development and progression of ROP, particularly in ROP requiring therapy (TR-ROP), which can lead to severe visual impairment if not diagnosed and treated early[1,2].

In recent studies, inflammation has been associated with age-related macular degeneration and diabetic retinopathy and ROP[3-6]. Several studies have investigated whether hematologic inflammatory biomarkers are potential predictors of an increased inflammatory response in ROP[7-11]. However, the majority of these studies have focused on infant inflammatory biomarkers, with limited exploration of maternal inflammatory biomarkers. Given that maternal health and intrauterine conditions influence fetal development, understanding the potential role of maternal inflammation in the pathogenesis of ROP may provide new insights into early risk assessment and prevention.

While extensive research has examined inflammatory biomarkers in infants, the potential impact of maternal biomarkers during pregnancy remains largely unexplored. Identifying maternal inflammatory biomarkers associated with ROP may allow for earlier interventions and improved neonatal outcomes. Therefore, our objective was to assess the predictive power of complete blood count (CBC) parameters and maternal blood inflammatory biomarkers for TR-ROP.

Highlights

- **Maternal inflammatory markers:** This study is the inaugural investigation into the correlation between maternal systemic inflammatory markers, including systemic immune-inflammatory index (SII), platelet mass index, and mean platelet volume, and treatment-requiring retinopathy of prematurity (TR-ROP).
- **Lymphocyte/monocyte ratio (LMR):** A significant association was observed between maternal LMR in the prenatal period and TR-ROP, suggesting that this parameter may serve as a predictive marker.
- **Predictive values:** Although the neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and SII were elevated in the TR-ROP group, they became non-significant after adjusting for gestational age.
- **Novel findings:** These findings underscore the potential utility of maternal inflammatory biomarkers in predicting TR-ROP.
- **Clinical implications:** LMR may serve as an early, non-invasive indicator for identifying infants at an elevated risk for TR-ROP.

Material and Method

Erciyes University Department of Ophthalmology is the site of this retrospective study and ethical approval was granted by Erciyes University Clinical Research Ethics Committee (approval number: 2023/116, date: 08.02.2023).

ROP screening was performed according to the latest national ROP screening guideline[12]. The study enrolled preterm infants with gestational age (GA) less than 34 weeks or BW less than 1,700 g and preterm infants with GA greater than 34 weeks or BW greater than 1,700 g who received cardiopulmonary support. The infants were grouped according to their condition, with the mothers assigned to each group accordingly: those who needed treatment for ROP and those who did not. Conditions including gestational diabetes, pre-eclampsia, systemic infections and clinical chorioamnionitis are known to cause systemic inflammation and significantly alter maternal inflammatory markers. To avoid these confounding factors that may affect the interpretation of our results, mothers with these conditions were excluded from the study. In addition, mothers who received antenatal steroids were not included in this study.

The newborns had their first ophthalmological examination at 31 weeks' GA for those born before 27 weeks, and at the fourth week after birth for those born after 27 weeks. The examination was performed according to the guidelines of the international classification of ROP[13]. A binocular indirect ophthalmoscope, a twenty-diopter lens, an infant speculum, and a pediatric scleral depressor were used for retinal examination. All infants were examined 1 hour after the instillation of 1% phenylephrine and 0.5% tropicamide. Treatment choices were based on the early treatment for ROP study criteria[14]. Patients who received vascular endothelial growth factor (VEGF) [0.625 mg in 0.025 mL Bevacizumab (Avastin®)] inhibitors were administered intravitreally for zone I and posterior zone II type 1 disease. Treated infants were defined as the TR-ROP group, and infants with ROP not requiring treatment were defined as the control group. In the study period, some patients received laser for zone 2 or 3 ROP and aiming a homogenous study population for disease severity and treatment modality those were excluded from the study. These treatment options were discussed with families and applied accordingly after informed consent. None of the infants had stage 4 or 5 ROP. The same ophthalmologist examined the infants and performed the intravitreal injections.

Maternal CBC samples, which were collected within 3 days before delivery, were analyzed. Electronic health records were screened to obtain the required data. White blood cell (WBC), lymphocyte, neutrophil, monocyte, platelet counts, and C-reactive protein (CRP) levels were recorded. Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), systemic immune-inflammatory index (SII) (neutrophil x platelet/lymphocyte), platelet mass index (PMI) [platelet count x mean platelet volume (mPV)], and mPV were calculated and recorded. The results of the groups were contrasted. All measurements were

performed in the same laboratory using the same method. This standardized approach aimed to minimize variability between samples, prevent potential laboratory-induced errors, and enhance the comparability of results.

Statistical Analysis

The data was analyzed using the statistical package for the social sciences (SPSS, Chicago, IL, USA) application, version 22.0. The data's normality was examined using the Shapiro-Wilk test. Parametric methods were applied for normally distributed numerical data, and results were expressed as mean ± standard deviation. Non-parametric methods were used for data that did not follow a normal distribution, and results were presented as median (minimum-maximum) or interquartile range (25^{th}-75^{th} percentile). To ascertain if the means of the two independent groups differed, the Mann-Whitney U test (for non-normally distributed data) and the Student's t-test (for regularly distributed data) were employed. Using logistic regression, the significant independent risk factors linked to the existence of ROP were calculated. The adjusted odds ratio (OR) and 95% confidence interval (CI) were estimated for each potential risk factor. The area under the curve (AUC) was calculated for each plot. In addition, sensitivity, specificity, and cut-off values were determined based on the LMR value and expressed via receiver operating characteristic (ROC) curve analysis. A p-value below 0.05 was considered statistically significant.

Results

A total of 40 mothers of infants with ROP were included in the study. Nineteen premature infants with ROP were treated with an intravitreal injection and represented the TR-ROP group, while 21 premature infants with ROP were followed without any treatment and represented the control group. Infants in the TR-ROP group had stage 3 ROP in 15 patients and aggressive ROP in 4 patients. The control group had stage 1 or 2 ROP that eventually resolved without treatment. **Table 1** shows the GA, BW, and maternal age data. The groups' differences in mother age and body weight of infants were not statistically significant. GA was lower in the TR-ROP groups (p=0.04).

Table 2 summarizes each group's maternal CBC parameters. The lymphocyte count was significantly lower in the TR-ROP group than in the control group (1.69±0.5 and 2.23±0.89 respectively, p=0.01). The TR-ROP group did not differ statistically significantly from the control group in terms of mPV, CRP, neutrophil count, platelet count, or monocyte count (p=0.08, p=0.345, p=0.405, p=0.649, p=0.127, respectively). NLR, PLR, and SII were increased and LMR was decreased in the TR-ROP group compared to the control group [NLR=5.9 (3.2-12.9) in TR-ROP group and 4.2 (0.9-11.8) in control group, p=0.02; PLR=143.8±26.3 in TR-ROP group and 123.1±36.2 in control group, p=0.02; SII=1,279 (826-4625) in TR-ROP group and 1040 (219-2401) in control group, p=0.05; LMR=2.06 (1.1-4.2) in TR-ROP group and 3.01 (1.2-5.9) in control group, p=0.001]. PMI was comparable between groups (p=0.260).

Table 1.
Comparison of maternal age, gestational age and birth weight of infants between groups

	TR-ROP group (n=19)	Control group (n=21)	p-value
Maternal age	31.2±5	28.7±5	0.156
Gestational age (wk)	28 (24-33)	30 (27-32)	**0.04***
Birth weight (gr)	1.176.9±353.9	1.357±343.1	0.108

TR; Treatment-requiring, ROP; Retinopathy of prematurity, *; Statistically significant

Table 2.
Comparison of maternal hemogram parameters

Maternal hemogram parameters	TR-ROP group n=19	Control group n=21	p-value
CRP (µg/mL)	12.1 (2.3-123.7)	6.43 (0.49-48.3)	0.345
WBC (x10³/mcL)	12.46 (1.06-29.13)	13.64 (8.15-21.77)	0.893
Platelets count (x10³/mcL)	227 (158-358)	234 (170-386)	0.649
Neutrophils count (x10³/mcL)	9.06 (6.7-25.58)	9.19 (1.56-18.88)	0.405
Lymphocytes count (x10³/mcL)	1.69±0.5	2.23±0.89	**0.01***
Monocytes (x10³/mcL)	0.84±0.24	0.71±0.27	0.127
MPV (fL)	10.6 (9.4-12.6)	10.7 (9.4-12.7)	0.08
NLR	5.9 (3.2-12.9)	4.2 (0.9-11.8)	**0.02***
LMR	2.06 (1.1-4.2)	3.01 (1.2-5.9)	**0.001***
SII	1.279 (826-4.625)	1.040 (219-2.401)	0.05
PLR	143.8±26.3	123.1±36.2	**0.02***
PMI	2.466±570	2.703±688	0.260

The mean was used to express normally distributed data (standard deviation), and the median (min-max) was used to express non-normally distributed data
WBC; White blood cell, NLR; Neutrophil-to-lymphocyte ratio, LMR; Lymphocyte-to-monocyte ratio, PLR; Platelet-to-lymphocyte ratio, CRP; C-reactive protein, SII; Systemic immune-inflammatory index (neutrophil x platelet /lymphocyte), PMI; Platelet mass index (platelet count x MPV), MPV; Mean platelet volume, TR; Treatment-requiring, ROP; Retinopathy of prematurity *; Statistically significant

Table 3 shows the variable logistic regression analysis of NLR, PLR, SII, and LMR. When these results were adjusted using logistic regression analysis based on week of birth for TR-ROP, the NLR, PLR, and SII were not statistically different (p=0.11, p=0.83, and p=0.13, respectively). However, only LMR was found to be a significant independent predictor for TR-ROP among all variables examined. [p=0.02, OR=0.38, 95% CI (0.16-0.88)].

