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From neonate to adolescent: A review of ovarian mass management in a single center

Yenidoğandan adölesan döneme: Tek bir merkezin over kitle yönetiminin derlemesi

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ABSTRACT

Aim: Pediatric ovarian and adnexal masses encompass a broad spectrum of benign and malignant pathologies, with management strategies ranging from observation to surgery. This study aimed to evaluate the clinical presentation, management approaches, surgical outcomes, and histopathological findings of pediatric ovarian and adnexal masses across the full age spectrum, from the neonatal period to adolescence, at a single tertiary center.

Materials and Methods: A retrospective analysis was conducted on the demographic, laboratory, sonographic, surgical, and histopathological data of pediatric patients (0-18 years) who were followed up and treated for adnexal cysts/masses in our clinic between 2018 and 2024. Subgroup analyses were conducted between neonatal and non-neonatal patients.

Results: A total of 786 of 1000 screened patients were included in the final analysis, with a mean age of 11.99 ± 5.28 years; 93 patients (11.8%) were in the neonatal period. Conservative management was the predominant strategy, used in 634 patients (80.7%), while 152 patients (19.3%) underwent surgery. Among operated patients, ovarian-sparing procedures were most common, with cyst excision performed in 99 patients. Oophorectomy was required in 32 patients, and salpingo-oophorectomy in 21 patients. Histopathological evaluation demonstrated predominantly benign lesions (98%), with only two malignant tumors identified. The rate of surgical intervention did not differ significantly between neonatal and non-neonatal patients (14.0% vs. 20.1%, p=0.163). However, neonatal patients had significantly higher ovarian loss rates among operated cases (p=0.007).

Conclusions: Pediatric adnexal masses are predominantly benign and can be safely managed conservatively in most patients. When surgery is required, ovarian preservation should be prioritized whenever feasible. Neonatal patients represent a distinct subgroup with longer surveillance needs and higher rates of ovarian loss, supporting age-specific management strategies.

Keywords: Pediatric, ovarian mass, adolescence, newborn

ÖZ

Amaç: *Pediatrik over ve adneksiyal kitleler benign ve malign patolojileri içeren geniş bir spektruma sahiptir ve yönetim stratejileri konservatif izlemden cerrahiye kadar değişmektedir. Bu çalışmada, üçüncü basamak bir merkezde yenidoğan dönemden adölesan döneme kadar pediatrik over ve adneksiyal kitlelerin klinik başvuru özellikleri, yönetim yaklaşımları, cerrahi sonuçları ve histopatolojik bulgularının değerlendirilmesi amaçlandı.*

Gereç ve Yöntem: *2018–2024 yılları arasında kliniğimizde adneksiyal kist/kitle nedeniyle takip ve tedavi edilen 0–18 yaş arası pediatrik hastaların demografik, laboratuvar, ultrasonografik, cerrahi ve histopatolojik verileri retrospektif olarak incelendi. Yenidoğan ve yenidoğan dışı hastalar arasında alt grup analizleri yapıldı.*

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Bulgular: *Toplam 1000 hastanın 786'sı çalışmaya dahil edildi. Ortalama yaş 11,99±5,28 yıl olup, 93 hasta (%11,8) yenidoğan dönemindeydi. Hastaların 634'ünde (%80,7) konservatif izlem tercih edilirken, 152 hastaya (%19,3) cerrahi tedavi uygulandı. Cerrahi uygulanan hastalarda en sık over koruyucu girişim kist eksizyonu olup 99 hastaya uygulandı. Otuz iki hastada ooforektomi, 21 hastada salpingo-ooforektomi yapıldı. Histopatolojik incelemede lezyonların büyük çoğunluğu benign (%98) olup yalnızca iki malign tümör saptandı. Cerrahi müdahale oranı yenidoğan ve yenidoğan dışı hastalar arasında anlamlı farklılık göstermedi (%14,0'a karşı %20,1; p=0,163). Ancak opere edilen olgularda over kaybı oranı yenidoğanlarda anlamlı olarak daha yüksekti (p=0,007).*

Sonuç: *Pediatrik adneksiyal kitleler çoğunlukla benign olup hastaların büyük kısmı güvenle konservatif izlenebilir. Cerrahi gerektiğinde mümkün olduğunca over korunmalıdır. Yenidoğan hastalar, daha uzun izlem gereksinimi ve daha yüksek over kaybı oranları nedeniyle ayrı bir alt grup olarak değerlendirilmelidir.*

