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Original Article

Normal Saline versus Baby Shampoo in the Care of Peristomal Skin Complications in Pediatric Stoma Patients: A Randomized Controlled Trial

Pediyatrik Stoma Hastalarında Peristomal Cilt Komplikasyonlarının Bakımında Normal Salin ile Bebek Şampuanının Karşılaştırılması: Randomize Kontrollü Bir Çalışma

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ABSTRACT

Objective: Complications such as irritant dermatitis, infection, hypergranulation tissue should not occur involving the peristomal area to maintain skin integrity. Correct stoma creation techniques and appropriate nursing care are essential to prevent complications. This study aimed to compare the effectiveness of two different skin care solutions on peristomal skin integrity.

Method: Twenty-six children with an ostomy hospitalized in the pediatric surgery intensive care unit were randomized. Stoma care of the children was performed using saline solution in Group 1, and distilled water + pH 5.5 baby shampoo in the standard care group for 7 days. On the 3rd and 7th days of the study, the peristomal skin integrity of the patients was evaluated using the peristomal integrity follow-up form and the Pittman ostomy complication severity index. The CONSORT checklist was used for the study.

Results: Concerning the measurements made on the 3rd and 7th day of the study, there was no difference between both groups in terms of peristomal temperature or Pittman ostomy complication severity index scores, but skin moistures measured on the 7th day differed (p=0.01).

Conclusion: The findings suggest that the use of distilled water + pH 5.5 baby shampoo as part of peristomal skin care may help maintain better skin moisture by the 7th day compared to saline solution, although no significant differences were observed between both groups in terms of skin temperature or complication severity.

Keywords: Ostomy, peristomal skin integrity, pediatric surgery, nursing

ÖZ

Amaç: Cilt bütünlüğünü korumak için peristomal bölgede tahriş edici dermatit, enfeksiyon, hipergranülasyon dokusu gibi komplikasyonlar meydana gelmemelidir. Komplikasyonları önlemek için doğru stoma açma teknikleri ve uygun hemşirelik bakımı çok önemlidir. Bu çalışma, iki farklı cilt bakım solüsyonunun peristomal cilt bütünlüğü üzerindeki etkilerini karşılaştırmayı amaçlamıştır.

Yöntem: Pediyatrik cerrahi yoğun bakım ünitesinde yatmakta olan ostomili 26 çocuk randomize edilmiştir. Çocukların stoma bakımı 7 gün boyunca, bir grupta salin ile, diğer grupta ise distile su + pH 5,5 bebek şampuanı ile gerçekleştirildi. Çalışmanın 3. ve 7. günlerinde, hastaların peristomal cilt bütünlüğü peristomal bütünlük takip formu ve Pittman ostomi komplikasyon şiddet endeksi ile değerlendirildi. Çalışma için CONSORT kontrol listesi kullanıldı.

Bulgular: Üçüncü ve 7. günlerde yapılan ölçümlerde, peristomal sıcaklık veya Pittman ostomi komplikasyon şiddet endeksi puanı açısından fark yoktu, ancak 7. günde cilt neminde fark vardı (p=0,01).

Sonuç: Bulgular, peristomal cilt bakımı kapsamında damıtılmış su + pH 5,5 bebek şampuanı kullanımının, cilt sıcaklığı veya komplikasyon şiddeti açısından anlamlı bir fark gözlemlenmemesine rağmen, 7. günde salin ile karşılaştırıldığında daha iyi cilt neminin korunmasına yardımcı olabileceğini göstermektedir.

Anahtar kelimeler: Stoma, peristomal cilt bütünlüğü, pediyatrik cerrahi, hemşirelik

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INTRODUCTION

A stoma refers to the surgical opening of a section of the intestine—either a loop or separate proximal and distal segments—onto the abdominal wall skin. It may be created in patients with congenital anomalies such as anorectal malformation, Hirschsprung's disease, intestinal atresia, trauma, or perineal burns[1]. Stoma-related complications such as prolapse, stenosis, retraction, or parastomal hernia may occur, in addition to systemic complications like fluid-electrolyte imbalance and vitamin B12 deficiency[2].

Peristomal complications are localized skin problems around the stoma site including irritant dermatitis, infections, hypergranulation tissue, bleeding, or necrosis, most of which result from continuous exposure to stoma effluents[2]. Although many peristomal complications are reported to develop after the first postoperative week, early skin changes such as irritant dermatitis, erythema, and moisture imbalance may become manifest within the first days following stoma creation. These early alterations are clinically important, as they may progress into more severe complications if not properly managed. Therefore, close monitoring and appropriate skin care interventions during the first postoperative week are critical for preventing long-term peristomal skin damage.

According to the Wound, Ostomy, and Continence Nurses Society, a healthy peristomal skin is defined as "an area which is intact, similar in color and texture to adjacent skin, free of inflammation, and without manifesting altered sensitivity such as itching, burning, or pain"[3]. To achieve this goal, comprehensive nursing assessment and the use of appropriate cleansing solutions are essential. Skin moisture and temperature are important indicators of peristomal skin integrity. Increased moisture may lead to maceration of the periostomal skin and facilitate skin breakdown, while changes in skin temperature may reflect inflammation or impaired perfusion. Therefore, maintaining optimal moisture balance and stable skin temperature is essential in preventing peristomal complications.

Different cleansing solutions have been used in stoma care, such as distilled water, saline solution, mild pH-balanced baby shampoos, or (historically) antiseptic solutions[4-6]. Saline solution is widely used due to its isotonic nature, which preserves tissue integrity without disrupting the skin barrier. It has been shown to support skin hydration without causing irritation[7,8]. Therefore, it was selected as a comparator in this study. Baby shampoo, although not routinely recommended, continues to be used in some clinics as part of "standard care" because of its mild pH and cleansing properties[9,10]. Given that our institution still applies baby shampoo in routine stoma care, this study aimed to compare its effects with those of saline solution in maintaining peristomal skin integrity in children.

MATERIALS and METHODS

This study aimed to compare the effect of two different solutions used in stoma care on peristomal skin integrity.

The hypotheses of this study are as follows:

H1-1: Children who receive skin care with saline solution experience fewer ostomy-related complications compared to those who receive care with distilled water + pH 5.5 baby shampoo.

H1-2: Children who receive skin care with saline solution have lower peristomal skin temperature compared to those who receive care with distilled water + pH 5.5 baby shampoo.

H1-3: Children who receive skin care with saline solution have higher peristomal skin moisturization compared to those who receive care with distilled water + pH 5.5 baby shampoo.

Study Design

This study was a prospective randomized controlled trial conducted between November 2023 and November 2024 in the pediatric surgery intensive care unit of a tertiary hospital (Figure 1). The study was registered at the U.S. National Library of Medicine Clinical Trials (NCT05686902, registration date: 06.01.2023).

Participants

Children with (a) a newly created stoma, (b) available parental informed consent (c) and follow-up data encompassing at least 7 days postoperatively (d) but without underlying conditions affecting peristomal skin integrity (e.g., obesity, malnutrition, corticosteroid therapy, atopic dermatitis, psoriasis)[11] were included in the study. Exclusion criteria were: (a) allergy to cleansing solutions, (b) early stoma closure within 7 days, (c) parental withdrawal of consent, or (d) need to switch cleansing solution during the study.

Randomization and Allocation

After obtaining baseline data on postoperative day 0, participants were randomized into two groups (n=13):

Standard Care Group: Whose periostomal skin was cleansed with distilled water + pH 5.5 baby shampoo (routine clinical practice in this unit).

Saline Group: Whose periostomal skin was cleansed with with 0.9% normal saline solution.

Randomization was performed by Researcher-1 using simple random sampling via a web-based tool (www.random.org). Each eligible participant was assigned a unique number and allocated accordingly. Due to the nature of the intervention, the caregiver nurse (Researcher-2) could not be blinded to allocation of the groups. However, both the outcome assessor (Researcher-3) and data analyst (Researcher-4) were blinded to group allocation to minimize assessment and analysis bias.

Intervention Protocols

All stoma care was performed once daily using the assigned cleansing solution. The pouching system was replaced daily by Researcher-2. Other aspects of nursing care continued according to routine clinical protocols.

The cleansing procedure was standardized for all participants. The peristomal area was cleaned once daily using sterile gauze soaked with the assigned solution. Approximately 10 mL of solution was used for each application. The solution was applied gently without friction, allowed to remain in contact with the skin for approximately 10 seconds, and then (if applicable) rinsed with distilled water. The cleansed area was subsequently dried using sterile gauze by gentle patting. Care was taken to ensure complete dryness before applying the pouching system.

Outcomes

The primary outcome of this study was the early postoperative complications, assessed using the Pittman ostomy complication severity index.

The secondary outcomes were peristomal skin temperature measured with a routinely calibrated infrared thermometer and peristomal skin moisture on day 7, measured with the OEM SK-8 Digital Skin Moisture Analyzer.

Sample Size and Power Analysis

Sample size was calculated using G*Power 3.1.9.2.[12]. Assuming a medium effect size (d=0.50), α=0.05, and 80% power for detecting a difference in the primary outcome (skin moisture at day 7), assessment of a minimum of 13 participants per group (total n=26) was required.

Data Collection Tools

Demographic data form was used to collect information on age, sex, and medical diagnosis of the children.

Peristomal skin integrity follow-up form was used to collect information on skin moisture and temperature on days 0, 3, and 7. Skin moisture was measured using the Digital Skin Moisture Analyzer (OEM SK-8), which provides percentage-based hydration values. The device was calibrated according to the manufacturer's instructions before each measurement session. Skin temperature was measured using a non-contact (Wohler) infrared thermometer, routinely calibrated by the biomedical unit of the hospital.

Pittman Ostomy Complication Severity Index[13] This scale is a 9-item assessment tool developed by Joyce Pittman in 2014, with its Turkish validity and reliability established by Arslantaş et al.[14] The purpose of using this scale was to assess the frequency and severity of early-stage postoperative complications in individuals with stomas during follow-up. This index assesses leakage, peristomal irritant dermatitis, pain, bleeding within or around the stoma, stoma necrosis, stenosis, retraction, mucocutaneous separation, and hyperplasia. All complications are scored on a Likert-like scale ranging from 0 to 3 (0=none, 1=mild, 2=moderate, 3=severe). The total score ranges from 0 to 27 points. Higher scores indicate more severe ostomy complications. The content validity index score of the scale is 0.971.

Statistical Analysis

Data were analyzed using SPSS 26.0. Descriptive statistics were presented as means ± standard deviation or percentages. The Kolmogorov-Smirnov test was used to assess normality of data distribution[15]. Independent Student's t-test or Mann-Whitney U test was applied for continuous variables, and chi-square test for categorical variables. Analysis of Covariance (ANCOVA) was performed to adjust for confounders (age, sex, diagnosis, stoma type). The level of statistical significance was set at $p \leq 0.05$.