For maternal LMR, a ROC test was carried out. It is shown in **Table 4** and **Figure 1**. The ROC analysis showed a cut-off value of 2,807, a sensitivity of 0.73, and a specificity of 0.71, with an area AUC of 0.807 (0.66-0.94) (95% CI).

Discussion

ROP is a multifactorial retinal vascular disease whose pathogenesis consists of two phases. The initial stage is characterized by postnatal hyperoxia, which arrests normal retinal vascularization. In the latter stage, the retina experiences hypoxia as a result of the increased demand of the growing retinal cells afterward. Increased levels of mediators including VEGF, erythropoietin, and insulin-like growth factor-1 cause neovascularization to start[15]. Studies also show a "pre-phase" due to placental inflammation that develops in the mother during the intrauterine period[11]. Studies have shown that neonatal and maternal systemic inflammatory responses are essential in the etiology of ROP[2,16].

To date, inflammatory markers from CBC have been suggested as potential markers of inflammation in various diseases, including bronchopulmonary dysplasia and kidney disease[17,18]. In addition, peripheral blood and biomarker studies are ongoing to predict or detect preterm delivery or ROP. With the increasing importance of the role of inflammation in ROP, studies in this area have increased in recent years. However, a number of different conditions, including normoblasts, earlier or later cord clamping, labor stress, and antenatal administration of steroids, can lead to discordant pediatric CBC results in the early stages of a newborn's life[19,20]. Prenatal maternal inflammation may also influence the pathogenesis of ROP. This study evaluated the potential of maternal inflammatory markers to predict TR-ROP.

The study by Çelik et al.[10] evaluated the CBC parameters of preterm infants treated for ROP treatment and their mothers. While maternal WBC was markedly more elevated in the TR-ROP group, maternal NLR, LMR, PLR, and PCI were not significantly different (maternal WBC AUC=0.69). In addition, infant WBC was significantly lower in the TR-ROP group. Woo et al.[21] found that clinical chorioamnionitis (excluding histological chorioamnionitis) and increased levels of the mother's WBC were a significantly important risk predictor for developing ROP at any stage. We found a significant reduction in maternal lymphocyte count in the TR-ROP. However, GA may affect the results when interpreting neonatal CBC results. Previous studies have reported that neutrophil abnormalities and lymphocyte maturation are altered in GA[22,23]. When the lymphocyte counts adjusted for GA were evaluated, the groups did not significantly differ from one another (p=0.06).

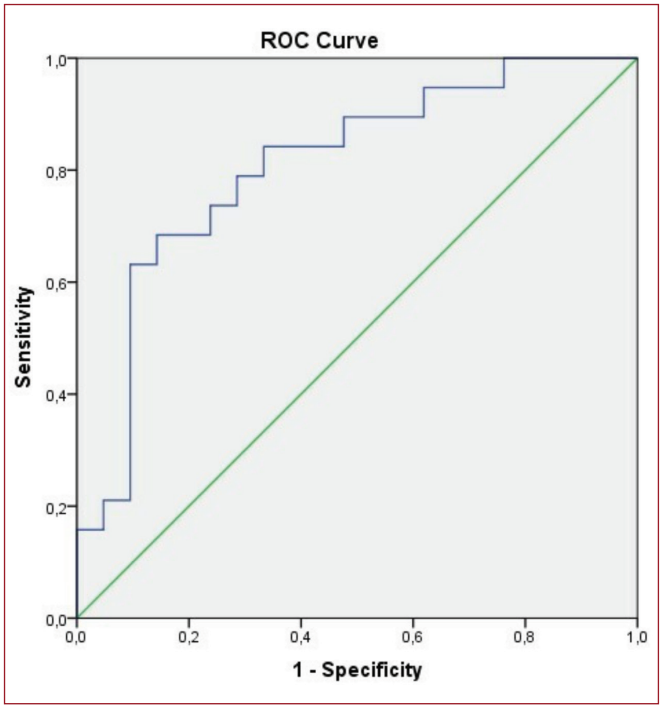

Figure 1. ROC curve for maternal LMR in predicting TR-ROP

ROC; Receiver operating characteristic, LMR; Lymphocyte/monocyte ratio, TR-ROP; Treatment-requiring retinopathy of prematurity

Table 3.
Logistic regression analysis

	OR	95% CI		p-value
		Lower	Upper	
NLR	1.19	0.95	1.48	0.11
LMR	0.38	0.16	0.88	**0.02***
SII	1.00	1.00	1.00	0.13
PLR	1.01	0.99	1.04	0.83

NLR; Neutrophil-to-lymphocyte ratio, LMR; Lymphocyte-to-monocyte ratio, PLR; Platelet-to-lymphocyte ratio, SII; Systemic immune-inflammatory index (neutrophil x platelet /lymphocyte), OR; Odds ratio, 95% CI; 95% confidence interval, *; Statistically significant

Table 4.
ROC analyses of maternal parameters

Maternal parameters	AUC (95%)	cut-off	p-value	Sensitivity %	Specificity %
LMR	0.807 (0.669-0.94)	2.807	**0.001***	73.7	71.4

AUC (95%); Area under the curve with 95% confidence intervals, LMR; Lymphocyte-to-monocyte ratio, *; Statistically significant

Novel inflammatory biomarkers generated from the infants' peripheral blood, including the NLR, PMI, LMR, and PLR, have been determined for predictive ability regarding developing ROP[7,8,24]. A LMR may reflects a suppressed adaptive immune response with heightened inflammation, which has been linked to poor outcomes in several conditions. Hu et al.[7] reported that infants with increased LMR have an independent risk factor for ROP. They suggested that ROP development is substantially and independently correlated with LMR. In a study by Peng et al.[25], maternal PLR was significantly higher in spontaneous preterm birth than in full-term controls, whereas maternal LMR did not differ between groups. In light of these findings, in the prenatal period, PLR may be helpful for predicting preterm delivery, while LMR may be useful for predicting TR-ROP. Furthermore, maternal LMR may be helpful in detecting TR-ROP during screening for ROP. Using ROC analysis, we determined threshold level of maternal LMR for predicting TR-ROP and found that the optimal level was 2.807. These findings suggest that preterm infants whose mothers' LMR is greater than 2.807 are at risk for TR-ROP. The significant inverse association between maternal LMR and TR-ROP in our study suggests that systemic maternal immune dysregulation during pregnancy may contribute to postnatal ROP development. Given its predictive potential, maternal LMR could be integrated into prenatal and perinatal risk assessment strategies for ROP. Maternal LMR measurement during pregnancy could be incorporated into routine prenatal care, particularly in high-risk pregnancies (e.g., preterm births, gestational diabetes, preeclampsia). In addition, infants born to mothers with high LMR could receive enhanced postnatal care, including optimized oxygen therapy, nutritional interventions (e.g., vitamin A, docosahexaenoic acid, and insulin-like growth factor-1 support), and anti-inflammatory strategies to mitigate ROP risk. Nevertheless, the findings require further prospective studies to provide robust support.

The SII is a new immune marker[26]. It has been widely studied in oncology, cardiovascular diseases, and neonatal disorders. Elevated SII levels have been demonstrated to be associated with worse outcomes in various cancers, as a high neutrophil and platelet count with a low lymphocyte count indicates tumour-associated inflammation[27]. Moreover, high SII levels correlate with increased cardiovascular risk, including atherosclerosis and myocardial infarction[28]. The formula for determining this was as follows: neutrophil x platelet/lymphocyte. Akdoğan et al.[8] reported the only study in the literature on the association of SII and ROP, and the present study is the initial to examine the association of the TR-ROP link with maternal SII. They reported that during the one-month observation period, infants with ROP had a greater SII value compared to newborns who did not present with ROP. They also stated that SII may be an independent predictor for ROP. According to our findings, there was no discernible variation in maternal SII between the groups. The data from the current study also showed that the prediction of TR-ROP by SII was not significant.

PMI has been the focus of research in a range of inflammatory and thrombotic conditions, given its established role in platelet function, vascular integrity, and coagulation[29]. In addition, Korkmaz et al.[9] compared premature infants who received laser photocoagulation therapy with premature infants who did not receive treatment. In the 1st phase of ROP, they did not find any variation in PMI levels across the groups; however, in the second phase of ROP, they discovered a substantial difference between the study groups. Their findings suggested that PMI levels during the 2nd stage of ROP might be significant for ROP follow-up. They stated that PMI levels may also rise in association with the rise in VEGF in the 2nd phase of ROP, as platelets play a role in the delivery, retention, and secretion of VEGF. mPV has been shown to be a reliable measure of the average size of platelets and serves as an indirect indicator of platelet activation. Increased platelet volume is frequently associated with an elevated risk of thrombosis, while lower mPV levels may be indicative of impaired platelet production. Research has demonstrated that mPV and PMI levels may be subject to alteration in the context of inflammatory bowel disease activity, underscoring their significance in chronic inflammation, Fournier's gangrene, and necrotizing soft tissue infection[30-32]. The relationship between ROP development and mPV values was examined. Özkaya[33] reported no difference in further platelet values such as PMI, mPV, platelet number, and platelet distribution width between the groups. Similar results were obtained in our study, and maternal mPV, platelet count, and PMI values did not differ across the groups.

Study Limitations

There are various limitations to this study. The retrospective design of this study is its primary limitation. The second is the study's low number of participants. The results of the ROC analysis may have been affected by this small sample size. Third, some maternal stress conditions (such as subclinical chorioamnionitis) that may affect systemic inflammatory markers could not be excluded.