Anahtar Sözcükler: *Pediatrik, over kitlesi, adölesan, yenidoğan*

INTRODUCTION

Adnexal lesions in childhood include ovarian, paraovarian, and paratubal masses, and may represent a broad spectrum of non-neoplastic, benign neoplastic, or malignant pathologies. Among them, ovarian cysts represent almost 60% of all ovarian pathologies and usually do not require surgical intervention as most of them are benign and self-limiting (1).

The estimated annual incidence of pediatric ovarian masses is reported to be 2.2–2.4 per 100.000 ranging from simple follicular cysts to malignant ovarian tumors (2).

The presentation of a benign or malignant adnexal lesion is nonspecific but typically is asymptomatic and has a slow course, making it difficult to diagnose early. The process of developing a differential diagnosis requires a thorough history and physical examination and often requires the use of imaging studies and a panel of tumor markers (3).

In the pediatric population, malignant ovarian tumors represent only 1% of all childhood cancers. Ovarian masses are classified as neoplastic or non-neoplastic, with simple cysts constituting the most common subtype (4). Given the long life expectancy of pediatric patients, preservation of ovarian tissue and ovarian endocrine function is of particular importance. Although most lesions are benign, concern for malignancy or complications may lead to unnecessary surgery. Consequently, ovarian-sparing surgery is generally preferred for both solid and cystic lesions. Nevertheless, oophorectomy may be required in cases with a high likelihood of malignancy, extensive mass-related destruction of ovarian tissue, or torsion-associated necrosis (5).

Standard imaging modalities for evaluating pediatric ovarian masses include ultrasonography (US), magnetic resonance imaging (MRI), and computed tomography (CT). Among these, US is typically the first-line choice, as it is widely available, noninvasive, free of ionizing radiation, and does not require sedation. In the pediatric population, the transabdominal approach is generally preferred (6,7).

Following a stepwise preoperative diagnostic workup and characterization of the adnexal mass, the number of benign cases requiring surgical intervention is expected to decrease. While all malignant cases must continue to be treated effectively with the most appropriate ovarian-preserving strategies, identification of benign lesions allows the adoption of minimally invasive surgical approaches, thereby reducing surgical morbidity through careful patient selection (8).

Although several studies have evaluated pediatric ovarian masses, most reports focus exclusively on surgically treated cases or specific age groups. Existing studies often focus on selected age groups or surgically treated cohorts, whereas comparative data spanning the neonatal period through adolescence remain limited. Therefore, this study aimed to evaluate the clinical presentation, management strategies, surgical outcomes, ovarian preservation rates, and histopathological features of pediatric ovarian and adnexal masses across a broad age spectrum, from the neonatal period to adolescence, in a single tertiary pediatric surgery center.

MATERIAL and METHODS

Following institutional review board approval, a retrospective analysis was conducted on 1,000 pediatric patients (aged 0–18 years) evaluated in our pediatric surgery clinic between 2018 and

2024. Patients meeting the inclusion criteria were included in the final analysis. Patients with radiologically or surgically confirmed ovarian or adnexal cysts/masses were eligible for inclusion.

Patients with ovarian torsion, which was defined based on intraoperative confirmation, were included in the overall cohort for descriptive purposes but were excluded from comparative analyses focusing on mass management. The primary analytic cohort consisted of patients with ovarian or adnexal masses.

Exclusion criteria included incomplete medical records, lack of adequate imaging confirmation, prior surgery performed at another institution, loss to follow-up, and duplicate records. Patients with concomitant endocrinological disorders that could affect ovarian morphology or hormonal ovarian function, including polycystic ovary syndrome, precocious puberty, congenital adrenal hyperplasia, or other documented endocrine disorders, were excluded to minimize potential confounding effects on ovarian pathology.

Demographic, clinical, radiological, and surgical data were systematically extracted from electronic medical records. Collected variables included age at diagnosis, presenting symptoms, lesion size and laterality, imaging characteristics (simple cystic vs. complex), type of management (conservative vs. surgical), surgical approach (laparoscopy vs. laparotomy), and surgical outcomes including ovarian preservation or oophorectomy. Histopathological findings were recorded for all patients who underwent surgical intervention and had available pathology reports.