Ethical Statement

The research protocol was approved by the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, İzmir Faculty of Medicine, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (IRB no: 2022121-05, date: 08.12.2022). The researcher informed the children's parents about the purpose of the study, and written informed consent forms

were obtained from the parents who agreed to participate in the study.

RESULTS

Demographics

The participants' median age was 19.5 days, and 53.8% were female. The most common indication for creation of a stoma was Hirschsprung's disease (38.5%), and 73.1% of the patients had a colostomy. There were no significant baseline differences between the groups regarding age (p=0.41), gender (p=0.61), diagnosis (p=0.69), or type of stoma (p=0.19) (Table 1).

Primary Outcome

Peristomal Complications (Pittman Ostomy Complication Severity Index)

At baseline, all children had a Pittman Index score of 0. On day 3, scores were slightly higher in the saline group, while on day 7, scores were higher in the baby shampoo group. However, these differences were not statistically significant (day 3: p=0.65, day 7: p=0.09).

Importantly, most often peristomal complications (dermatitis, irritant redness, minor bleeding at the skin edge) were recorded. No major stoma-related complications (e.g., necrosis due to vascular insufficiency, retraction, prolapse) were observed during the 7-day follow-up period (Table 2).

Table 1. Comparison of the demographic data between the groups (n=26)

	Saline group		Baby shampoo group		Statistical analysis
Children's age (day)	Median: 21.00 Mode: 2.00*		Median: 17.00 Mode: 4.00		p=0.41 U=68.500
Gender	n	%	n	%	
Girl Boy	8 5	61.5 38.5	6 7	46.2 53.8	p=0.61 chi-square=0.431
Medical diagnosis Hirschprung's disease Anorectal malformation Necrotizing enterocolitis	 6 5 2	 46.2 38.5 15.4	 4 6 3	 30.8 46.2 23.1	 p=0.69 chi-square=0.708
Type of stoma Ileostomy Colostomy	 3 10	 23.1 76.9	 4 9	 30.8 69.2	 p=0.19 chi-square=0.658

*Multiple modes exist. The smallest value is shown

Table 2. Comparison of the mean scores between the groups (n=26)

	Saline group	Ph 5.5 baby shampoo group	p*
Skin moisture Baseline 3rd day 7th day	 46.00±4.58 42.07±7.07 43.62±4.20	 43.76±3.98 36.69±5.93 38.70±5.18	 0.22 0.057 **0.01**
Skin temperature Baseline 3rd day 7th day	 30.96±3.32 32.15±3.68 32.27±2.09	 30.62±3.09 31.19±3.33 31.83±2.44	 0.80 0.51 0.65
Pittman ostomy complication severity index score Baseline 3rd day 7th day	 0.00±0.00 4.61±2.69 5.30±2.83	 0.00±0.00 4.07±2.84 7.61±3.64	 1.000 0.65 0.09

*Mann Whitney U test

Secondary Outcomes

Peristomal Skin Temperature

Baseline skin temperatures were similar across groups. On days 3 and 7, the baby shampoo group had slightly lower skin temperatures, but the differences regarding peristomal skin temperatures between both groups were not statistically significant (p=0.51 and p=0.65, respectively).

Peristomal Skin Moisture

At baseline, there was no significant difference between groups in terms of peristomal skin moisture. On day 3, the saline group showed higher mean skin moisture compared to the baby shampoo group, but this intergroup difference did not reach statistical significance (p=0.057). On day 7, the intergroup difference became significant, with higher moisture levels in the saline group (p=0.01) (Table 2).

After adjustment for age, sex, diagnosis, and stoma type using ANCOVA, the saline group maintained significantly higher skin moisture at day 7 (mean difference =5.048, standard error =2.057, p=0.02) (Table 3, Figure 2).

Clinical Significance

Since there is no established clinically important and minimum difference in the literature regarding peristomal skin integrity in children using either of the stoma cleansing solutions, clinical significance was based on the premise that a post hoc effect size exceeding the a priori effect size is considered clinically significant—a method also cited in the literature[16]. Accordingly, in this study, a post-hoc power analysis confirmed that the achieved effect size (1.04) and power (0.81) exceeded the planned thresholds (0.50 and 0.80, respectively), supporting the clinical relevance of the observed difference in skin moisture. Since the achieved effect size and power of the study are greater than the priori effect size (0.50) and power (0.80) the finding was considered to be clinically significant.

DISCUSSION

We conducted this randomized controlled study to compare the effect of saline solution versus pH 5.5 baby shampoo on peristomal skin integrity in children with newly created stomas.

Our results showed that there were no significant differences in skin temperature or complication severity scores between both groups. In our study, no significant difference was found in peristomal skin temperature between groups which may indicate that both cleansing solutions are similarly effective in preventing inflammation in the early postoperative period. Also, no significant intergroup difference was observed in Pittman index scores. In contrast to our findings, Kulawik-Pióro's study concluded that the use of shampoo-like products could damage the lipids and proteins in the stratum corneum layer of the skin around the stoma, thereby increasing the risk of complications[17]. Consistent with our results, D' Ambrosio's study also concluded that peristomal skin complications were less common in the early postoperative period[18]. This finding may be explained by the short follow-up period and the low incidence of serious complications in the early phase which suggests that, although both solutions are used in clinical practice, the saline solution may be more effective in maintaining skin moisture—a critical factor in preventing long-term peristomal damage.

Our results showed that skin moisture was significantly higher in the saline group by day 7. Pars and Çavuşoğlu[19] compared saline solution with, pH 5.5 baby soap, and hydrogel, reporting that skin moisturization was higher in the saline group. Although hydrogel was included in that study, current evidence does not support hydrogel for routine peristomal skin care, as it is primarily indicated for wound management rather than preventive stoma care. Salami et al.[20] compared chlorhexidine, saline solution, and tap water in wound healing, showing that saline solution maintained better skin hydration. Although chlorhexidine has been evaluated for its use as a stoma cleansing agent, guidelines advise against its

Table 3. Evaluation of factors affecting skin moisture at 7th postoperative day

Covariance analysis						
Groups		**Mean difference**	**SE**	**p**	**95% CI for Exp(β)**	
					Lower	**Upper**
Saline	Baby shampoo	5.048	2.057	0.02	0.757	9.339

Variances included in the model: group, gender, ostomy type, medical diagnosis, age
SE: Standard error, CI: Confidence interval

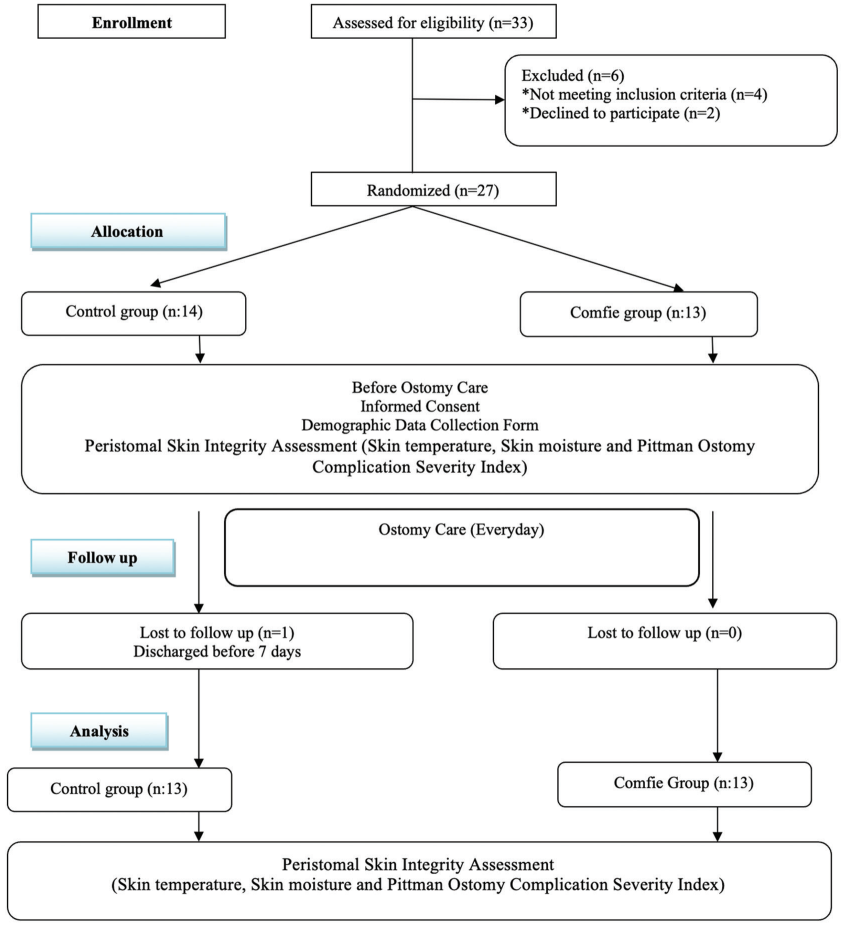

Figure 1. Research process flow chart

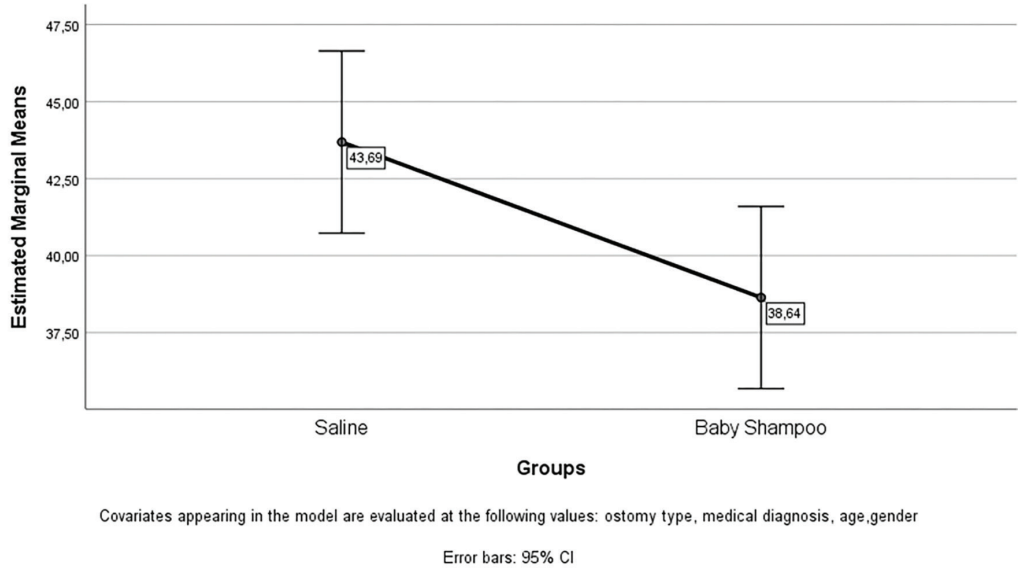

Figure 2. Estimated marginal means of 7th day skin moisture

CI: Confidence interval

use on peristomal skin due to irritation risk. Karaca and Korkmaz[21] found that saline solution was more effective in maintaining peristomal skin moisture and temperature compared with barrier cream. Similarly, barrier creams are not routinely recommended for peristomal skin, except in special circumstances of significant irritation

Baby cleansers with pH 5.5 are formulated to be mild and support physiological skin balance[22]. However, randomized studies on newborn skin care have demonstrated that soaps and shampoos can increase transepidermal water loss and alter skin pH[23]. This finding may explain why the baby shampoo group in our study had lower skin moisture by day 7. Although saline solution is widely recommended, some studies suggest that mild cleansers may improve skin comfort and provide cleansing efficiency without damaging the skin barrier[9]. Additionally, a study by Qin et al.[24] suggests that warm water is the most appropriate cleansing product. However, inconsistent findings in the literature highlight the need for further conduction of high-quality randomized studies.