Conclusion

The relationship of maternal SII, PMI, and mPV parameters with TR-ROP was shown for the first time in this study. Maternal LMR in the prenatal period may help predict TR-ROP. Additional studies are needed before these conclusions can be applied to daily clinical practice.

Ethics

Ethical Approval: Ethical approval was granted by Erciyes University Clinical Research Ethics Committee (approval number: 2023/116, date: 08.02.2023).

Informed Consent: These treatment options were discussed with families and applied accordingly after informed consent.

Footnotes

Author Contributions: Polat OA: Surgical and Medical Practices; Karaca Ç, Özer F: Consept; Polat OA, Özer F: Design; Polat OA, Özer F: Data Collection or Processing; Polat OA, Özer F: Analysis or Interpretation; Karaca Ç: Literature Search; Karaca Ç, Polat OA, Özer F: Writing.

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References

1. Cavallaro G, Filippi L, Bagnoli P, et al. The pathophysiology of retinopathy of prematurity: an update of previous and recent knowledge. *Acta Ophthalmol.* 2014;92:2-20. *[CrossRef]*
2. Chen J, Stahl A, Hellstrom A, et al. Current update on retinopathy of prematurity: screening and treatment. *Curr Opin Pediatr.* 2011;23:173-178. *[CrossRef]*
3. Ilhan N, Daglioglu MC, Ilhan O, et al. Assessment of neutrophil/lymphocyte ratio in patients with age-related macular degeneration. *Ocul Immunol Inflamm.* 2015;23:287-290. *[CrossRef]*
4. Yue S, Zhang J, Wu J, et al. Use of the monocyte-tolymphocyte ratio to predict diabetic retinopathy. *Int J Environ Res Public Health.* 2015;12:10009-10019. *[CrossRef]*
5. Dammann O. Inflammation and retinopathy of prematurity. *Acta Paediatr.* 2010;99:975-977. *[CrossRef]*
6. Moysidis SN, Thanos A, Vavvas DG. Mechanisms of inflammation in proliferative vitreoretinopathy: from bench to bedside. *Mediators Inflamm.* 2012;2012:815937. *[CrossRef]*
7. Hu YX, Xu XX, Shao Y, et al. The prognostic value of lymphocyte-to-monocyte ratio in retinopathy of prematurity. *Int J Ophthalmol.* 2017;10:1716. *[CrossRef]*
8. Akdoğan M, Ustundag Y, Cevik SG, et al. Correlation between systemic immune-inflammation index and routine hemogram-related inflammatory markers in the prognosis of retinopathy of prematurity. *Indian J Ophthalmol.* 2021;69:2182. *[CrossRef]*
9. Korkmaz L, Baştuğ O, Özdemir A, et al. Platelet mass index can be a reliable marker in predicting the prognosis of retinopathy of prematurity in very preterm infants. *Pediatr Neonatol.* 2018;59:455-463. *[CrossRef]*
10. Çelik K, Ekinci D, Asena M, et al. Can hematological parameters be a indicator risk factor in the development of retinopathy of prematurity? *Klin Padiatr.* 2021;233:216-220. *[CrossRef]*
11. Lee J, Dammann O. Perinatal infection, inflammation, and retinopathy of prematurity. *Semin Fetal Neonatal Med.* 2012;17:26-29. *[CrossRef]*
12. Koc E, Bas YA, Ozdek S¸ et al. TOD ROP commission, TND ROP Study Group. Turkey's screening guideline for retinopathy of prematurity. *Turkish Neonatal Society and Turkish Ophthalmological Association.* Accessed 14 January 2021. *[CrossRef]*
13. An International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity. *Arch Ophthalmol.* 2005;123:991-999. *[CrossRef]*
14. Early treatment for retinopathy of prematurity cooperative group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol.* 2003;121:1684-1694. *[CrossRef]*
15. Smith LEH. Pathogenesis of retinopathy of prematurity. *Growth Horm IGF Res.* 2004;14 Suppl A:S140-S144. *[CrossRef]*
16. Hellström A, Smith LE, Dammann O. Retinopathy of prematurity. *Lancet.* 2013;382:1445-1457. *[CrossRef]*
17. Yan L, Ren Z, Wang J, et al. The correlation between bronchopulmonary dysplasia and platelet metabolism in preterm infants. *Front Pediatr.* 2021;9:670469. *[CrossRef]*
18. George C, Matsha TE, Erasmus RT, et al. Haematological profile of chronic kidney disease in a mixed-ancestry South African population: a cross-sectional study. *BMJ Open.* 2018;8:e025694. *[CrossRef]*
19. Lawrence SM, Eckert J, Makoni M, et al. Is the use of complete blood counts with manual differentials an antiquated method of determining neutrophil composition in newborns? *Ann Clin Lab Sci.* 2015;45:403-413. *[CrossRef]*
20. Schmutz N, Henry E, Jopling J, et al. Expected ranges for blood neutrophil concentrations of neonates: the Manroe and Mouzinho charts revisited. *J Perinatol.* 2008;28:275-281. *[CrossRef]*
21. Woo SJ, Park KH, Jung HJ, et al. Effects of maternal and placental inflammation on retinopathy of prematurity. *Graefes Arch Clin Exp Ophthalmol.* 2012;250:915-923. *[CrossRef]*
22. Segura-Cervantes E, Mancilla-Ramirez J, Gonzalez-Canudas J, et al. Inflammatory response in preterm and very preterm newborns with sepsis. *Mediators Inflamm.* 2016;2016:6740827. *[CrossRef]*
23. Juul SE, Haynes JW, McPherson RJ. Evaluation of neutropenia and neutrophilia in hospitalized preterm infants. *J Perinatol.* 2004;24:150-157. *[CrossRef]*
24. Ozturk T, Durmaz Engin C, Kaya M, et al. Complete blood count parameters to predict retinopathy of prematurity: when to evaluate and what do they tell us? *Int Ophthalmol.* 2021;41:2009-2018. *[CrossRef]*
25. Peng L, Cao B, Hou F, et al. Relationship between platelet-to-lymphocyte ratio and lymphocyte-to-monocyte ratio with spontaneous preterm birth: a systematic review and meta-analysis. *J Immunol Res.* 2023;2023:6841344. *[CrossRef]*
26. Ustundag Y, Huysal K, Geçgel S, et al. Relationship between Creactive protein, systemic immuneinflammation index, and routine hemogramrelated inflammatory markers in lowgrade inflammation. *Int J Med Biochem.* 2018;1:24-28. *[CrossRef]*
27. Menyhart O, Fekete JT, Győrffy B. Inflammation and colorectal cancer: a meta-analysis of the prognostic significance of the systemic immune-inflammation index (SII) and the systemic inflammation response index (SIRI). *Int J Mol Sci.* 2024;25:8441. *[CrossRef]*
28. Gur DO, Efe MM, Alpsoy S, et al. Systemic immune-inflammatory index as a determinant of atherosclerotic burden and high-risk patients with acute coronary syndromes. *Arq Bras Cardiol.* 2022;119:382-390. (English, Portuguese). *[CrossRef]*
29. Unal M. Platelet mass index is increased in psoriasis. A possible link between psoriasis and atherosclerosis. *Arch Med Sci Atheroscler Dis.* 2016;1:e145-e149. *[CrossRef]*
30. Galijašević M, Dervišević A, Fajkić A, et al. Platelet mass index and other platelet parameters in the assessment of inflammatory bowel diseases activity. *Curr Health Sci J.* 2021;47:566-574. *[CrossRef]*
31. Girgin R, Cinar O, Bulut E, et al. The role of the platelet mass index (PMI) as a new prognostic factor in Fournier's gangrene. *African Journal of Urology.* 2018;24:226-232. *[CrossRef]*
32. Tao Y, Dong Y, Lu CW, et al. Mean platelet volume in retinopathy of prematurity. *Graefes Arch Clin Exp Ophthalmol.* 2015;253:2047-2048. *[CrossRef]*
33. Özkaya, D. The role of thrombocyte parameters in retinopathy of prematurity development. *Int J Clin Pract.* 2022;2022:7518533. *[CrossRef]*

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Pediatric Hyperprolactinemia: Clinical Features, Diagnostic Groups, and Treatment Approaches

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Abstract

Hyperprolactinemia (HPRL) is a rare endocrinopathy in childhood caused by tumors, pituitary stalk interruption, and systemic diseases. In this retrospective study, we examined the clinical characteristics of pediatric patients with prolactin (PRL) elevation. The study examined 70 pediatric and adolescent patients with elevated PRL. The patients (52 female, 18 male; age range, 0.03-18) were divided into two groups: Physiological (n=46, 65.7%) and pathological (iatrogenic+sellar mass) (n=24, 34.3%) HPRL. Six patients (8.6%) were included in the pathological group due to iatrogenic causes and 18 patients (25.7%) due to a sellar mass. Subdiagnostic groups were found in the pathological group: 14 patients with prolactinoma (10 microadenomas; 4 macroadenomas), 6 patients with drug-induced HPRL, 2 patients with craniopharyngioma, 1 patient with dysgerminoma, and 1 patient with tuberculoma. Symptoms such as headache (p=0.004), galactorrhea (p=0.000), amenorrhea (p=0.037), and menstrual irregularity (p=0.037) were more common in the pathological group. Short stature and early thelarche complaints were more common in the physiological group (p=0.004, p=0.045, respectively). The presence of galactorrhea was significant in predicting pathological PRL elevation (p=0.002) (odds ratio=56.1%, 95% confidence interval=4.33-728.1). Twenty-seven point one percent (n=19) received cabergoline treatment, and 8.5% (n=6) received levothyroxine treatment. Three patients underwent surgical treatment for dysgerminoma and craniopharyngioma, respectively. The probability of detecting HPRL is high in the presence of galactorrhea. In prolactinoma, if there are significant pituitary compression symptoms, the disease can be controlled with medical treatment.