The neonatal period was defined as the first 28 days of life. Lesions were classified as simple cysts if they were unilocular, anechoic, and thin-walled on ultrasonography, and as complex masses if they exhibited septations, solid components, or internal echoes. Ovarian preservation was defined as conservation of viable ovarian tissue following cystectomy.

Elective surgical intervention was considered in patients with lesions larger than 5 cm, persistence without size regression or interval growth during serial ultrasonographic follow-up for at least 2 months, recurrent or persistent symptoms, complex morphology including septations, solid components or internal echoes, or radiological suspicion of neoplasia or malignancy. Emergency surgery was performed in patients presenting with acute abdomen, suspected torsion, rupture, hemorrhage, or clinical instability.

The surgical approach was determined according to clinical presentation, lesion size, imaging morphology, suspicion of malignancy, emergency status, and surgeon preference. Laparoscopy was preferred in clinically stable patients with presumed benign cystic lesions and technically favorable conditions. Laparotomy was preferred in patients with acute abdomen, suspected torsion with nonviable ovarian tissue, very large lesions limiting safe laparoscopic manipulation, complex or solid morphology, suspected malignancy, or when safe dissection and ovarian preservation were considered difficult through a minimally invasive approach.

Subgroup analyses were performed to evaluate differences in management strategies and outcomes between neonatal and non-neonatal patients, as well as between cystic and complex lesions. Additional analyses compared conservatively managed and surgically treated patients to identify factors associated with surgical intervention and ovarian loss.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences) 23.0 Software was used for statistical analysis. Continuous variables were assessed for normality using the Shapiro–Wilk test and are presented as mean ± standard deviation (SD) for normally distributed data or median (interquartile range, IQR) otherwise. Categorical variables are presented as counts and percentages. Group comparisons were performed between neonatal and non-neonatal patients, as well as between conservatively managed and surgically treated groups. For continuous variables, the independent samples t-test (Welch correction when variances were unequal) or the Mann–Whitney U test was used as appropriate. For categorical variables, the Pearson chi-square test was applied, and Fisher's exact test was used when expected cell counts were <5. Factors associated with surgical intervention and ovarian loss were evaluated using appropriate univariate analyses. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

Overall Cohort Characteristics

A total of 786 patients met the inclusion criteria and were included in the final analysis. The mean age of the cohort was 11.99 ±5.28 years (range: 0–18 years), and 93 patients (11.8%) were in the neonatal period.

Lesions were located on the right side in 60.4% of patients, on the left side in 38.6%, and were bilateral in 0.9% of cases. Ovarian torsion was identified in 85 patients (10.8%), including 31 isolated torsion cases without a detectable mass. These isolated torsion cases were excluded from comparative analyses focusing on general management.

The majority of patients were managed conservatively (634/786, 80.7%). Conservative management consisted of serial ultrasonographic follow-up, and 41 patients (5.2%) received hormonal therapy during surveillance, mainly combined oral contraceptive treatment for functional or recurrent cysts in adolescent patients. Hormonal treatment was planned in coordination with pediatric endocrinology when clinically indicated. The mean follow up duration was 4.87 ± 7.01 months.

All patients underwent pelvic ultrasonography at diagnosis and during follow-up using a transabdominal approach. Magnetic resonance imaging was performed in 172 patients (21.9%) when further characterization was required. Ovarian localization was observed in 656 patients (83.5%), paratubal localization in 99 patients (12.6%), and paraovarian or other adnexal localization in 31 patients (3.9%). (Table-1).

Ovarian masses were predominantly cystic in morphology. Pure cystic lesions constituted the majority (64.4%), followed by necrotic or nonviable ovarian tissue (23.0%). Mixed solid–cystic lesions accounted for 10.5% of cases, while purely solid masses were rare (1.9%) (Table-2).