Clinical Implications

Making distinction between peristomal complications (e.g., irritant dermatitis, minor bleeding, redness) and stoma-related complications (e.g., necrosis due to ischemia, retraction, prolapse) is essential for guiding both research and clinical practice. In our study, only peristomal complications were observed within the 7-day follow-up, reinforcing the need to focus on appropriate cleansing methods as preventive measures.

Strengths and Limitations

Its randomized design, the use of validated assessment tools, and the blinding of both the outcome assessor and the data analyst can be assessed as the strengths of this study. Limitations include the small sample size, and the short 7-day follow-up period. The study is planned to be repeated by measuring skin pH, and using different solutions in a larger sample size.

CONLUSION

For nurses and caregivers, these findings are clinically meaningful. Saline is widely available cost-effective solution, and its relevant use is supported by guidelines. In contrast, baby shampoo continues to be used in some clinics despite limited supporting evidence. Our study contributes to clarifying this practice gap and may support the standardization of pediatric stoma care protocols.

Ethics

Ethics Committee Approval: The research protocol was approved by the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, İzmir Faculty of Medicine, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (IRB no: 2022121-05, date: 08.12.2022).

Informed Consent: The researcher informed the children's parents about the purpose of the study, and written informed consent forms were obtained from the parents who agreed to participate in the study.

Declaration of AI Use: No artificial intelligence tools were used in the preparation of this manuscript.

Footnotes

This study was presented as a pilot study poster presentation at the 9th European Academy of Pediatric Societies held in Vienna, Austria, on October 17-20, 2024.

Author Contributions

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

Conflict of Interest: The authors have no conflict of interest to declare.

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Original Article

Assessment of Ventricular Functions by Tissue Doppler Echocardiography in Follow-up of Patients with Kawasaki Disease

Kawasaki Hastalığı Olan Hastaların Takibinde Doku Doppler Ekokardiyografi ile Ventriküler Fonksiyonların Değerlendirilmesi

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ABSTRACT

Objective: To evaluate ventricular functions using tissue Doppler echocardiography in long-term follow-up of children with Kawasaki disease after acute phase treatment.

Method: Thirty patients (16 boys, 14 girls; mean age 4.41±3.07 years) treated for Kawasaki disease at our unit between September 1999 and June 2009 were compared with 24 healthy controls of similar age and gender. All subjects underwent standard and tissue Doppler echocardiographic evaluations. Systolic (S') and diastolic (E', A') myocardial velocities were measured from left ventricular basal segments, and myocardial performance indices (MPIs) were calculated.

Results: Mean follow-up period was 24.53±19.06 months. Coronary artery involvement occurred in 13 (43.3%) patients during acute phase, but no aneurysms persisted during follow-up period. Standard echocardiographic parameters including left ventricular ejection fraction, shortening fraction, mitral flow velocities, and aortic velocity showed no significant differences between groups (p>0.05). Tissue Doppler echocardiography measurements of lateral wall velocities and time intervals were comparable. However, left ventricular MPIs were significantly higher in patients (0.518±0.028) compared to controls (0.497±0.028) (p=0.01).

Conclusions: Despite normal conventional echocardiography findings after average 2-year follow-up period, elevated myocardial performance indices indicated subclinical global ventricular dysfunction in children with Kawasaki disease. Tissue Doppler-derived MPI represents a valuable non-invasive parameter for long-term cardiac surveillance in these patients.

Keywords: Kawasaki disease, tissue Doppler echocardiography, myocardial performance index, ventricular function

ÖZ

Amaç: Kawasaki hastalığı olan çocukların akut faz tedavisi sonrası uzun dönem takibinde doku Doppler ekokardiyografi ile ventriküler fonksiyonların değerlendirilmesi.

Yöntem: Ünitemizde Kawasaki hastalığı nedeniyle tedavi edilen 30 hasta (16 erkek, 14 kız; ortalama yaş 4,41±3,07 yıl) (Eylül 1999-Haziran 2009) benzer yaş ve cinsiyetteki 24 sağlıklı kontrol ile karşılaştırıldı. Tüm olgulara standart ekokardiyografi ve doku Doppler değerlendirmesi yapıldı. Sol ventrikül bazal segmentlerinden sistolik (S') ve diyastolik (E', A') miyokardiyal hızlar ölçüldü ve miyokardiyal performans indeksi (MPİ) hesaplandı.

Bulgular: Ortalama takip süresi 24,53±19,06 ay idi. Akut fazda 13 hastada (%43,3) koroner arter tutulumu görüldü, ancak takipte anevrizma saptanmadı. Sol ventrikül ejeksiyon fraksiyonu, kısalma fraksiyonu, mitral akım hızları ve aortik hız dahil standart ekokardiyografik parametreler gruplar arasında anlamlı fark göstermedi (p>0,05). Lateral duvar hızları ve zaman aralıklarının doku Doppler ölçümleri benzerdi. Ancak, sol ventrikül MPİ hasta grubunda (0,518±0,028) kontrol grubuna (0,497±0,028) göre anlamlı olarak yüksek bulundu (p=0,01).

Sonuç: Ortalama 2 yıllık takip sonrası konvansiyonel ekokardiyografi bulgularının normal olmasına rağmen, artmış miyokardiyal performans indeksi Kawasaki hastalığı olan çocuklarda subklinik global ventriküler disfonksiyonu göstermektedir. Doku Doppler ile elde edilen MPİ, bu hastaların uzun dönem kardiyak izleminde değerli bir non-invaziv parametre olarak kullanılabilir.

Anahtar kelimeler: Kawasaki hastalığı, doku Doppler ekokardiyografisi, miyokart performans indeksi, ventrikül fonksiyonu

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INTRODUCTION

Kawasaki disease (KD) is an acute inflammatory vasculopathy characterized by its predilection for medium-sized vessels, with its peak incidence observed in the pediatric population under five years of age[1,2]. The pathological involvement of coronary vasculature represents the most clinically significant sequela of KD, with potential risks including aneurysmal formation, ischemic myocardial injury, and potentially fatal cardiac events[3].

The diagnosis of KD depends on clinical assessment demonstrating fever persisting for five days or longer in conjunction with at least four of five characteristic clinical features including bilateral bulbar conjunctival hyperemia without exudate, mucocutaneous changes affecting the oral cavity and lips, polymorphous truncal rash, peripheral extremity manifestations, and enlarged cervical lymphadenopathy[4,5]. Early initiation of therapy using intravenous immunoglobulin (IVIG) together with aspirin has proven instrumental in substantially diminishing the incidence of coronary complications[6].

Despite effective therapeutic interventions in KD, ongoing cardiovascular complications necessitate further research. Recent studies have revealed that patients without visible coronary artery abnormalities may still experience latent myocardial dysfunction after resolution of the initial disease[7,8]. Routine echocardiographic examinations do not adequately capture the intricate cardiac structural and functional shifts present in affected patients[9].

Tissue Doppler echocardiography (TDE) offers a quantitative approach to evaluate myocardial function through direct measurement of tissue velocities[10]. Among its derived parameters, the myocardial performance index (MPI)—often referred to as the Tei index incorporates both systolic and diastolic components, making it particularly valuable for assessing overall ventricular function[11]. Evidence suggests that TDE-based MPI measurements can identify subtle myocardial abnormalities that conventional echocardiographic methods may overlook[12].

In this study we have aimed to evaluate ventricular functions using TDE in long-term follow-up of children with KD after acute phase treatment and to compare findings with those of a healthy control group.

MATERIALS and METHODS

Study Population

This study was designed as a retrospective cohort with cross-sectional follow-up. We included 30 patients (16 boys, 14 girls; mean age 4.41±3.07 years) who were diagnosed and treated for KD at our unit between September 1999 and June 2009. All patients attended regular cardiology follow-up visits and were in the convalescent phase of the disease. The diagnosis of KD was established according to the criteria of the American Heart Association[13], which remain consistent with recent Japanese diagnostic guidelines[5].

The control group consisted of 24 healthy children (14 boys, 10 girls) of similar age and gender without any cardiac pathology, systemic disease, or family history of cardiovascular disease. All control subjects had normal physical examination and electrocardiographic findings.

Patients and control subjects with congenital heart disease, acquired heart disease other than KD, systemic diseases affecting cardiovascular system, and those with poor echocardiographic image quality were excluded from the analyses.

Echocardiographic Examination

All echocardiographic examinations were performed using a Vivid 7 ultrasound system (GE Healthcare, Milwaukee, WI, USA) equipped with 2.5-5 MHz transducers. Standard two-dimensional, M-mode, and Doppler echocardiographic studies were performed according to the recommendations of the American Society of Echocardiography[14].

TDE

Tissue Doppler imaging was performed in the apical four-chamber view. Pulsed-wave tissue Doppler sample volume was placed at the basal segments of the left ventricular lateral wall and interventricular septum. The following parameters were measured (Figure 1):

- Systolic myocardial velocity (S')
- Early diastolic myocardial velocity (E')
- Late diastolic myocardial velocity (A')
- E'/A' ratio
- Isovolumetric relaxation time (IVRT)
- Deceleration time (DT)
- Isovolumetric contraction time (IVCT).

Calculation of MPI

The MPI was calculated using the formula: MPI = (IVCT + IVRT) / ET, where ET is the ejection time. All measurements were averaged over three consecutive cardiac cycles. For the final statistical analysis, MPI values

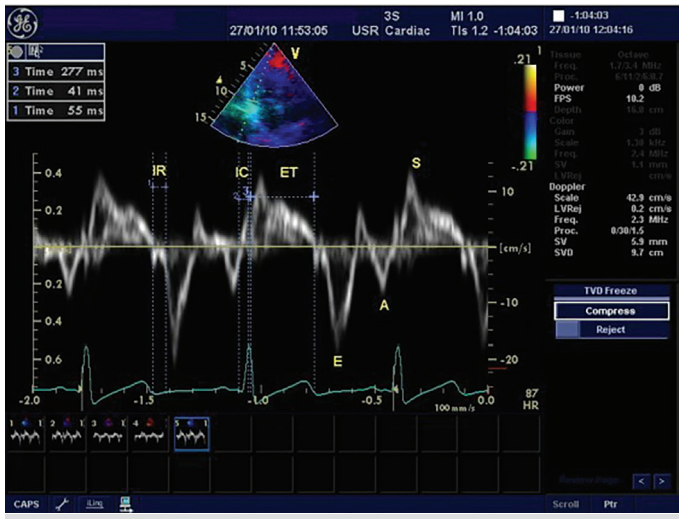

Figure 1. Representative pulsed wave tissue Doppler echocardiography tracing from the left ventricular septal wall showing myocardial velocity patterns

S: Systolic velocity, E: Early diastolic velocity, A: Late diastolic velocity, DT: Deceleration time, IVRT (IR): Isovolumetric relaxation time, IVCT (IC): Isovolumetric contraction time, LVET: Left ventricular ejection time

derived from the (lateral wall/septal wall/average of both walls) were utilized.