Keywords: Childhood, galactorrhea, hyperprolactinemia, prolactinoma

Introduction

Prolactin (PRL) is a hormone primarily secreted by lactotroph cells in the anterior pituitary, playing a crucial role in reproductive function. Factors such as disruption of dopamine inhibition due to pituitary stalk interruption, stress, estrogen, and oxytocin stimulate PRL release[1]. Hyperprolactinemia (HPRL) is a rare endocrinopathy in childhood, which can be physiological, pathological, or iatrogenic, with a prevalence ranging from 0.4% to 5%[2]. Physiologically, PRL levels may rise during stress, REM sleep, pregnancy, or a high-protein diet. Pathological

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causes include tumors, pituitary stalk interruption, and systemic diseases, with chronic kidney failure, hypothyroidism, and polycystic ovary syndrome being significant systemic conditions. Iatrogenic elevation of PRL levels can occur due to the use of antihypertensive drugs, oral contraceptives, antiepileptic drugs, and antipsychotic medications[3].

Childhood HPRL is most commonly attributed to medications and adenomas[3,4]. Prolactinomas are the most frequent type of pituitary adenoma[5].

The clinical presentation of HPRL varies depending on the etiology, ranging from asymptomatic cases to complaints such as delayed puberty, amenorrhea, menstrual irregularities, galactorrhea, headaches, and vision problems[6]. HPRL can also occur in children with short stature and obesity[7]. PRL is known to play a role in breast development in girls and gynecomastia in boys[8,9].

Highlights

- The etiology of hyperprolactinemia is known.
- Medical therapy is the first choice of treatment for prolactin-secreting pituitary adenomas, including macroadenomas.
- Physiological prolactin elevation is a common condition in childhood.
- We believe that our study will guide clinicians in the diagnosis and treatment of hyperprolactinemia.
- Measuring prolactin levels is important in the etiology of short stature in childhood.
- Galactorrhea is almost always a sign of pathological hyperprolactinemia.

Since PRL is released in a pulsatile manner, a single measurement may not be reliable. PRL levels above 100 ng/mL do not require confirmation, but levels between 20-100 ng/mL necessitate at least two measurements. Values exceeding 500 ng/mL are indicative of macroprolactinomas[10]. In patients with HPRL, pituitary magnetic resonance imaging (MRI) and visual field examination are crucial for diagnosis and follow-up[11]. Treatment involves etiology-specific interventions and the use of dopamine agonist drugs such as cabergoline and bromocriptine. Cabergoline is better tolerated and more effective in pediatric cases[12,13]. Surgical treatment is necessary for patients who do not respond to medical treatment and experience vision problems. Caution is required postoperatively due to the risk of pituitary insufficiency. In this retrospective study, we examined the clinical, etiological, and treatment characteristics of pediatric patients with elevated PRL levels.

Material and Method

This study is a single-center retrospective analysis conducted with the approval of the local ethics committee (protocol code: 2023-240, date 07/06/2023). Seventy children and adolescents who presented to the pediatric endocrinology clinic between 2021 and 2023 with elevated PRL levels were screened. Age, sex, presenting symptoms, comorbidities, medications used, and physical examination findings were recorded. Pubertal signs were classified according to Tanner's staging[14,15]. Patients were categorized into two groups: Physiological and pathological (iatrogenic+sellar mass) HPRL. Patients whose PRL levels spontaneously returned to normal were considered physiologically elevated PRL (within 1 week-3 months period). PRL, adrenocorticotropic hormone, cortisol, thyroid-stimulating hormone (TSH), and free thyroxine levels were analyzed in venous blood taken in the morning after overnight fasting. PRL levels between 4.79 and 23.3 ng/mL were considered normal. Patients with at least two measurements showing elevated levels, taken at least one week apart, were regarded as having HPRL. The measurement was repeated to exclude elevation due to stress, infection, and other similar factors. PRL measurement intervals of patients under treatment after diagnosis varied among patients.

Those not considered physiological underwent pituitary MRI. Some of the physiological group also underwent MRI before the diagnosis was clear. MRI was performed on patients with at least two PRL measurements over 45 ng/mL. MRI was not performed during temporary mild elevations. The study states that patients diagnosed with adenomas with a diameter of 1 cm or less were defined as having microadenomas, while those larger than 1 cm were defined as macroadenomas. Patients diagnosed with prolactinoma underwent visual field examination. Dopamine agonist treatment was applied to all patients diagnosed with macroadenomas and symptomatic microadenomas (galactorrhea, amenorrhea). The dose and duration of treatment for those who received treatment were recorded. PRL levels were checked after treatment (at least two weeks later). Patients requiring brain surgery underwent a control pituitary MRI and regression was assessed. An echocardiogram was taken during the follow-up of patients, who had been using cabergoline for a long period.

Statistical Analysis

The study data were analyzed using Statistical Package for the Social Sciences 24.0 (SPSS Inc., Chicago, Illinois). Descriptive statistics were presented as mean ± standard deviation (SD) and frequency (%). The Kolmogorov-Smirnov test assessed the normal distribution of continuous variables between groups. Parameters that fit the normal distribution were compared using Student's t-test, and those that did not follow a normal distribution were compared using the Mann-Whitney U test. Categorical variables were compared between groups using the chi-square test. A p-value <0.05 was considered statistically significant. Logistic regression analysis was used to determine predictive factors for pathological findings.

Results

A total of 70 patients with a mean age of 11.35±4.73 years (range=0.03-18 years) were evaluated in our study, including 52 females (74.3%) and 18 males (25.7%). The patients' anthropometric measurements are presented in

the table (**Table 1**). Patients were divided into two groups: Physiological (n=46, 65.7%) and pathological (n=24, 34.3%) (iatrogenic+sellar mass). Six patients (8.6%) were included in the iatrogenic group (drug-related, four patients on risperidone, one on sertraline and fluoxetine, and one on levodopa), and 18 patients (25.7%) were included in the pathological group due to sellar masses. Among the pathological group, subdiagnostic groups were identified: 14 patients with prolactinoma, six with drug-induced HPRL, two with craniopharyngioma, one with dysgerminoma, and one with tuberculoma. In the physiological group, six patients had transient HPRL due to TSH elevation, and one patient had elevated PRL due to mini puberty. Normalization of PRL levels was observed with hypothyroidism treatment. In cases of elevated PRL levels without an identified etiology, levels often returned to normal upon repeated measurements. The mean age was lower in the physiological group. Height, body weight, and body mass index (BMI) SD score were significantly higher in the pathological group (**Table 1**).

The presenting complaints are shown in **Table 2**. Headaches, galactorrhea, amenorrhea, and menstrual irregularities were more frequent in the pathological group, with p-values of p=0.004 for headaches, p<0.001 for galactorrhea, and p=0.037 for amenorrhea and menstrual irregularities. Short stature and early telarche complaints were more frequent in the physiological group (p=0.004, p=0.045). Among the additional diseases, 14 patients (20%) had hypothyroidism, five (7.1%) had adrenal insufficiency, five (7.1%) had growth hormone deficiency, and four (5.7%) had hypogonadism.

Patients were at the following pubertal stages: 35.1% at stage 1, 15.7% at stage 2, 4.3% at stage 3, 2.9% at stage 4, and 41.4% at stage 5. The physiological group was more often at stage 1 (41.3%), but this was not statistically significant (p=0.17). The pathological group was more frequently at stage 5 (62.5%), significantly higher than the other group (p=0.01). Three patients (4.3%) had visual field problems and were diagnosed with craniopharyngioma and dysgerminoma. PRL levels were significantly higher in the pathological group (**Table 1**). PRL levels in the drug-induced group were 77.9±51.01 ng/mL (minimum=42, maximum=188). Laboratory findings of patients with primary hypothyroidism are presented in **Table 3**.

Among the 36 patients evaluated with contrast-enhanced pituitary MRI, ten patients (14.3%) had microadenomas, four (5.7%) had macroadenomas, two (2.9%) had craniopharyngioma, one (1.4%) had dysgerminoma, one (1.4%) had tuberculoma, one (1.4%) had hydrocephalus, one (1.4%) had an arachnoid cyst, and one (1.4%) had pituitary hypoplasia. Fifteen patients (21.4%) had a normal MRI.

In the etiological investigation, 38 patients (54.2%) had no underlying pathology; 14 patients (20%) had prolactinoma (10 microadenomas and four macroadenomas); six (8.5%) had drug-induced HPRL (four risperidone, one levodopa, and one fluoxetine); six (8.5%) had HPRL secondary to TSH elevation due to primary hypothyroidism; two (2.8%) had craniopharyngioma; one (1.4%) had dysgerminoma; one (1.4%) had tuberculoma; one (1.4%) had hydrocephalus; and one (1.4%) had HPRL due to mini puberty. Fifty percent of macroadenoma cases and all microadenoma cases were female. The mean age of patients with microadenomas was 14.29±4.34 years (range=3.3-17.5), and for those with macroadenomas, it was 14.42±2.59 years (range=11.2-17.4).