Table-1. Baseline Demographic and Imaging Characteristics of the Study Cohort (n=786)

	Value
Age, mean ±SD (years)	11.99 ± 5.28
Neonatal patients, n (%)	93 (11.8%)
Left-sided, n (%)	304 (38.6%)
Right-sided, n (%)	475 (60.4%)
Bilateral, n (%)	7 (0.9%)
Ovarian localization, n (%)	656 (83.5%)
Paratubal localization, n (%)	99 (12.6%)
Paraovarian/other adnexal, n (%)	31 (3.9%)
Torsion presence, n (%)	85 (10.8%)
MRI performed, n (%)	172 (21.9%)

Table-2. Morphological Characteristics of Surgically Treated Lesions (n=152)

	n (%)
Pure cystic	98 (64.4)
Mixed solid–cystic	16 (10.5)
Solid mass	3 (1.9)
Necrotic / nonviable ovarian tissue	35 (23.0)

Overall Management Outcomes

The majority of patients were managed conservatively (634/786, 80.7%), while 152 patients (19.3%) underwent surgical intervention. Patients who underwent surgery were significantly younger than those managed conservatively (10.83 ± 4.92 vs. 12.15 ± 5.32 years, p = 0.002).

Among surgically treated patients, 73 procedures (48.0%) were performed laparoscopically and 79 (52.0%) via open approach. Emergency operations accounted for 58.6% of surgical cases, whereas 41.4% were elective. No conversion from laparoscopy to laparotomy was recorded among included patients.

Ovarian-sparing surgery was the predominant approach, with cyst excision performed in 99 patients. Oophorectomy was required in 32 patients, and salpingo-oophorectomy in 21 patients (Table-3).

Table-3. Overall Management Strategies and Treatment Distribution

Management	n (%)
Conservative follow-up	634 (80.7)
Surgical treatment	152 (19.3)
Emergency surgery among operated patients	89/152 (58.6%)
Elective surgery among operated patients	63/152 (41.4%)

Percentages for conservative follow-up and surgical treatment are calculated according to the total cohort (n=786). Percentages for emergency and elective surgery are calculated among surgically treated patients (n=152).

Neonatal vs Non-Neonatal Comparison

A total of 93 patients were identified in the neonatal period and were compared with non-neonatal patients. The rate of surgical intervention did not differ significantly between neonatal and non-neonatal patients (14.0% vs. 20.1%, p=0.163). However, among surgically treated patients, neonatal cases had a significantly higher rate of ovarian loss, as reflected by increased oophorectomy rates compared to non-neonatal patients (p = 0.007).

Histopathological findings in neonatal patients were predominantly hemorrhagic infarction and simple cysts, consistent with antenatal or complicated lesions.

The median follow-up duration was 6 months (IQR: 4–7) in neonatal patients and 2 months (IQR: 1–4) in non-neonatal patients. Follow-up duration was significantly longer in neonatal patients (p<0.001) (Table-4).

Table-4. Neonatal vs Non-Neonatal Comparison of Surgical Outcomes

	Neonatal (n=93)	Non-neonatal (n=693)	p-value
Surgical intervention, n (%)	13 (14.0%)	139 (20.1%)	0.163
Oophorectomy (among operated), n (%)	9 (69.2%)	23 (16.5%)	0.007*
Follow-up duration, median (IQR), months	6 (4–7)	2 (1–4)	<0.001
Predominant Histopathology	Hemorrhagic infarction, simple cysts	Predominantly benign neoplasms	–

* Fisher's exact test was used for comparison of oophorectomy rates among operated patients.

Surgical Procedures and Operative Characteristics

Among surgically treated patients, emergency procedures accounted for 58.6% of cases, whereas 41.4% were performed electively. The surgical approach was nearly evenly distributed between laparoscopic (48.0%) and open (52.0%) techniques.

Cyst excision was the most commonly performed procedure (65.1%), reflecting a preference for ovarian-sparing management. Oophorectomy was performed in 21.1% of patients, while salpingo-oophorectomy accounted for 13.8% of cases. Ovarian loss was primarily associated with nonviable ovarian tissue or complicated presentations.

Among the 152 surgically treated patients, open surgery was performed in 79 cases and laparoscopy in 73 cases. Oophorectomy was significantly more frequent in patients undergoing open surgery compared with those treated laparoscopically (30.4% vs. 11.0%; p = 0.013). These findings suggest that minimally invasive surgery was more commonly associated with ovarian preservation (Table-5).