Statistical Analysis

Statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation. The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Independent samples t-test was used to compare continuous variables between groups. Chi-square test was used for categorical variables. A p-value <0.05 was considered statistically significant.

The study was approved by Local Non-Drug Ethics Committee of Ege University (decision no: 09-7/63, date: 28.06.2009). Written informed consent was obtained from parents or legal guardians of all participants.

RESULTS

Baseline Characteristics

The mean follow-up period of the study group was 24.53±19.06 months (range: 6-72 months). During the acute phase of KD, coronary artery involvement was detected in 13 (43.3%) patients. However, no coronary aneurysm was found in any patient during the follow-up period. All patients received standard treatment with IVIG and aspirin during the acute phase.

There were no significant differences between the patient and control groups regarding the parameters of age, gender, body weight, height, heart rate, and blood pressure (Table 1).

Standard Echocardiographic Findings

Standard echocardiographic parameters including left ventricular ejection fraction, left ventricular shortening fraction, mitral flow velocities (E, A, E/A ratio), and aortic maximum velocity showed no significant differences between the patient and control groups (p>0.05) (Table 2).

Tissue Doppler Echocardiographic Findings

Analysis of tissue Doppler echocardiographic findings of the left ventricular lateral wall showed no significant differences in terms of S', E', A', E'/A' ratio, IVRT, DT, and IVCT values between the groups (Table 3). Similarly, septal wall tissue Doppler echocardiographic parameters showed no significant differences between the patient and control groups (Table 4).

MPI

The most significant finding of the study was that left ventricular MPI in the patient group (0.518±0.028) was statistically significantly higher compared to the control group (0.497±0.028) (p=0.01) (Figure 2).

Table 1. Demographic and clinical characteristics of the study population

Parameter	Kawasaki patients Mean ± SD	Control Mean ± SD	p
Age (years)	4.41±3.07	4.6±3.34	0.826
Body weight (kg)	18.91±10.27	17.67±7.3	0.617
Height (cm)	99.6±20.89	102±23.87	0.403
Heart rate (bpm)	102.2±10.1	97.1±9.44	0.064
Systolic blood pressure (mmHg)	88.26±8.31	90.29±9.73	0.414
Diastolic blood pressure (mmHg)	62.4±6.14	63.83±5.69	0.383

SD: Standard deviation

Table 2. Conventional echocardiographic parameters			
Parameter	**Kawasaki patients Mean ± SD**	**Control Mean ± SD**	**p**
Mitral E (cm/s)	102.73±12.12	106.96±13.46	0.231
Mitral A (cm/s)	64.03±9.23	62.62±11.58	0.621
Mitral E/A ratio	1.63	1.75	0.139
DT (ms)	143.5±18.6	133.8±16.97	0.802
Aortic peak velocity (cm/s)	113.8±15.63	110.41±12.62	0.390
LVEF (%)	68.34±3.69	65.12±4.80	0.443
LVFS (%)	31.94±2.67	29.72±3.08	0.452
DT: Deceleration time, LVEF: Left ventricular ejection fraction, LVFS: Left ventricular fractional shortening, SD: Standard deviation, E: Early diastolic velocity, A: Late diastolic velocity			

Table 3. Tissue Doppler echocardiographic findings of the LV lateral wall in the study group			
Parameter	**Kawasaki patients Mean ± SD**	**Control Mean ± SD**	**p**
S' lateral (cm/s)	7.97±1.37	7.95±1.0	0.990
E' lateral (cm/s)	16.83±3.43	16.62±11.58	0.109
A' lateral (cm/s)	7.66±1.37	7.92±1.24	0.309
E'/A' lateral	2.24±0.5	2.38±0.41	0.692
IVRT lateral (cm/s)	55.46±3.08	55.5±2.70	0.945
DT lateral (cm/s)	65.81±5.14	60.41±2.68	0.900
IVCT lateral (cm/s)	55.9±4.54	55.95±3.54	0.909
SD: Standard deviation, IVCT: Isovolumetric contraction time, IVRT: Isovolumetric relaxation time, LV: Left ventricle, S': Systolic velocity, E': Early diastolic velocity, A': Late diastolic velocity, DT: Deceleration time			

Table 4. Tissue Doppler echocardiographic findings of the LV septal wall in the study group			
Parameter	**Kawasaki patients Mean ± SD**	**Control Mean ± SD**	**p**
S' septal (cm/s)	7.16±1.41	7.83±1.3	0.269
E' septal (cm/s)	13.63±2.12	15.95±1.73	0.050
A' septal (cm/s)	6.66±1.02	7.58±1.05	0.050
E'/A' septal	2.07±0.036	2.12±0.26	0.927
IVRT septal (cm/s)	51.43±3.82	53.66±3.14	0.676
DT septal (cm/s)	57.73±3.82	59.37±3.67	0.850
IVCT septal (cm/s)	54.5±5.0	55.83±3.98	0.405
SD: Standard deviation, IVCT: Isovolumetric contraction time, IVRT: Isovolumetric relaxation time, LV: Left ventricle, S': Systolic velocity, E': Early diastolic velocity, A': Late diastolic velocity, DT: Deceleration time			

DISCUSSION

This study demonstrates that children with a history of KD may have subclinical global ventricular dysfunction detectable by tissue Doppler-derived MPI, even when conventional echocardiographic parameters appear normal during an average 2-year follow-up after the onset of acute phase. The significantly elevated MPIs in the patient group suggests that the myocardial effects of KD may persist beyond the acute inflammatory phase.

The MPI is a Doppler-derived parameter that provides information on global ventricular performance[15]. An elevated MPI indicates impaired ventricular function, and its prognostic value has been documented to be correlated with clinical outcomes in various cardiac conditions[16].

Previous studies have reported conflicting results regarding long-term cardiac function in KD patients. Several investigators have found that cardiac function was preserved in long-term follow-up [17,18], yet others have

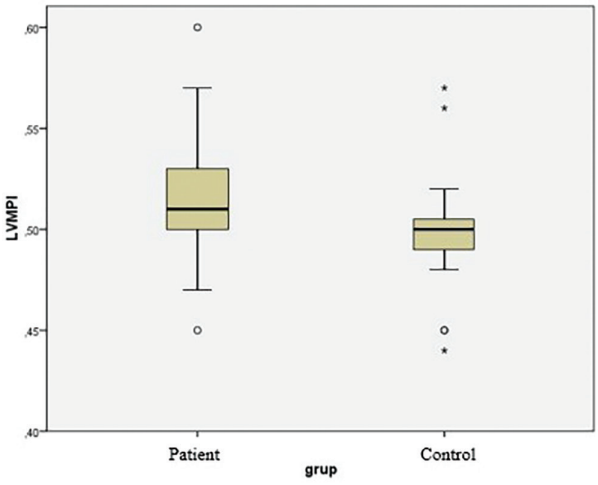

Figure 2. Left ventricular MPI values in patient and control groups

MPI: Myocardial performance index, LVMPI: Left ventricular myocardial performance index

identified persistent abnormalities[19-21]. These conflicting findings may be due to variability in patient population, the length of observation periods, and methods used for evaluation.

TDE has shown greater sensitivity for detection of early myocardial dysfunction than conventional echocardiography. Although standard indices—ejection fraction and shortening fraction—were within normal ranges in our cohort, an elevated MPI indicated subclinical impairment that these conventional measures would not detect.

KD is characterized by systemic inflammation of blood vessels, affecting coronary arteries and heart tissue, although the long-term impact on myocardial function remains incompletely understood[22]. Studies of tissue samples have revealed that KD patients experience persistent myocardial inflammation and scarring, hinting that these adverse effects may last beyond the early phase and lead to enduring functional disabilities[23].

Our finding of elevated MPI in KD patients is consistent with prior studies which have used tissue Doppler imaging to assess myocardial function in this population of patients with KD[24,25]. Selamet Tierney et al.[26] reported diastolic dysfunction in children with KD using tissue Doppler imaging. Likewise, other studies have found evidence of subclinical myocardial dysfunction using various advanced imaging techniques[27,28]. The clinical significance of subclinical myocardial dysfunction in KD patients remains to be determined. It is hard to say whether these changes represent a benign finding or a precursor to clinically significant cardiac dysfunction in later life. Therefore, long-term prospective studies are needed to determine the natural history and clinical implications of these findings.

The 2017 American Heart Association scientific statement on the diagnosis, treatment, and long-term management of KD emphasizes the importance of long-term cardiac surveillance in all KD patients, including those without documented coronary artery abnormalities. The statement recognizes that myocardial involvement may persist beyond the acute phase and recommends periodic cardiac evaluation, though specific guidance on tissue Doppler-based parameters for follow-up remains limited[2].

The most notable finding of this study is the significantly elevated tissue Doppler-derived MPIs in children with a history of KD (0.518±0.028) compared to healthy controls (0.497±0.028; p=0.010), despite normal conventional echocardiographic parameters. Although the absolute difference of 0.021 may appear numerically modest, MPI is a dimensionless index with a narrow physiological range, and Tei et al.[11] established that values exceeding 0.50 indicate impaired global ventricular performance. The mean MPI of our patient cohort (0.518) crosses this validated threshold into the range of subclinical dysfunction, whereas the MPI of the control group (0.497) remains within normal limits.

Study Limitations

This study has several limitations that should be acknowledged. First, the sample size was relatively small (n=30), which restricted statistical power and the generalizability of findings. The wide heterogeneity in follow-up duration (range: 6-72 months) introduces variability that may affect the interpretation of MPI values, as myocardial recovery or progression may differ at various time points after the acute phase. As a single-center study, the results may not be representative of broader KD populations with varying ethnic backgrounds and treatment practices. The cross-sectional design of the study did not allow for assessment of changes in cardiac function over time.

Although echocardiographic assessments were prospectively performed during follow-up visits, the identification of patients was performed using a retrospective study design covering a 10-year period (1999-2009), during which treatment protocols and diagnostic criteria may have evolved. The cross-sectional

nature of the follow-up evaluation did not allow for assessment of temporal changes in MPI or longitudinal trajectories of ventricular function.