Table 1.
Relationship between patients' anthropometric measurements and PRL levels

	Physiological; 35/52 girl, 11/18 boy		Pathological (iatrogenic+sellar mass); 17/52 girl, 7/18 boy		95% CI lower	p-value
	Mean ± SD	Minimum-maximum	Mean ± SD	Minimum-maximum		
Age	10.3±4.9	0.03-18	13.3±3.7	3.3-17.5	0.89-5.08	0.006
Weight SDS	-0.4±1.8	-4.1-3.3	0.4±1.8	-2.80-4.2	-0.15-1.85	0.054
Height SDS	-1.05±1.8	-6.3-4.0	-0.6±1.6	-5.4-1.56	-0.48-1.21	0.398
BMI SDS	0.07±1.4	-2.6-2.9	0.9±1.4	-2.07-3.5	0.12-1.57	0.023
Prolactin levels (ng/mL)	46.2±23.4	24-154	163.3±270.2	27.2-1.356	2.79-231-402	0.045

SD; Standard deviation, CI; Confidence interval, SDS; Standard deviation score, BMI; Body mass index

Table 2.
Patients' complaints

Complaint (n,%)	Physiological group (percentage %)	Pathological group (percentage %)	p-value
Short stature (25, 35.7%)	45.7%	16.7%	0.004
Galactorrhea (10, 14.3%)	2.2%	37.5%	<0.001
Menstrual irregularities (9, 12.9%)	6.5%	25%	0.037
Early breast development (7.10%)	15.2%	0	0.045
Increased body hair (6, 8.6%)	10.9%	4.2%	
Headaches (5, 7.1%)	0	20.8%	0.004
Vision problems (4, 5.7%)	2.2%	12.5%	
Amenorrhea (3, 4.3%)	0	12.5%	0.037

Sixty-four point three percent (n=45) of patients did not require treatment. Twenty-seven point one percent (n=19) received cabergoline treatment, and 8.5% (n=6) received levothyroxine treatment. Surgical treatment was applied to three patients with dysgerminoma and craniopharyngioma cabergoline treatment was discontinued for nine patients as it was no longer needed. The average duration of cabergoline treatment was 8.57±8.76 months (range=1-24). The treatment period for microadenomas was 7±7.9 months and for macroadenomas it was 13.5±9.6 months. The cabergoline dose was adjusted between 0.5 mg/week and 2 mg/week. No drug side effects were observed. Nine patients were still on cabergoline when the study was completed. The adenomas of the patients still on treatment had not completely regressed and their PRL levels were increasing without medication. Three patients with iatrogenic elevated PRL were treated with cabergoline, because they were symptomatic. The treatment duration was 2-3 months. Treatment durations were short for patients whose PRL levels improved quickly, whose adenomas regressed, or whose iatrogenic causes were eliminated. The duration of treatment was longer in patients with macroadenoma. The adenoma sizes on MRIs, control MRI durations, and adenoma sizes after regression, are shown in **Table 4** for the ten patients diagnosed with adenoma. An echocardiogram was taken during the follow-up of patients using cabergoline for for more than 6 months. Tricuspid regurgitation or aortic valve calcification was not observed in the patients. In regression analysis, galactorrhea complaints significantly predicted pathological HPRL (p=0.002) (odds ratio=56.1, 95% confidence interval=4.33-728.1). Logistic regression analysis was performed on variables that were found to be significant with the chi-square test (headache, galactorrhea, amenorrhea, menstrual irregularity, short stature, and premature telarche). Galactorrhea was found to be significant. The large range of odds ratio was attributed to the small proportions. Short stature, delayed puberty, amenorrhea, and menstrual irregularities were not significant in predicting pathology.

Discussion

HPRL is rare in childhood, and physiological elevations are sometimes encountered[2]. HPRL is caused by excessive secretion from pituitary lactotroph cells or by the removal of dopamine inhibition on PRL (such as pituitary stalk incision, stress, oxytocin, and oestrogen effects). Drug-induced HPRL can also be seen in a considerable number of cases in childhood[3,4]. Pathological HPRL is often due to pituitary adenomas[3]. In a study by Kontbay et al.[16], 40.7% of 27 children with HPRL were found to have prolactinoma (6 macroadenomas and 5 microadenomas). In our study,

Table 3.
Thyroid hormone and prolactin levels in primary hypothyroid patients

	TSH (uIU/mL)	ft4 (ng/dL)	PRL before treatment (ng/mL)	PRL after treatment (ng/mL)
n	6	6	6	6
Mean	235.5	0.63	46.25	22.6
Median	185	0.65	35	22.5
Standard deviation	258.26	0.39	20.5	3.85
Minimum	7	0.05	30	17
Maximum	772	1.20	85	29

TSH; Thyroid-stimulating hormone, ft4; Free thyroxine, PRL; Prolactin

Table 4.
Pituitary adenoma sizes

Adenoma size (mm)	Prolactin levels (ng/mL) (before-after treatment)	MRI check-up time (month)	Adenoma size (mm) after treatment
38	204-28	3-6-12-24	30-21-12-6
30	unfollowed	unfollowed	
16	365-10	3-8	0
10	351-4.9	3	3
9	34-25 (amenorrhea)	3	7.9
9	75-11 (galactorrhea)	7	0
6.6	91-12 (galactorrhea)	4	0
6	155-3	4	1
5.6	180-25	11	1
4.5	156-19 (amenorrhea)	3	0
4	95-37 (amenorrhea)	8	1
3.5	68-7 (short stature)	4	0
2	42-0.4 (galactorrhea)	3	0
1	95-37 (amenorrhea)	3	0

MRI; Magnetic resonance imaging

34.3% of the cases had pathological HPRL, and there was a 25.7% prevalence of sellar masses.

The prevalence of macroadenomas is higher in affected males[17]. In a study by Eren et al.[18], 93.4% of microadenoma cases were female patients, and 77.7% of macroadenoma cases were female patients. In our study, the prevalence of macroadenomas was equal in both females and males, while microadenomas were more frequent in females, consistent with the literature.

The presenting complaints of HPRL vary according to etiology. Delayed puberty, amenorrhea, menstrual irregularities, galactorrhea, headaches, and visual problems are common reasons for consultation, though these conditions can sometimes be asymptomatic at first[6]. In a study by Breil et al.[13], the most common symptoms in 12 children with prolactinomas, who account for 21 HPRL cases, were headaches and delayed puberty, emphasizing the need to investigate HPRL in the presence of these symptoms. In a study of 39 patients, aged 9-20, with prolactinomas (30 macroadenomas, 9 microadenomas), 23 cases (all females) had galactorrhea[19]. In another study, 89% of those diagnosed with prolactinoma were symptomatic, with the most common symptom being headaches (54.5%)[16]. In our study, symptoms such as headaches, galactorrhea, amenorrhea, and menstrual irregularities were significantly more prevalent in pathological HPRL. Although the headache rate in the pathological group was lower than in previous studies, headaches were still more common in the pathological group than in the physiological group. In pediatric patients, symptoms such as short stature, amenorrhea, menstrual irregularity, early thelarche, narrowing of the visual field, and headache require measurement of routine PRL levels. Galactorrhea was particularly predictive of pathological PRL elevation. The presence of galactorrhea is an important finding that requires investigation for elevated PRL levels, as emphasized in the Pituitary Society International Consensus Statement[20].

Elevation of TSH can lead to HPRL due to subunit similarity. A study by Arslan et al.[21] compared non-prolactinoma HPRL, prolactinoma, and a healthy control group, showing that hyperprolactinemic patients had increased thyroid volume, thyroid nodules, and thyroid autoimmunity. The prevalence of HPRL in subclinical hypothyroidism in children is unknown. In a study evaluating hormonal data from 602 pediatric patients, overt primary hypothyroidism was more predictive of HPRL, and subclinical hypothyroidism predicted HPRL more frequently than in euthyroid patients[22]. In our study, HPRL due to TSH elevation was detected in 6 patients, and PRL levels returned to normal with levothyroxine treatment. Due to the small sample size, no statistical conclusions could be drawn regarding thyroid volume and autoimmunity.

Drug use is a significant cause of HPRL, especially since many antipsychotic drugs affect the dopaminergic system and increase PRL levels[23]. In a multicenter study, drug-induced HPRL was observed in 6% of cases[16]. In our study, drug-induced HPRL was found in 8.6% of cases. A meta-analysis of 32 studies involving 4,643 pediatric participants examined the effects of antipsychotics on PRL levels, reporting that risperidone, paliperidone, and olanzapine significantly increased PRL levels, while aripiprazole, decreased them[24]. In our study, four patients were using risperidone, one was using levodopa, and one was using sertraline and fluoxetine. Three of our patients were treated with short-term cabergoline because they were symptomatic as psychiatric medication could not be stopped. However, we did not have enough data for statistical analysis.

Disruption of normal dopaminergic inhibition of PRL occurs in pituitary stalk lesions, leading to HPRL. In a study of 55 pituitary stalk incisions, the frequency of HPRL was 36.4%[25]. In our study, three patients with sellar masses had HPRL. PRL levels above 100 ng/mL do not require further investigation, but values between 20-100 ng/mL warrant at least two measurements. Values above 500 ng/mL are diagnostic of macroadenomas[10]. In a study, the average PRL level in the prolactinoma group was 118 (range=34-4.340) ng/mL, while in the non-prolactinoma group, it was 38.7 (range=22.9-200) ng/mL[16]. In our study, PRL levels were significantly higher in the pathological group, consistent with the literature.

Children with short stature and obesity are at risk and should be investigated for HPRL[7]. In our study, short stature was more common in the physiological group, whereas BMI increased in the pathological group. In a study by Eren et al.[18], 22.6% of cases reported weight gain, and 30.9% were overweight or obese. In our clinic, PRL levels are routinely checked for short stature; this may explain the higher incidence observed in our study.