Table-5. Surgical Procedures and Operative Characteristics (n=152)

	n (%)
Emergency surgery	89 (58.6%)
Elective surgery	63 (41.4%)
Laparoscopic	73 (48.0%)
Open	79 (52.0%)
Cyst excision	99 (65.1%)
Isolated oophorectomy	32 (21.1%)
Oophorectomy in open surgery	24 (30.4%)
Oophorectomy in laparoscopic surgery	8 (11.0%)
Salpingo-oophorectomy	21 (13.8%)

Histopathological Findings

Histopathological evaluation was available in 100 of the 152 surgically treated patients. Pathology was not available in the remaining patients because no excisional specimen was obtained in procedures such as cyst aspiration/drainage or non-resective surgical management. The vast majority of lesions were benign (98%), with only two malignant tumors identified: one yolk sac tumor and one Sertoli-Leydig cell tumor.

The most common pathological diagnoses were simple ovarian cysts, corpus luteum cysts, and mature cystic teratomas, confirming the predominantly benign nature of pediatric ovarian and adnexal masses (Table-6).

Table-6. Histopathological Findings in Surgically Treated Patients with Available Pathology (n=100)

Pathological Diagnosis	n
Malignant tumors	**2**
Yolk sac tumor	1
Sertoli-Leydig cell tumor	1
Benign lesions	**98**
Mature cystic teratoma	18
Mucinous cystadenoma	4
Papillary serous cystadenoma	2
Serous cystadenoma	4
Paratubal cyst	5
Endometriosis	1
Simple cyst	29
Corpus luteum cyst	15
Necrosis / infarction	20

Values are presented as number of patients. Percentages were not shown because the denominator was 100.

DISCUSSION

Abdominal masses in pediatric patients are most often of ovarian origin, with ovarian pathology ranging from non-neoplastic lesions to neoplastic tumors observed throughout all stages of childhood and adolescence. This study presents a comprehensive evaluation of the management of ovarian masses, from the neonatal period to adolescence, treated at a single tertiary pediatric surgery center.

Our findings confirm that the majority of pediatric ovarian and adnexal lesions are benign (98%) and can be managed safely without surgical intervention in most patients. Conservative follow-up was feasible in more than 80% of cases, among surgical patients, only 8% of the total cohort required elective surgery for the mass itself.

In addition, the overall malignancy rate was very low, supporting previous literature demonstrating that malignant ovarian lesions are uncommon in children and adolescents (1, 2, 5, 9). These findings reinforce a conservative-first approach in patients with benign radiologic characteristics and stable clinical presentation.

Although most lesions were managed non-operatively, surgery remained necessary in selected patients with persistent, symptomatic, large, or complex masses. Among surgically treated patients, ovarian-sparing procedures constituted the predominant approach. Our results support current management principles favoring individualized treatment selection and preservation of viable ovarian tissue whenever technically feasible (3, 8, 10, 11).

Operated lesions in our cohort were predominantly cystic in morphology, with pure cystic lesions accounting for the majority of surgical specimens, whereas purely solid lesions were uncommon. This distribution is consistent with previous pediatric series demonstrating that most ovarian lesions in children are benign cystic formations rather than solid neoplasms or invasive tumors (4, 5, 9, 12). Radiologic reviews have similarly emphasized that simple and complex cystic lesions constitute the largest subgroup of pediatric adnexal pathology, while true malignant solid tumors remain rare (6, 8).

Histopathological findings in the operated cohort were overwhelmingly benign, with only a very small number of malignant tumors identified. The most common diagnoses included simple ovarian cysts, corpus luteum cysts, and mature cystic teratomas. These findings are in line with previous reports showing that benign lesions account for the vast majority of pediatric ovarian masses requiring treatment (2, 5, 9). Several contemporary reviews have likewise concluded that, although malignancy must always be considered, most adnexal masses in children and adolescents can be managed with ovarian-preserving strategies when preoperative imaging and clinical findings are reassuring (1, 3, 8, 10).

Our findings are also consistent with previous Turkish pediatric series. Banlı-Cesur et al. reported that pediatric and adolescent ovarian masses were predominantly benign, with ovarian-sparing management being an important treatment principle. Similarly, in the present cohort, malignant tumors were rare and ovarian-sparing surgery was the most common operative strategy. These similarities support the applicability of conservative follow-up and ovarian-preserving surgical principles in Turkish pediatric surgery practice (9).