We did not perform speckle-tracking strain analysis or cardiac magnetic resonance imaging. Strain would have shown whether the dysfunction is regional or diffuse; CMR would have indicated whether it reflects fibrosis or oedema. We also recorded no clinical outcomes—cardiac events, heart failure symptoms, exercise capacity—so we cannot say whether an elevated MPI matters to the patient. That second gap is the more consequential one. A multicentre cohort followed with serial imaging into adolescence would establish whether these values predict later events or simply normalise on their own.

CONCLUSION

MPI was higher in our KD group than in controls despite normal conventional echocardiographic indices, which suggests that routine measurements are not sensitive enough to exclude residual myocardial involvement at a mean of two years after the acute phase. Tissue Doppler-derived MPI is quick to obtain and requires no additional equipment, so it can reasonably be added to long-term follow-up echocardiography in these children. Whether the abnormality we detected progresses, resolves, or predicts later events is not answerable from a cross-sectional design; prospective follow-up into adolescence would be needed to establish that.

Ethics

Ethics Committee Approval: The study was approved by Local Non-Drug Ethics Committee of Ege University (decision no: 09-7/63, date: 28.06.2009).

Informed Consent: Written informed consent was obtained from parents or legal guardians of all participants.

Declaration of AI Use: No artificial intelligence tools were used in the preparation of this manuscript.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: M.O.B., Concept: M.O.B., Design: M.O.B., Data Collection or Processing: M.O.B., M.D., B.A., Analysis or Interpretation: Z.Ü., E.L., A.R.Ö., Literature Search: M.O.B., Writing: M.O.B., Z.Ü., E.L.

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

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Original Article

Clinicopathological Spectrum and Imaging Features of Non-lymphadenopathic Superficial Masses in Children: A Retrospective Cohort Study

Çocuklarda Lenfadenopatik Olmayan Yüzeyel Kitlelerin Klinikopatolojik Özellikleri ve Görüntüleme Bulguları: Retrospektif Bir Kohort Çalışması

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ABSTRACT

Objective: Superficial mass lesions in children encompass a broad spectrum of congenital, benign, and, rarely, malignant entities. Despite their predominantly benign nature, overlapping clinical and imaging features may complicate establishment of preoperative diagnosis. This study aimed to evaluate the clinicopathological spectrum, anatomical distribution, and imaging characteristics of non-lymphadenopathic superficial masses in children, with additional analysis of diagnostic concordance among isolated neck lesions.

Method: This retrospective cohort study population consisted of children aged 0-18 years who underwent surgical excision of superficial mass lesions between 2018 and 2026. Lymphadenopathic lesions and non-excisional cases were excluded, except for 5 cases with benign aspiration cytology results who were treated with bleomycin. Histopathological diagnoses were standardized into major groups. Clinical, anatomical, and imaging data were analyzed descriptively and comparatively. In the isolated neck mass subgroup, clinicoradiologic prediagnosis was compared with final histopathology findings.

Results: A total of 201 patients were included (median age, 8 years; 55.2% female). Adnexal/keratinous benign lesions (50.0%) and congenital/developmental lesions (26.5%) were the most common groups. Pilomatrixoma, epidermal-type keratinous cyst, and thyroglossal duct cyst were the leading diagnoses. Lesions were most frequently located in the head and neck. Vascularity was predominantly observed in vascular/lymphatic lesions, whereas calcification was largely confined to adnexal/keratinous lesions, particularly in cases with pilomatrixoma ($p<0.001$). In isolated neck masses, diagnostic concordance was highest between clinical and histopathological diagnoses in cases with pilomatrixoma (91.7%) and thyroglossal duct cyst (75.7%), but lower among cases with branchial cyst and dermoid/epidermoid cyst ($p=0.001$).

Conclusion: Pediatric superficial mass lesions are predominantly benign, with characteristic anatomical and imaging patterns that may help refine preoperative assessment. Diagnostic concordance was highest for cases with pilomatrixoma and thyroglossal duct cyst, whereas prediagnoses of branchial cyst and dermoid/epidermoid cyst showed greater heterogeneity, particularly among neck lesions.

Keywords: Pediatrics, soft tissue neoplasms, head and neck masses, ultrasonography, magnetic resonance imaging, pathology

ÖZ

Amaç: Çocuklarda yüzeyel kitle lezyonları, konjenital, benign ve nadiren malign oluşumlardan oluşan geniş bir spektrumu kapsar. Çoğunlukla benign olmalarına rağmen, örtüşen klinik ve görüntüleme bulguları preoperatif tanıyı güçleştirebilir. Bu çalışmada, çocuklarda lenfadenopatik olmayan yüzeyel kitlelerin klinikopatolojik spektrumu, anatomik dağılımı ve görüntüleme özelliklerinin değerlendirilmesi ve izole boyun lezyonlarında tanısal uyumun analiz edilmesi amaçlandı.

Yöntem: Bu retrospektif kohort çalışmaya, 2018-2026 yılları arasında yüzeyel kitle nedeniyle cerrahi eksizyon uygulanan 0-18 yaş arası çocuklar dahil edildi. Lenfadenopatik lezyonlar ve eksizyon uygulanmayan olgular, cerrahi dışı izlenen sınırlı sayıda lenfatik lezyon dışında dışlandı. Histopatolojik tanılar ana gruplar halinde

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standardize edildi. Klinik, anatomik ve görüntüleme verileri tanımlayıcı ve karşılaştırmalı olarak analiz edildi. İzole boyun kitlesi alt grubunda klinik-radyolojik ön tanılar ile nihai histopatoloji karşılaştırıldı.

Bulgular: Toplam 201 hasta dahil edildi (medyan yaş: 8 yıl; %55,2 kız). En sık görülen gruplar adneksiyal/keratinöz benign lezyonlar (%50,0) ve konjenital/gelişimsel lezyonlardı (%26,5). En sık tanılar pilomatriksoma, epidermal tip keratinöz kist ve tiroglossal kanal kistiydi. Lezyonlar en sık baş-boyun bölgesinde yerleşmişti. Vaskülarite çoğunlukla vasküler/lenfatik lezyonlarda izlenirken, kalsifikasyon özellikle pilomatriksoma olmak üzere adneksiyal/keratinöz lezyonlarla ilişkiliydi (p<0,001). İzole boyun kitlelerinde tanısal uyum pilomatriksoma (%91,7) ve tiroglossal kanal kistinde (%75,7) yüksek, brankial kist ve dermoid/epidermoid kistlerde daha düşüktü (p=0,001).

Sonuç: Çocukluk çağı yüzeyel kitleleri çoğunlukla benign olup, karakteristik anatomik ve görüntüleme özellikleri preoperatif değerlendirmeyi yönlendirebilir. Tanısal uyum pilomatriksoma ve tiroglossal kanal kistinde yüksekken, brankiyal ve dermoid/epidermoid kistlerde daha heterojen seyretmektedir.

Anahtar kelimeler: Pediyatri, yumuşak doku kitlesi, baş ve boyun kitleleri, ultrasonografi, manyetik rezonans görüntüleme, patoloji

INTRODUCTION

Superficial mass lesions of childhood comprise a heterogeneous group that includes congenital/developmental lesions, benign cutaneous and subcutaneous tumors, vascular and lymphatic anomalies, inflammatory/reactive processes, and, less commonly, malignant neoplasms. Although most of these lesions are benign, they have overlapping clinical and imaging findings may complicate preoperative diagnosis. Ultrasonography is usually the first-line imaging modality for superficially located lesions, whereas magnetic resonance imaging (MRI) is generally reserved for larger, deeper, or more complex masses[1-3]. Unlike many previous pediatric reports that focused on a single diagnosis, a single anatomical region, or an imaging-centered perspective, the present study evaluates a broader clinicopathological spectrum of non-lymphadenopathic superficial mass lesions and includes a dedicated isolated neck mass subgroup analysis.

The present study was designed to evaluate the histopathological spectrum, anatomical distribution, and imaging characteristics of non-lymphadenopathic superficial mass lesions in children treated in a pediatric surgery unit over an extended period. In addition, because the neck mass lesions represented a clinically important subset within the cohort, an isolated subgroup of these lesions was analyzed separately to examine the relationship between clinicoradiologic prediagnosis and final histopathology. By integrating clinical, anatomical, imaging, and pathological data within a standardized classification framework, we aimed to provide a practical overview of these lesions.

MATERIALS and METHODS

Study Design and Patients

This retrospective cohort study was approved by the Non-Interventional Clinical Research Ethics Committee of University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (protocol number: GOA-335, approval number: 2026/06-10, date: 26.03.2026), and was conducted in accordance with the principles of the Declaration of Helsinki.

This retrospective observational study was conducted in the department of pediatric surgery of a university hospital and included children evaluated for superficial mass lesions between 2018 and 2026. Medical records, operative notes, pathology reports, and available imaging studies were reviewed. For this study, a superficial mass lesion was defined as a palpable lesion arising from the skin, subcutaneous tissue, or superficial fascia, and managed surgically or, in selected lymphatic lesions, by a documented minimally invasive therapeutic approach. Among patients aged 0-18 years having at least basic clinical data and a final pathology result but without lymphadenopathic lesions, those who were evaluated in the pediatric surgery clinic for a superficial mass lesion, and underwent surgical excision of the mass lesions that were submitted for histopathological examination were included in the study. Patients having lymphadenopathy, abscesses managed by drainage alone, markedly incomplete records, lesions originating from bone, intrathoracic structures, or intra-abdominal organs, and deeply located lesions not meeting the definition of a superficial mass, and those undergoing only incisional or diagnostic biopsy without complete excision or lymph node excision were excluded from the study. Lymphatic lesions that were evaluated based on only histological examination of their aspiration cytology material rather than their tissue excision specimens were also generally excluded from the analyses. However, five superficially located lymphatic lesions managed with bleomycin without total excision were retained in the descriptive cohort because aspiration cytology was benign and the clinicoradiologic findings were considered sufficiently characteristic. Thus, among the lymphatic lesions included in the final cohort, some underwent complete excision,

whereas a small subset of lesions with benign aspiration cytology results managed non-excisionally.

Data Collection and Imaging

Demographic and clinical variables recorded included age at surgery, sex, presenting complaint, lesion multiplicity, anatomical location, and laterality, where applicable. Preoperative imaging data were also collected, including the availability of ultrasonography and MRI, the maximum lesion diameter reported on ultrasonography, and descriptive imaging features such as vascularity and calcification when documented. Because imaging reports were not uniformly diagnostic in all cases, imaging was not analyzed as a standalone diagnostic test. Instead, preoperative diagnosis was defined as the working clinicoradiologic impression based on physical examination and available imaging test results, and it was evaluated in relation to the final histopathological diagnosis.