Repeated measurements are necessary when PRL levels are less than five times the upper limit of normal, as physiological increases occur in stress-related situations[20]. Temporary increases were also observed in our study. Unnecessary further examinations were avoided by repeating measurements. Dopamine agonist drugs, such as cabergoline and bromocriptine, are used to treat prolactinomas. Cabergoline is better tolerated and more effective in childhood compared to other similar medications[12,13]. In a study of 39 patients aged 9-20 with prolactinomas (30 macroadenomas, 9 microadenomas), only two patients underwent surgery and radiotherapy, while all others received medical treatment. The average follow-up period was 56 months, and medical treatment is concluded to be reliable and preserves pituitary functions[19]. In a study by Breil et al.[13], cabergoline reduced tumor sizes by 80% in 12 pediatric patients with prolactinomas over a treatment period of 12-89 months. Additionally, the study included 21 patients with HPRL.

Preserving vision is essential for patients with treatment-resistant vision problems, and surgical treatment is often performed using the transsphenoidal method in these cases[7]. Rarely, radiotherapy is recommended[13]. In a study of 11 pediatric patients with prolactinomas, surgical treatment was performed on three patients with vision problems[16]. In our study, none of the patients with prolactinomas required surgical treatment. Even patients with macroadenomas responded to medical treatment. Surgery was performed on only three patients diagnosed with dysgerminoma and craniopharyngioma.

Medical treatment reduced tumor size, with an average treatment duration of 8.57 months. The short duration was due to the presence of microadenomas in most of our cases. However, since the longest follow-up period was 24 months, our average duration of treatment appears short, and we still have patients undergoing treatment.

Study Limitations

This study has several limitations, including its retrospective design, potential selection bias, and the relatively small sample size. While the findings may be generalizable to certain populations, larger and more extensive prospective studies are needed to validate the results. Additionally, the study did not assess long-term outcomes or potential complications associated with different treatment modalities. The maximum duration of treatment is 24 months, and long-term studies are needed. Future research should address these limitations and provide more comprehensive insights into the management and outcomes of HPRL in children and adolescents.

Conclusion

Our study aimed to highlight both the physiological and pathological causes of HPRL by presenting cases with elevated PRL levels. Although most of our patients with short stature were in the physiological group, a significant proportion were also in the pathological group. Measurement of PRL levels should be among the first investigations in cases of short stature. The likelihood of detecting HPRL is high in the presence of galactorrhea, as it is almost always considered a pathological finding. In cases of prolactinoma, where there are no visual field defects or significant signs of pituitary compression, the disease can typically be effectively controlled with medical treatment.

Ethics

Ethical Approval: This study is a single-center retrospective analysis conducted with the approval of the local ethics committee (protocol code: 2023-240, date 07/06/2023).

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

Footnotes

Author Contributions: Aytaç Kaplan EH, Kocabey Sütçü Z, Önal H: Surgical and Medical Practices; Aytaç Kaplan EH: Consept; Aytaç Kaplan EH: Design; Aytaç Kaplan EH, Kocabey Sütçü Z, Önal H: Data Collection or Processing; Aytaç Kaplan EH, Önal H: Analysis or Interpretation; Aytaç Kaplan EH, Kocabey Sütçü Z: Literature Search; Aytaç Kaplan EH, Önal H: Writing.

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References

1. Saranac L, Zivanovic S, Radovanovic Z, et al. Hyperprolactinemia: different clinical expression in childhood. *Horm Res Paediatr.* 2010;73:187-192. *[CrossRef]*
2. Mancini T, Casanueva FF, Giustina A. Hyperprolactinemia and prolactinomas. *Endocrinol Metab Clin North Am.* 2008;37:67-99. *[CrossRef]*
3. Catli G, Abaci A, Altincik A, et al. Hyperprolactinemia in children: clinical features and long-term results. *J Pediatr Endocrinol Metab.* 2012;25:1123-1128. *[CrossRef]*
4. Saito E, Correll CU, Gallelli K, et al. A prospective study of hyperprolactinemia in children and adolescents treated with atypical antipsychotic agents. *J Child Adolesc Psychopharmacol.* 2004;14:350-358. *[CrossRef]*
5. Palubska S, Adamiak-Godlewska A, Winkler I, et al. Hyperprolactinaemia - a problem in patients from the reproductive period to the menopause. *Prz Menopauzalny.* 2017;16:1-7. *[CrossRef]*
6. Fideleff HL, Boquete HR, Suárez MG, Azaretzky M. Prolactinoma in children and adolescents. *Horm Res.* 2009;72:197-205. *[CrossRef]*
7. Eren E, Yapıcı Ş, Çakır ED, et al. Clinical course of hyperprolactinemia in children and adolescents: a review of 21 cases. *J Clin Res Pediatr Endocrinol.* 2011;3:65-69. *[CrossRef]*
8. Frantz AG. The breasts. In : Textbook of Endocrinology 1981, edited by R.H. Williams, W.B. Saunders, Philadelphia, pp. 400-411. *[CrossRef]*
9. Kaplan SL, Grumbach MM, Friesen HG, Costom BH. Thyrotropin releasing factor (TRF) effect on secretion of human pituitary prolactin and thyrotropin in children and in idiopathic hypopituitary dwarfism: further evidence for hypophysiotropic hormone deficiencies. *J Clin Endocrinol Metab.* 1972;35:825-830. *[CrossRef]*
10. Karavitaki N, Thanabalasingham G, Shore HC, et al. Do the limits of serum prolactin in disconnection hyperprolactinaemia need re-definition? A study of 226 patients with histologically verified non-functioning pituitary macroadenoma. *Clin Endocrinol (Oxf).* 2006;65:524-529. *[CrossRef]*
11. Özçetin M, Karacı M, Toroslu E, Edebali N. A pediatric case of pituitary macroadenoma presenting with pituitary apoplexy and cranial nerve involvement: case report. *Turk Pediatri Ars.* 2016;51:162-165. *[CrossRef]*
12. Webster J, Piscitelli G, Polli A, Ferrari CI, Ismail I, Scanlon MF. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. Cabergoline Comparative Study Group. *N Engl J Med.* 1994;331:904-909. *[CrossRef]*
13. Breil T, Lorz C, Choukair D, et al. Clinical features and re-sponse to treatment of prolactinomas in children and ado-lescents: a retrospective single-centre analysis and review of the literature. *Horm Res Paediatr.* 2018;89:157-165. *[CrossRef]*
14. Marshall WAT, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child.* 1970;45:13-23. *[CrossRef]*
15. Marshall WAT, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child.* 1969;44:291-303. *[CrossRef]*
16. Kontbay T, Şıklar Z, Özsu E, et al. Hyperprolactinemia in children and adolescents and longterm follow-up results of prolactinoma cases: a single-centre experience. *Turk J Pediatr.* 2022;64:892-899. *[CrossRef]*
17. Hoffmann A, Adelmann S, Lohle K, Claviez A, Müller HL. Pediatric prolactinoma: initial presentation, treatment, and long-term prognosis. *Eur J Pediatr.* 2018;177:125-132. *[CrossRef]*
18. Eren E, Törel Ergür A, İşgüven ŞP, et al. Clinical and laboratory characteristics of hyperprolactinemia in children and adolescents: national survey. *J Clin Resp Pediatr Endocrinol.* 2019;11:149-156. *[CrossRef]*
19. Acharya SV, Gopal RA, Bandgar TR, et al. Clinical profile and long term follow up of children and adolescents with prolactinomas. *Pituitary.* 2009;12:186-189. *[CrossRef]*
20. Petersenn S, Fleseriu M, Casanueva FF, et al. Diagnosis and management of prolactin-secreting pituitary adenomas: a Pituitary Society International Consensus Statement. *Nat Rev Endocrinol.* 2023;19:722-740. *[CrossRef]*

21. Arslan MS, Sahin M, Topaloğlu O, et al. Hyperprolactinaemia associated with increased thyroid volume and autoimmune thyroiditis in patients with prolactinoma. *Clin Endocrinol (Oxf).* 2013;79:882-886. *[CrossRef]*

22. Sharma N, Dutta D, Sharma LK. Hyperprolactinemia in children with subclinical hypothyroidism. *J Clin Resp Pediatr Endocrinol.* 2017;9:350-354. *[CrossRef]*

23. Ajmal A, Joffe H, Nachtigall LB. Psychotropic-induced hyperprolactinemia: a clinical review. *Psychosomatics.* 2014;55:29-36. *[CrossRef]*

24. Kroigaard SM, Clemmmensen L, Tarp S, Pagsberg AK. A meta-analysis of antipsychotic-induced hypo- and hyperprolactinemia in children and adolescents. *J Child Adolesc Psychopharmacol.* 2022;32:374-389. *[CrossRef]*

25. Guo Q, Yang Y, Mu Y, et al. Pituitary stalk interruption syndrome in Chinese people: clinical characteristic analysis of 55 cases. *PLoS One.* 2013;8:e53579. *[CrossRef]*

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Case Report

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A Rare Case of Osteoblastoma of the Sacrum

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Abstract

Osteoblastoma (OB) is a rare bone tumor. It is classified as benign and represents about 1% of all bone neoplasms. While it typically occurs in the axial skeleton, sacral involvement is extremely rare. Despite its non-malignant nature, OB can be locally aggressive and may lead to considerable morbidity if not addressed in a timely manner. This report discusses a unique case of sacral, focusing on the clinical, radiological, and surgical features. A 14-year-old male patient reported experiencing increasing pain in his left lower limb and lumbosacral region for two years. A magnetic resonance imaging (MRI) of the lumbosacral area identified a mass measuring 50x43 mm on the left side of the sacrum in T2-weighted images. Further evaluation with a positron emission tomography/computerized tomography (PET/CT) scan indicated a destructive bone lesion in the left sacrum, measuring 43x40 mm, with a soft tissue component and increased fluorodeoxyglucose (FDG) uptake (standardized uptake value maximum: 11). The patient underwent surgical excision by a neurosurgery team, and histopathological analysis confirmed the diagnosis of OB. Although OB is a benign tumor, its location can cause significant symptoms, particularly in rare areas like the sacrum. Diagnostic imaging modalities such as MRI and PET/CT are crucial for identifying the tumor and planning surgical intervention. The elevated FDG uptake observed on PET/CT indicated a metabolically active lesion, reinforcing the need for surgical treatment. Sacral OB is an exceptionally rare entity. This case underscores the need to include OB in the differential diagnosis of sacral lesions and illustrates the value of imaging in facilitating accurate diagnosis and management. Surgical resection remains the cornerstone of treatment, offering good clinical outcomes.