Preservation of ovarian tissue has become a central principle in modern pediatric ovarian surgery (3, 8, 11, 13). In our series, ovarian-sparing procedures represented the predominant surgical approach, reflecting the growing preference for cyst excision, partial resection, or tissue-preserving surgery whenever technically feasible. Multicenter studies have demonstrated substantial variability in operative management of benign ovarian lesions across institutions, particularly regarding the use of oophorectomy versus ovarian-sparing surgery (11). Our findings support the ongoing shift toward ovarian-preserving management in children and adolescents.

Although long-term fertility outcomes could not be assessed because of the retrospective design and pediatric age of the cohort, ovarian preservation was evaluated as a clinically relevant surrogate outcome. Preservation of viable ovarian tissue may contribute to future endocrine and reproductive potential, and therefore ovarian-sparing surgery should be prioritized whenever oncologically and technically feasible.

Minimally invasive surgery also played an important role in our cohort, with nearly half of procedures performed laparoscopically. Recent studies evaluating laparoscopic ovarian-sparing surgery in pediatric patients have reported favorable perioperative outcomes, reduced morbidity, and high rates of ovarian preservation in benign lesions (13, 14). Together with these reports, our experience supports the use of minimally invasive techniques whenever lesion characteristics and surgical expertise permit.

One of the major strengths of the present study is the inclusion of neonatal patients as a distinct subgroup. Neonatal ovarian lesions are frequently detected antenatally or incidentally and often differ from lesions seen in older children with respect to natural history and management priorities. In our cohort, neonatal patients did not undergo surgery more frequently than older children; however, when surgery was required, they had significantly higher rates of ovarian loss and significantly longer follow-up duration. These findings suggest that neonatal ovarian pathology represents a

separate clinical subgroup requiring individualized surveillance and management strategies. Previous long-term institutional experiences have similarly shown that many neonatal cysts regress spontaneously, whereas complicated lesions may require intervention and may be associated with lower ovarian salvage rates (14). The shorter follow-up duration in the non-neonatal group was mainly related to the high proportion of functional cysts that regressed or resolved during early ultrasonographic surveillance. After regression or clinical stabilization, patients were discharged from pediatric surgery follow-up and were referred to pediatric endocrinology, pediatric gynecology, or general pediatric follow-up when necessary.

Another notable finding was the high overall success rate of conservative management. More than four out of five patients were managed without surgery, indicating that observation remains an appropriate primary strategy for many pediatric adnexal lesions. Evidence-based diagnostic algorithms increasingly emphasize structured radiologic assessment, selective laboratory evaluation when indicated, and interval follow-up rather than immediate surgery for all masses (10). Quality-improvement studies have further shown that standardized pathways can reduce unnecessary oophorectomy without increasing missed malignancies (15). Our results strongly support this management strategy.

Limitations

This study has several limitations. First, its retrospective design may have introduced selection and information bias. Second, this was a single-center study, which may limit the generalizability of the findings. The study population was heterogeneous, including patients across a wide age range as well as different types of ovarian and adnexal pathologies, which may have affected the uniformity of the analysis. In addition, histopathological evaluation was available for only 100 surgically treated cases, which may limit the accuracy of the pathological distribution, and long-term follow-up data regarding ovarian function outcomes were limited. Variations in diagnostic imaging, surgical decision-making, and management strategies over the study period may also have influenced the results. Finally, the absence of standardized criteria for surgical intervention may have introduced variability in treatment approaches.

CONCLUSION

Pediatric ovarian and adnexal masses are predominantly benign conditions and can be managed safely with a conservative approach in the majority of patients. When surgical intervention is required, ovarian preservation and minimally invasive techniques should be prioritized whenever feasible. Neonatal patients represent a distinct subgroup characterized by longer follow-up requirements and higher rates of ovarian loss, highlighting the need for age-specific surveillance and management strategies.

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Conflict of Interest: The authors have no relevant financial or non-financial interests to disclose.

Ethics Approval: This study was approved by the Ethics Committee of Health Sciences University Dr. Behcet Uz Pediatric Diseases and Surgery Training and Research Hospital (11/07/2024-GOA-51), and it was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards, and informed consent was obtained from all patients.

Availability of Data and Materials: The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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