Histopathological and Anatomical Classification

Histopathological diagnoses were standardized and grouped into seven major categories for analysis: Congenital/developmental lesions, adnexal/keratinous benign lesions, vascular/lymphatic lesions, benign mesenchymal/neural lesions, fibroblastic/myofibroblastic lesions, inflammatory/reactive lesions, and malignant lesions. Standardized diagnostic labels were used to harmonize minor terminology differences across pathology reports. Anatomical distribution was classified into five major regions: head and neck, trunk, upper extremity, lower extremity, and perineal/genital region. For subgroup analysis, an isolated neck mass subgroup was additionally defined, comprising lesions localized to the neck region without concomitant lesions at other anatomical sites. In this subgroup, clinicoradiologic prediagnosis, final histopathology, and laterality were evaluated in greater detail to assess concordance patterns, particularly for lesions initially considered to be thyroglossal duct cysts, branchial cysts, dermoid/epidermoid cysts, pilomatrixomas, and vascular/lymphatic lesions.

The primary outcome of the study was the distribution of standardized histopathological diagnoses and major histopathological groups in children with non-lymphadenopathic superficial mass lesions. Secondary outcomes included the anatomical distribution of lesions across the major histopathological groups, ultrasonographic dimensions of the lesion, preoperative imaging patterns, and ultrasonographic features such as vascularity and calcification. In the isolated neck mass subgroup, additional secondary outcomes were the concordance between clinicoradiologic prediagnosis and final histopathology and the laterality pattern of the lesions. Continuous variables were summarized as medians and interquartile ranges (IQRs) because the distributions of age and lesion size were not assumed to be normal. Categorical variables were expressed as numbers and percentages. Percentages for standardized histopathological diagnoses were calculated both within each major histopathological group and, where appropriate, relative to the total cohort.

Statistical Analysis

Continuous variables were summarized as medians and IQRs, whereas categorical variables were expressed as numbers and percentages. Comparisons of age across major histopathological groups were performed using the Kruskal-Wallis test. Categorical variables, including sex, lesion multiplicity, anatomical distribution, vascularity, calcification, and clinicoradiologic-histopathologic concordance in the isolated neck mass subgroup, were compared using Pearson's chi-square test. A two-sided p-value<0.05 was considered statistically significant. Given the small sizes of some groups, inferential results were interpreted cautiously and used primarily to support key descriptive findings.

RESULTS

A total of 201 children with non-lymphadenopathic superficial mass lesions were included in the final cohort. The median age of the children at surgery was 8 years (IQR, 5-11), and 111 patients (55.2%) were female. Histopathologically, the largest category included adnexal/keratinous benign lesions (100/201, 50.0%), followed by congenital/developmental (53/201, 26.5%), vascular/lymphatic (23/201, 11.5%), and benign mesenchymal/neural lesions (16/201, 8.0%). In contrast, fibroblastic/myofibroblastic, inflammatory/reactive, and malignant lesions were uncommon (Table 1). There were no significant between-group differences in terms of age, sex distribution, or lesion multiplicity across the major histopathological groups (p=0.139, p=0.268, and p=0.178, respectively). Among the standardized diagnoses, pilomatrixoma (55 cases) and keratinous cyst (epidermal type) (43 cases) were the two most frequent individual entities in the entire cohort. Among congenital/developmental lesions, thyroglossal duct cyst was the most common diagnosis (31/53, 58.5%), followed by dermoid cyst (11/53, 20.8%) and branchial cyst (7/53, 13.2%). In the vascular/lymphatic group, lymphangioma

(10/23, 43.5%) and capillary hemangioma (7/23, 30.4%) were the most common diagnoses (Table 2).

Anatomical distribution varied substantially, and statistically significant across the major histopathological

Table 1. Demographic and lesion characteristics according to major histopathological groups

Histopathological groups	n (%)	Age, median (IQR), years	Male, n (%)	Female n (%)	Solitary lesions, n (%)	Cystic lesions, n (%)	Multiple lesions, n (%)
Congenital/developmental lesions	53 (26.5%)	7 (4-9)	29 (55%)	24 (45%)	8 (15%)	45 (85%)	0 (0%)
Adnexal/keratinous benign lesions	100 (50%)	8 (6-11)	37 (37%)	63 (63%)	57 (57%)	43 (43%)	3 (3%)
Vascular/lymphatic lesions	23 (11.5%)	8 (5.5-10.5)	12 (52.1%)	11 (47.9%)	13 (56.5%)	10 (43.5%)	3 (13%)
Benign mesenchymal/neural lesions	16 (8%)	7.5 (5-10.3)	7 (43.7%)	9 (56.3%)	13 (81.2%)	3 (18.8%)	1 (6%)
Fibroblastic/myofibroblastic lesions	5 (2.5%)	12 (8-13)	2 (40%)	3 (60%)	3 (60%)	2 (40%)	0 (0%)
Inflammatory/reactive lesions	2 (1%)	7 (6-8)	2 (100%)	0 (0%)	2 (100%)	0 (0%)	0 (0%)
Malignant lesions	2 (1%)	4.5 (4-5)	1 (50%)	1 (50%)	2 (100%)	0 (0%)	0 (0%)
Total	201 (100%)	8 (5-11)	90 (44.8%)	111 (55.2%)	98 (48.7%)	103 (51.3%)	7 (3.5%)

Data are presented as n (%) unless otherwise indicated. Age is presented as median (IQR). Multiple lesions refer to patients with more than one lesion. Cystic lesions were classified according to the final histopathological diagnosis. IQR: Interquartile ranges

Table 2. Standardized histopathological diagnoses within the major histopathological groups

Major histopathological groups	Standardized histopathological diagnosis	n	% within group	% of total cohort
Congenital/developmental lesions	Thyroglossal duct cyst	31	58.5	15.4
	Branchial cyst	7	13.2	3.5
	Dermoid cyst	11	20.8	5.5
	Median raphe cyst	1	1.9	0.5
	Subcutaneous bronchogenic cyst	1	1.9	0.5
	Accessory tragus	2	3.8	1.0
Adnexal/keratinous benign lesions	Pilomatrixoma	55	55.0	27.4
	Keratinous cyst (epidermal type)	43	43.0	21.4
	Follicular cyst	1	1.0	0.5
	Eccrine spiradenoma	1	1.0	0.5
Vascular/lymphatic lesions	Capillary hemangioma	7	30.4	3.5
	Cavernous hemangioma	4	17.4	2.0
	Lymphangioma	10	43.5	5.0
	Lobular capillary hemangioma	1	4.3	0.5
	Masson tumor (intravascular papillary endothelial hyperplasia)	1	4.3	0.5
Benign mesenchymal/neural lesions	Lipoma	8	50.0	4.0
	Neurofibroma	3	18.8	1.5
	Leiomyoma	1	6.2	0.5
	Neurothekeoma	1	6.2	0.5
	Soft tissue chondroma (extraskeletal chondroma)	1	6.2	0.5
	Benign chondroid lesion	2	12.5	1.0
Fibroblastic/myofibroblastic lesions	Nodular fasciitis	2	40.0	1.0
	Desmoid fibromatosis	1	20.0	0.5
	Myofibroblastic proliferation	1	20.0	0.5
	Pleomorphic fibroma	1	20.0	0.5
Inflammatory/reactive lesions	Calcified nodule	1	50.0	0.5
	Subcutaneous granuloma annulare	1	50.0	0.5
Malignant lesions	Low-grade fibromyxoid sarcoma	1	50.0	0.5
	Alveolar rhabdomyosarcoma	1	50.0	0.5

Percentages in the fourth column are calculated within each major histopathological group; percentages in the fifth column are based on the total cohort (n=201). Histopathological diagnoses were standardized for analysis

groups (p<0.001) (Table 3, Figure 1). Congenital/developmental lesions were strongly concentrated in the head and neck region (46/53, 86.8%). In contrast, adnexal/keratinous benign lesions showed a broader distribution, involving the head and neck (44.0%), trunk (25.0%), and upper extremities (23.0%). Vascular/lymphatic lesions were distributed more evenly between the head, neck and trunk (each 39.1%), whereas benign mesenchymal/neural lesions were predominantly located on the trunk (50.0%). Fibroblastic/myofibroblastic lesions were confined to the head, neck and trunk, while the two malignant lesions were located on the trunk and lower extremities, respectively. Lesion size on ultrasonography also differed across histopathological groups. Congenital/developmental lesions and adnexal/keratinous benign lesions tended to be relatively small, with median maximum diameters of 1.5 cm (IQR, 1.1-2.2) and 1.4 cm (IQR, 0.8-1.6), respectively. Vascular/lymphatic lesions were generally larger, with a median maximum diameter of 2.5 cm (IQR, 1.0-5.0), whereas benign mesenchymal/neural lesions had the

Table 3. Anatomical distribution and ultrasonographic lesion size according to major histopathological groups

Major histopathological groups	Head and neck, n (%)	Trunk, n (%)	Upper extremity, n (%)	Lower extremity, n (%)	Perineal/genital, n (%)	Max lesion diameter on USG, median (IQR), cm
Congenital/developmental lesions	46 (86.8)	6 (11.3)	-	-	1 (1.9)	1.5 (1.1-2.2)
Adnexal/keratinous benign lesions	44 (44.0)	25 (25.0)	23 (23.0)	-	8 (8.0)	1.4 (0.8-1.6)
Vascular/lymphatic lesions	9 (39.1)	9 (39.1)	3 (13.0)	2 (8.7)	-	2.5 (1.0-5.0)
Benign mesenchymal/neural lesions	6 (37.5)	8 (50.0)	1 (6.2)	-	1 (6.2)	4.0 (2.0-5.3)
Fibroblastic/myofibroblastic lesions	3 (60.0)	2 (40.0)	-	-	-	2.3 (1.5-2.4)
Inflammatory/reactive lesions	1 (50.0)	-	1 (50.0)	-	-	2.1 (1.2-3.0)*
Malignant lesions	-	1 (50.0)	-	1 (50.0)	-	4.8 (4.0-5.5)*

Data are presented as n (%) unless otherwise indicated. Ultrasonographic lesion size is presented as median (IQR) in centimeters: For groups with very small sample sizes (n=2), lesion size is presented as median (range). IQR: Interquartile range, USG: Ultrasonography