Keywords: Osteoblastoma, sacrum, primary bone tumor, case report

Introduction

Osteoblastoma (OB) is an uncommon, non-cancerous bone tumor. It represents roughly 1% of all bone tumors.[1] Of these, 40% are found in the axial skeleton. OBs are very rare in the sacrum.[2,3] OBs are reported to occur in children aged 10-15 years.[4] OB is more common in males. It often arises in the spine.[5] Clinically, it presents with pain, swelling, warmth, and tenderness. In OB, the pain typically does not improve with non-steroidal anti-inflammatory drugs (NSAIDs). Some OBs may present with paresthesias and paraparesis.[6] The standard treatment for OBs is total surgical excision. Thermoablation and high-intensity focused ultrasound can be used, especially for small

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lesions.[7] We present an unusual case of OB located in the sacrum.

Case Report

A 14-year-old male patient reported experiencing increasing pain in his left lower limb and lumbosacral region for two years. The patient stated that these symptoms appeared 2 years ago and intensified in the 4 months before the admission. In the lumbosacral magnetic resonance imaging (MRI) of the patient, a mass lesion was detected in the sacrum on the T2 sequence with the size of 50x43 mm measured in the coronal sections on the left. In positron emission tomography/computed tomography (CT), a destructive bone lesion with soft tissue component, measuring 43x40 mm, was detected in the axial plane, showing increased fluorodeoxyglucose metabolism (standardized uptake value maximum:11) in the left sacrum (**Figure 1**). He was operated by neurosurgery. Histopathology was reported as OB. In the lumbosacral MRI taken after the operation, no residual mass lesion was observed in the operation area. Informed consent was obtained from the patient's parents.

Pathological Findings

OB, benign osteoblastic lesion was detected. The special AT-rich sequence-binding protein 2 was positive.

Treatment

The primary treatment for patients with OB is surgery.[8] Currently, the preferred treatments for these lesions include percutaneous thermoablation techniques, with radiofrequency ablation under CT guidance being considered the gold standard.[9-11]

Discussion

OBs are uncommon tumors, making up less than 1% of all bone neoplasms. They predominantly affect males, with an approximate male-to-female ratio of 2.5:1.[12,13] OBs are typically diagnosed during adolescence,[14] and our patient's diagnosis at the age of 14 falls within this expected range. While 30-40% of OB cases involve the spine, the cervical region is the most frequent site, with the lumbar spine and sacrum being less frequently affected.[15] In our case, the OB was detected in the sacrum.

Histologically, OB is composed of highly vascularized connective tissue and immature bone.[16] Although it is a benign, slow-growing tumor, sacral OBs can be particularly challenging due to their location. It typically presents with pain. It often does not respond to NSAIDs.[17] OBs generally measure between 3 to 4 cm; however, those located in the sacrum tend to be larger,[18] as seen in our patient, whose tumor measured approximately 5 cm.

The preferred treatment approach is complete surgical excision, as this provides the highest likelihood of a cure and lowers the risk of recurrence.[19] Our patient underwent successful surgical removal of the tumor. Recurrence rates can reach up to 25%, and some patients may experience multiple local recurrences. The use of adjuvant chemotherapy or radiotherapy in OB treatment remains unclear, with no consensus on its effectiveness.[20]

Conclusion

Sacral OBs are rare and can be challenging to diagnose. However, with modern imaging and treatment techniques, precise surgical planning has

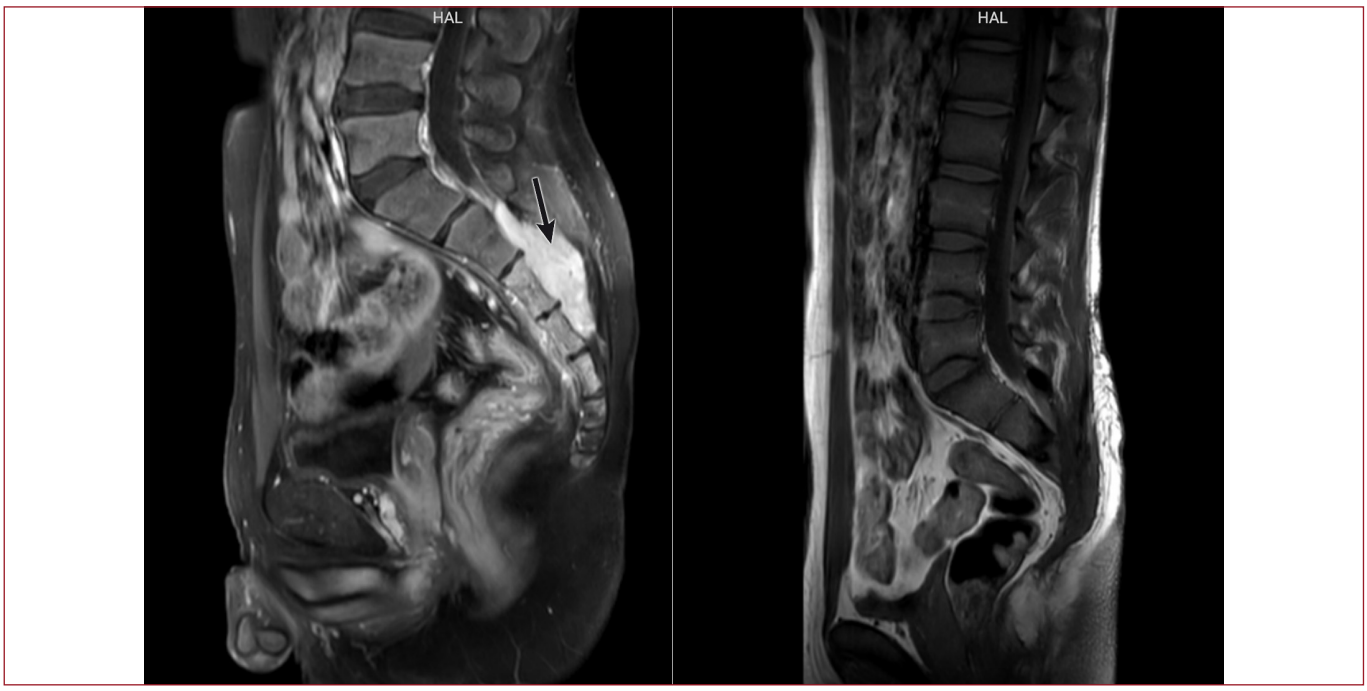

Figure 1. Preoperative and postoperative MRI images for osteoblastoma
MRI: Magnetic resonance imaging

become feasible even for difficult locations such as the sacrum.