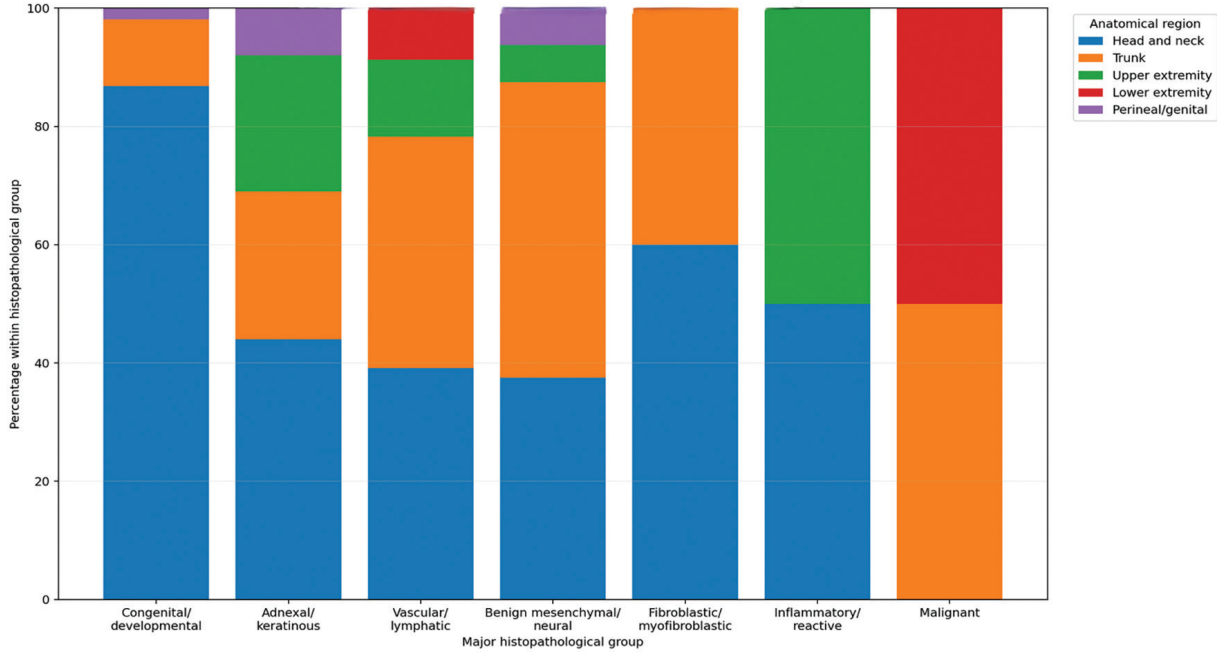

Figure 1. Anatomical distribution across major histopathological groups

A hundred percent stacked bar chart showing the proportional anatomical distribution of lesions within each major histopathological group (n=201). Anatomical regions were classified as head and neck, trunk, upper extremity, lower extremity, and perineal/genital region. Major histopathological groups comprised congenital/developmental lesions, adnexal/keratinous benign lesions, vascular/lymphatic lesions, benign mesenchymal/neural lesions, fibroblastic/myofibroblastic lesions, inflammatory/reactive lesions, and malignant lesions

greatest median diameter (4.0 cm; IQR, 2.0-5.3) among the common benign groups. The two malignant lesions measured 4.8 cm (range, 4.0-5.5) on ultrasonography.

Preoperative imaging results were available in 183 of 201 patients (91.0%). Ultrasonography alone was performed in 138 patients (68.7%), whereas both ultrasonography and MRI were performed in 45 patients (22.4%). While 18 patients (9.0%) had not undergone preoperative imaging tests. Frequency of MRI use varied by lesion category. In relative terms, MRI was most frequently performed in the malignant group (2/2) and in patients with benign mesenchymal/neural lesions (7/16, 43.8%) and vascular/lymphatic lesions (9/23, 39.1%). In absolute numbers, however, congenital/developmental lesions accounted for the most MRI examinations n=16, followed by adnexal/keratinous benign lesions (n=11). Anatomically, most MRI examinations were performed for head and neck lesions (29/45, 64.4%), followed by trunk lesions (13/45, 28.9%), whereas each one of lower, upper extremity, and perineal/genital lesions had undergone MRI examinations only once (2.2% per se). Two notable ultrasonographic patterns emerged. The distribution of vascularity differed significantly across the major histopathological groups ($p<0.001$) which was most prominent among vascular/lymphatic lesions (n=6), while only a few additional vascularized lesions were detected in cases with benign mesenchymal/neural (n=2), fibroblastic/myofibroblastic n=1, and malignant (n=2) lesions. No vascularity was documented in congenital/developmental, adnexal/keratinous benign, or inflammatory/reactive lesions. Likewise, distribution of calcification differed significantly across groups ($p<0.001$) and was overwhelmingly concentrated in benign adnexal/keratinous lesions (44/48), particularly in pilomatrixomas n=39. Only isolated calcified lesions were observed in the vascular/lymphatic, benign mesenchymal/neural, fibroblastic/myofibroblastic, and inflammatory/reactive groups (1 case each).

Among 103 patients with isolated neck masses, the most frequent clinicoradiologic prediagnoses were thyroglossal duct cyst (n=37), dermoid/epidermoid cyst (n=21), branchial cyst (n=15), and pilomatrixoma (n=12). While vascular/lymphatic lesions accounted for 5 cases, and the remaining 13 cases were grouped as other clinicoradiologic prediagnoses (Table 4, Figure 2). Histopathologic confirmation rates differed significantly across these prediagnostic categories ($p=0.001$). Thyroglossal duct cyst showed a relatively high clinicoradiologic-pathologic concordance, with histopathological confirmation in 28 of 37 cases (75.7%). These lesions were overwhelmingly localized at midline (35/37), with only 2 left-sided cases. In contrast, branchial cysts were histopathologically confirmed preoperatively in only 6 of 15 cases (40.0%) and showed greater heterogeneity, with 5 lesions proving to be epidermal/dermoid cysts and 4 cases falling into other pathological categories. Lesions initially considered branchial cysts were characteristically lateral, with a slight right-sided predominance (8 right, 5 left, and 2 midline). Prediagnosis of dermoid/epidermoid cyst was confirmed in 8 of 21 cases (38.1%), whereas 8 lesions were ultimately diagnosed as pilomatrixoma, highlighting substantial overlap between these entities in routine preoperative assessment. By contrast, pilomatrixoma showed the highest concordance

Table 4. Clinicoradiologic prediagnosis and final histopathology in the isolated neck mass subgroup

Clinicoradiologic prediagnoses	Patient, n	Histopathologic confirmation, n (%)	Alternative final histopathology	Laterality
Thyroglossal duct cyst	37	28 (75.7)	Dermoid cyst (3); epidermal cyst (6)	Midline (35); left-sided, (2)
Branchial cyst	15	6 (40.0)	Epidermal/dermoid cystic lesions (5); other (4)	Right-sided (8); left-sided(5); midline(2)
Dermoid/epidermoid cyst	21	8 (38.1)	Pilomatrixoma (8); other (5)	Right-sided (5); left-sided (11); midline (5)
Pilomatrixoma	12	11 (91.7)	Hemangioma (1)	Right-sided (7); left-sided (2); midline (3)
Vascular/lymphatic lesion	5	5 (100.0)	None	Left-sided (5)
Other clinicoradiologic prediagnoses	13	—	Heterogeneous	—

Histopathologic confirmation was defined as concordance between the clinicoradiologic prediagnosis and the final histopathologic diagnosis. Laterality was classified as midline, right-sided, or left-sided. Histopathologic confirmation was not calculated for the "other clinicoradiologic prediagnoses" category because it comprised heterogeneous infrequent diagnostic impressions grouped for tabular simplicity

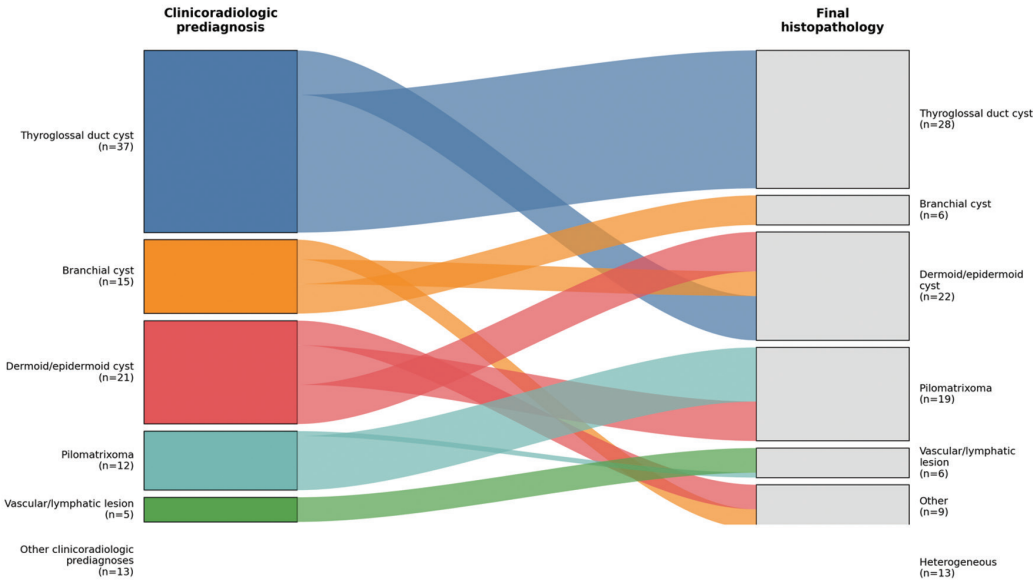

Figure 2. Alluvial plot of clinicoradiologic prediagnosis and final histopathology in the isolated neck mass subgroup

Alluvial plot showing the relationship between clinicoradiologic prediagnosis and final histopathological diagnosis in children with isolated neck masses (n=103). The width of each flow is proportional to the number of cases within each diagnostic pathway. Infrequent prediagnostic categories were grouped under "Other clinicoradiologic prediagnoses" for visual clarity

among the main prediagnostic categories, with histopathological confirmation in 11 of 12 cases (91.7%). All of 5 left-sided clinicoradiologically suspected vascular/lymphatic lesions were histopathologically confirmed.

DISCUSSION

In the present series, the clinicopathological spectrum of non-lymphadenopathic superficial mass lesions in children was clearly dominated by benign lesions, with adnexal/keratinous benign lesions forming the largest histopathological group, followed by congenital/developmental lesions. While pilomatrixoma, epidermal-type keratinous cyst, and thyroglossal duct cyst were the most frequently encountered entities, and the head and neck was the most commonly involved anatomical region. These findings are broadly consistent with those of previous pediatric studies showing that most superficial and neck masses encountered in childhood are benign, and that developmental lesions, along with benign cutaneous and subcutaneous tumors, account for a substantial proportion of surgically treated cases[1,2,4,5]. The predominance of the head and neck region in our cohort is also consistent with those indicated in earlier reports that emphasized this region as the most common site involved in a large proportion of pediatric congenital and superficial soft-tissue lesions[3,6,7]. In addition, the prominence of thyroglossal duct cyst and pilomatrixoma in our series is consistent with the relevant literature data, which identifies thyroglossal duct cyst as one of the most frequent congenital neck lesions in children and pilomatrixoma as one of the most common superficial head and neck tumors in the pediatric age group[8-12].