References

1. Unni KK. Benign osteoblastoma (giant osteoid osteoma). In: Unni KK, ed. Dahlin's Bone Tumours: General Aspects and Data on 11 087 Cases. 5th ed. Philadelphia, PA: *Lippincott-Raven,* 1996:131-142. *[Crossref]*
2. Burn SC, Ansorge O, Zeller R, et al. Management of osteoblastoma and osteoid osteoma of the spine in childhood. *J Neurosurg Pediatr.* 2009;4:434-438. *[Crossref]*
3. Rana V, Saxena V, Sahai K, et al. Epithelioid osteoblastoma of maxilla: a rare and aggressive variant of a benign neoplasm at an uncommon site. *J Oral Maxillofac Pathol.* 2016;20:332. *[Crossref]*
4. Galgano MA, Goulart CR, Iwenofu H, et al. Osteoblastomas of the spine: a comprehensive review. *Neurosurg Focus.* 2016;41:4. *[Crossref]*
5. Thakur NA, Daniels AH, Schiller J, et al. Benign tumors of the spine. *J Am Acad Orthop Surg.* 2012;20:715-724. *[Crossref]*
6. Atesok KI, Alman BA, Schemitsch EH, et al. Osteoid osteoma and osteoblastoma. *J Am Acad Orthop Surg.* 2011;19:678-689. *[Crossref]*
7. Arrigoni F, Bruno F, Palumbo P, et al. Magnetic resonance-guided focused ultrasound surgery treatment of non-spinal intra-articular osteoblastoma: feasibility, safety, and outcomes in a single-center retrospective analysis. *Int J Hyperthermia.* 2019;36:768-775. *[Crossref]*
8. Ozaki T, Liljenqvist U, Hillmann A, et al. Osteoid osteoma and osteoblastoma of the spine: experiences with 22 patients. *Clin Orthop Relat Res.* 2002:394-402. *[Crossref]*
9. Beyer T, van Rijswijk CSP, Villagrán JM, et al. European multicentre study on technical success and long-term clinical outcome of radiofrequency ablation for the treatment of spinal osteoid osteomas and osteoblastomas. *Neuroradiology.* 2019;61:935-942. Erratum in: *Neuroradiology.* 2019;61:943. *[Crossref]*
10. Masciocchi C, Arrigoni F, La Marra A, et al. Treatment of focal benign lesions of the bone: MRgFUS and RFA. *Br J Radiol.* 2016;89:20150356. *[Crossref]*
11. Rehnitz C, Sprengel SD, Lehner B, et al. CT-guided radiofrequency ablation of osteoid osteoma and osteoblastoma: Clinical success and long-term follow up in 77 patients. *Eur J Radiol.* 2012;81:3426-3434. *[Crossref]*
12. Saglik Y, Atalar H, Yildiz Y, et al. Surgical treatment of osteoblastoma: a report of 20 cases. *Acta Orthop Belg.* 2007;73:747-753. *[Crossref]*
13. Saccomanni B. Osteoid osteoma and osteoblastoma of the spine: a review of the literature. *Curr Rev Musculoskelet Med.* 2009;2:65-67. Erratum: *Curr Rev Musculoskelet Med.* 2012;5:263. *[Crossref]*
14. Chotel F, Franck F, Solla F, et al. Osteoid osteoma transformation into osteoblastoma: fact or fiction? *Orthop Traumatol Surg Res.* 2012;98(6 Suppl):98-104. *[Crossref]*
15. Avadhanam PK, Vuyyur S, Panigrahi MK. A rare occurrence of osteoblastoma in a child. *J Pediatr Neurosci.* 2010;5:153-156.
16. Campanacci M. Bone and Soft Tissue Tumors. New York, NY: *Springer-Verlag,* 1993. *[Crossref]*
17. Pavanello M, Melloni I, Fiaschi P, et al. A rare case of osteoblastoma associated to aneurysmal bone cyst of the spine. Case report. *Br J Neurosurg.* 2016;30:106-109. *[Crossref]*
18. Nguyen VD, Hersh M. A rare bone tumor in an unusual location: Osteoblastoma of the vertebral body. *Comput Med Imaging Graph.* 1992;16:11-16. *[Crossref]*
19. Hu H, Wu J, Ren L, et al. Destructive osteoblastoma with secondary aneurysmal bone cyst of cervical vertebra in an 11-year-old boy: Case report. *Int J Clin Exp Med.* 2014;7:290-295. *[Crossref]*
20. Berry M, Mankin H, Gebhardt M, et al. Osteoblastoma: a 30-year study of 99 cases. *J Surg Oncol.* 2008;98:179-183. *[Crossref]*

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Letter to the Editor

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Ballantyne Syndrome-The Uncommon in Common Rh Isommunization

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Dear Editor,

Ballantyne or Mirror syndrome is a rare condition characterized by maternal disease that mimics fetal hydrops. This report presents a case that initially manifested as birth asphyxia, severe thrombocytopenia, hydrops, direct hyperbilirubinemia, hypoglycemia, and late-onset hemolysis presenting as anemia.

A 27-year-old gravida 3, para 1, abortion 2 patient, with a history of adverse obstetric outcomes, was admitted to our hospital for labor induction. The pregnancy was considered precious, as the couple had been attempting conception for 10 years. The gestational age was 40 weeks. The patient was a registered case having conceived spontaneously with AB negative blood group. Both previous abortions were spontaneous. Anti-D immunoglobulin was administered during pregnancy. The indirect Coombs test was negative. The patient reported decreased fetal movements during pregnancy. Additionally, she experienced a 4 kg weight gain over a two-week period prior to presentation, with significant pedal edema. Her blood pressure levels remained within normal parameters. An emergency lower segment cesarean section was performed due to non-progression of labor. A female infant weighing 2.3 kg was delivered. Fetal hydrops, placentomegaly, and polyhydramnios were observed. The neonate did not exhibit spontaneous respiration at birth and was managed as a case of birth asphyxia. Following initial resuscitation, the infant was transferred to the neonatal intensive care unit, intubated, placed on mechanical ventilation, and administered broad-spectrum antibiotics. The infant was extubated on day 7.

Initial investigations on day 1 of life revealed hemoglobin 13.2 g/dL; the direct Coombs test was negative. The neonate presented with severe thrombocytopenia (platelet: 35.000/mm^3), which was managed with intravenous immunoglobulin (IVIG) and repeated platelet transfusions.

By the tenth day, the hydrops gradually subsided. On the third day, the infant experienced hypoglycemia (35 mg/dL), necessitating a high glucose infusion rate (exceeding 20 mg/kg/min). This rate was progressively decreased, and oral feeding was initiated on day 12.

On the fourth day, the infant exhibited direct hyperbilirubinemia, with total bilirubin at 11.2 mg/dL and direct bilirubin at 4.7 mg/dL, accompanied by transaminitis. The levels progressively increased, reaching a peak of 22 mg/dL total, and 12.5 mg/dL direct bilirubin by day 12. The condition resolved, returning to normal levels by the conclusion of the second month.

One month after birth, significant anemia was observed (hemoglobin: 5.3 g/dL). A repeated direct Coombs test yielded positive results, indicating ongoing hemolysis. The anemia was treated with a combination of blood transfusion and additional IVIG administration.

Various diagnostic tests were conducted to investigate potential metabolic disorders, including tandem mass spectrometry, gas chromatography mass spectrometry,

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fundus examination, and thyroid-stimulating hormone analysis. Clinical exome studies were performed to exclude genetic causes. Toxoplasmosis, other agents, rubella, cytomegalovirus, herpes and syphilis titers, urine culture, and cytomegalovirus polymerase chain reaction were carried out as part of the assessment for direct hyperbilirubinemia. A critical sample was obtained and examined for serum insulin and cortisol levels to evaluate resistant hypoglycemia. However, all test results were inconclusive. The infant is currently under regular monitoring, showing weight gain, successfully breastfeeding, and progressing well.

Ballantyne syndrome, also known as mirror syndrome, is an uncommon pregnancy complication characterized by a triad of symptoms: fetal hydrops, placental edema, and maternal edema. The underlying mechanisms of this condition remain unclear, but it is believed that placental dysfunction, similar to that observed in pre-eclampsia, may play a role.[1] This syndrome can occur in various circumstances, including rhesus incompatibility, pregnancies with multiple fetuses, viral infections, fetal abnormalities, and tumors affecting the placenta or fetus.

Rh incompatibility typically occurs when a woman with Rh-negative blood is exposed to Rh-positive red blood cells, triggering the production of Rh antibodies. Common manifestations include jaundice, anemia, and, in severe instances, hydrops fetalis. Despite anti-D immunoglobulin prophylaxis, it may manifest as a pseudosyndrome characterized by temporary congenital hyperinsulinism, anemia, and inspissated bile syndrome with conjugated hyperbilirubinemia. This presentation is likely due to late-occurring fetomaternal hemorrhage.[2]

In some instances, infants who initially show minimal or no symptoms at birth may later develop severe hemolytic anemia.[3] There are also reports of early-onset anemia without hyperbilirubinemia as the sole manifestation of Rh isoimmunization.[4] Hydrops fetalis in Rh isoimmunization is frequently accompanied by thrombocytopenia.[5]

Initially, this case was treated as birth asphyxia due to a negative direct Coombs test, and the mother received anti-Rh D. However, as symptoms progressed and other conditions were excluded, mirror syndrome became a likely explanation. After ruling out congenital hyperinsulinism, severe hypoglycemia was attributed to perinatal hypoxia. The failure of anti-D Ig prophylaxis was also considered in this case.

When managing cases that present as hydrops fetalis, birth asphyxia, severe thrombocytopenia, direct hyperbilirubinemia, hypoglycemia, and hemolytic anemia, it is crucial to consider mirror syndrome. Given that mothers with mirror syndrome exhibit symptoms similar to pre-eclampsia, it is essential to rule out mirror syndrome in pregnant women showing signs of pre-eclampsia. Additionally, our case demonstrates that Rh isoimmunization can manifest as hydrops without significant anemia and with an initially negative direct Coombs test.

Footnotes

Author Contributions: Kumar DV: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Literature Search, Analysis or Interpretation, Writing.; Kumar A: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Literature Search, Analysis or Interpretation, Writing.; Tiwari S: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Literature Search, Analysis or Interpretation, Writing.

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References

1. Goa S, Mimura K, Kakigano A, et al. Normalisation of angiogenic imbalance after intra-uterine transfusion for mirror syndrome caused by parvovirus B19. *Fetal Diagn Ther.* 2013;34:176-179. *[Crossref]*
2. Riis SST, Joergensen MH, Rasmussen KF, et al. Transient congenital hyperinsulinism and hemolytic disease of a newborn despite rhesus D prophylaxis: a case report. *J Med Case Reports*. 2021;15:573. *[Crossref]*
3. Haider M, Memon S, Tariq F, Fatima S, Hameed A. Rhesus isoimmunization: late-onset hemolytic disease of the newborn without jaundice. *Cureus*. 2020;12:e6559. *[Crossref]*
4. Roda J, Mimoso G, Benedito M, Pereira DF. Isolated anaemia as a manifestation of Rh isoimmunisation. *BMJ Case Rep*. 2012;2012:bcr1120115101. *[Crossref]*
5. Van den Akker ESA, de Haan TR, Lopriore E, Brand A, Kanhai HHH, Oepkes D. Severe fetal thrombocytopenia in Rhesus D alloimmunized pregnancies. *Am J Obstet Gynecol*. 2008;199:387.e1-387.e4. *[Crossref]*