The anatomical distribution in our cohort was not random. It differed significantly across the major histopathological groups, with congenital/developmental lesions showing a marked predominance on the head and neck region. In contrast, adnexal/keratinous benign lesions and benign mesenchymal/neural lesions demonstrated a broader distribution involving the trunk and extremities. This pattern is clinically plausible and consistent with the known embryologic concentration of congenital lesions in the cervical region and the broader somatic distribution of cutaneous, adnexal, and mesenchymal superficial lesions in childhood[2,6,7,13]. Our imaging findings also followed recognizable lesion-specific patterns. Calcification was overwhelmingly concentrated in the adnexal/keratinous benign group, particularly in cases with pilomatrixoma, which is in keeping with the well-established sonographic appearance of pilomatrixoma as a superficially located lesion frequently associated with internal calcification or echogenic foci[14-16]. In contrast, given the biological nature of these aforementioned lesions and their known imaging behavior, vascularity was most prominent in the vascular/lymphatic group, as expected[2,17-19]. Similarly, the more frequent use of MRI in cases with vascular/lymphatic, benign mesenchymal/neural, and malignant lesions likely

reflects the need for better delineation of lesion extent, tissue planes, and possible deep extension in larger or more complex mass lesions. In contrast, ultrasonography was sufficient as the primary imaging modality for the delineation of most small, clearly superficial lesions[2,13,17].

Pilomatrixoma deserves particular emphasis in our cohort, not only because it was the single most frequently revealed individual diagnosis, but also because it showed a high clinicoradiologic-pathologic concordance in the isolated neck mass subgroup, with histopathological confirmation in 11 of 12 cases. This finding is clinically important, as pilomatrixoma has repeatedly been identified as one of the most common benign superficial head and neck tumors in children. Yet, it is still a preoperatively underrecognized or misdiagnosed entity as other benign cystic or subcutaneous lesions[10,11,20]. In our series, the substantial overlap between the prediagnostic category of dermoid/epidermoid cyst and the final diagnosis of pilomatrixoma further supports our assertion, suggesting that pilomatrixoma should be considered more actively in the differential diagnosis of superficially located pediatric head and neck masses. The relatively high concordance observed in our cohort may reflect increasing familiarity with its characteristic clinicoradiologic profile, particularly its superficial location, firm consistency, and frequent association with internal calcification detected on ultrasonograms[14,15]. From a practical standpoint, our findings suggest that heightened awareness of pilomatrixoma may improve preoperative diagnostic accuracy and reduce misclassification, especially in lesions initially thought to represent dermoid or epidermoid cysts[16].

In the isolated neck mass subgroup, thyroglossal duct cyst showed a substantially higher clinicoradiologic-histopathologic concordance than branchial cyst and dermoid/epidermoid cyst, and it was overwhelmingly associated with a midline location in our series. This finding is consistent with the well-established embryologic and clinical profile of thyroglossal duct cysts which are the most common congenital midline neck lesions in children, and supports the practical value of midline localization in narrowing the spectrum of preoperative differential diagnoses[6,7,9]. By contrast, lesions initially considered branchial cysts showed lower histopathologic confirmation and greater diagnostic heterogeneity, which is also in line with the broader literature data emphasizing that lateral pediatric neck masses may encompass a wider range of congenital and acquired cystic lesions, even when branchial anomaly is the leading preoperative impression[21]. Similarly, the relatively low confirmation rate observed in the dermoid/epidermoid cyst category suggests that this prediagnostic label often serves as a broad clinicoradiologic descriptor rather than a highly specific diagnosis, particularly for superficially located neck lesions[22,23]. Taken together, our findings indicate that clinicoradiologic assessment appears more reliable for thyroglossal duct cysts, particularly when a lesion is clearly midline. In contrast, branchial and dermoid/epidermoid prediagnoses should be interpreted more cautiously because of their broader pathological overlap[21,24].

Vascular/lymphatic lesions characterized by relatively larger lesion size, more frequent documentation of internal vascularity, and more selective use of MRI compared with the more common congenital/developmental and adnexal/keratinous benign lesions constituted a smaller but clinically distinctive subgroup in our cohort. These findings are consistent with the known biological and radiologic behavior of pediatric vascular and lymphatic anomalies, which often require more extensive preoperative characterization because of their infiltrative pattern, anatomical complexity, or uncertain deep extension[2,25]. In addition, our decision to retain a small number of superficially located lymphatic lesions managed with antineoplastic drug bleomycin despite the absence of total excision reflects contemporary practice, in which selected lymphatic malformations are increasingly treated with image-guided or minimally invasive approaches rather than primary surgery alone[25-28]. Although these five non-excised lymphatic lesions introduced minor heterogeneity into the cohort, their exclusion did not alter the overall anatomical distribution or the predominant role of vascular/lymphatic lesions within the cohort, supporting the robustness of our main findings.

A major strength of this study is that it examines a broad spectrum of non-lymphadenopathic superficial mass lesions in children rather than a single diagnosis. Histopathological diagnoses were standardized into clinically meaningful groups, allowing a structured analysis of a heterogeneous cohort. In addition, clinical, imaging, anatomical, and pathological findings were evaluated together, providing a practical overview of these lesions in routine pediatric surgical practice. The isolated neck mass subgroup also enabled a focused assessment of clinicoradiologic–pathologic concordance in a clinically relevant subset.

Study Limitations

This study has several limitations, including its retrospective, single-center design, potential selection

and documentation bias, and the fact that the cohort was composed mainly of surgically treated lesions rather than the full spectrum of superficially located pediatric masses. Preoperative imaging was not standardized and was not uniformly diagnostic, so clinicoradiologic impressions were evaluated descriptively rather than as formal test-accuracy measures. Some histopathological groups were represented by small numbers, limiting subgroup-level interpretation. In addition, a small number of superficial lymphatic lesions managed with bleomycin rather than total excision were retained in the descriptive cohort, introducing some heterogeneity into an otherwise excision-based series. Finally, histopathological terminology was standardized retrospectively for analysis.

CONCLUSION

In conclusion, superficial non-lymphadenopathic mass lesions in children were predominantly benign and most commonly involved the head and neck region. Pilomatrixoma, epidermal-type keratinous cyst, and thyroglossal duct cyst were the leading diagnoses. While clinicoradiologic prediagnosis showed relatively high concordance for thyroglossal duct cyst and pilomatrixomas, the prediagnoses of branchial cyst and dermoid/epidermoid cyst were more heterogeneous. In particular, pilomatrixoma should be actively considered in the differential diagnosis of firm, calcified superficial head and neck lesions in children, as it is frequently misclassified preoperatively as a dermoid or epidermoid cyst. A structured approach combining clinical, anatomical, imaging, and pathological assessment may facilitate more accurate assessment of these lesions in pediatric surgical practice.

Ethics

Ethics Committee Approval: Approved by the Non-Interventional Clinical Research Ethics Committee of University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (protocol number: GOA-335, approval number: 2026/06-10, date: 26.03.2026).

Informed Consent: Retrospective study.

Declaration of AI Use: Artificial intelligence-assisted technologies were used only for language editing during the preparation of this manuscript. All scientific content, data analysis, and interpretation were performed, reviewed, and approved by the authors, who take full responsibility for the content of the publication.

Footnotes

Author Contributions

Surgical and Medical Practices: Ö.O., H.E., M.C., Concept: Ö.O., Design: Ö.O., M.C., Data Collection or Processing: Ö.O., H.E., T.Y., M.C., Analysis or Interpretation: Ö.O., H.E., M.C., Literature Search: Ö.O., T.Y., Writing: Ö.O.

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Original Article

The Effect of Computerized Decision Support System in Preventing of High-risk Medication Errors in Pediatric Patients

Pediyatrik Hastalarda Yüksek Riskli İlaç Hatalarının Önlenmesinde Bilgisayarlı Karar Destek Sisteminin Etkisi

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ABSTRACT

Objective: This study aimed to examine the effect of a web-based double check program, developed as a computerised decision support system, on preventing high-risk medication errors among pediatric nurses.

Method: This quasi-experimental study was conducted using a single-group pretest-posttest design in the pediatric surgery clinics of a university hospital. The sample consisted of all high-risk medication administrations performed by 24 nurses. Medication error rates were determined through direct observation before the intervention. Subsequently, nurses administered medications using the web-based double check program, and medication error rates were reassessed after the interventions. Data were analysed using IBM Statistical Package for the Social Sciences software program. Ethical approval, institutional permission, and informed consent were obtained.

Results: The average rates of medication error were 47.8% before and 19.4% after the interventions, indicating a substantial reduction in medication error rates following implementation of the web-based double check program. The overall medication error rate was calculated as the arithmetic mean of stage-specific (preparation, administration, patient monitoring, and documentation).

Conclusion: The use of the web-based double check program significantly reduced medication error rates among pediatric nurses. Integration of computerized decision support systems into clinical practice may contribute to improved medication safety in pediatric settings.

Keywords: Child, pediatric nursing, medication errors, decision support systems, clinical patient safety

ÖZ

Amaç: Bu çalışma, bilgisayarlı bir karar destek sistemi olarak geliştirilen web tabanlı bir çift kontrol programının, pediyatri hemşireleri arasında yüksek riskli ilaç hatalarının önlenmesine etkisini incelemek amacıyla yapılmıştır.

Yöntem: Bu yarı deneysel çalışma, bir üniversite hastanesinin pediyatrik cerrahi kliniklerinde tek grup ön-son test tasarımı kullanılarak gerçekleştirilmiştir. Örneklem, 24 hemşire tarafından gerçekleştirilen tüm yüksek riskli ilaç uygulamalarından oluşmuştur. Müdahale öncesinde ilaç hatası oranları doğrudan gözlem yoluyla belirlenmiştir. Ardından, hemşireler web tabanlı çift kontrol programını kullanarak ilaçları uygulamışlar ve müdahalenin ardından ilaç hatası oranları yeniden değerlendirilmiştir. Veriler SPSS yazılımı kullanılarak analiz edilmiştir. Etik kurul onayı, kurum izni ve bilgilendirilmiş onam alınmıştır.

Bulgular: Müdahale öncesinde ortalama ilaç hatası oranı %47,8 iken, müdahale sonrasında bu oran %19,4'e düşmüştür; bu durum, web tabanlı çift kontrol programının uygulanmasının ardından hatalarda önemli bir azalma olduğunu göstermektedir. Genel ilaç hatası oranı, aşamalara özgü hata oranlarının (hazırlama, uygulama, izleme ve belgeleme) aritmetik ortalaması olarak hesaplanmıştır.

Sonuç: Web tabanlı çift kontrol programının kullanımı, çocuk hemşireleri arasında ilaç hatası oranlarını önemli ölçüde azaltmıştır. Bilgisayarlı karar destek sistemlerinin klinik uygulamaya entegrasyonu, çocuk sağlığı hizmetlerinde ilaç güvenliğinin iyileştirilmesine katkıda bulunabilir.

Anahtar kelimeler: Çocuk, pediyatri hemşireliği, ilaç hataları, karar destek sistemleri, klinik hasta güvenliği

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INTRODUCTION

Medication administration is one of the fundamental legal responsibilities of nurses and plays a critical role in patient safety. Medication errors are defined as preventable malpractices that may lead to inappropriate medication use or patient harm during prescribing, preparation, or administration processes of medications[1,2]. These malpractices remain among the most common adverse events reported in healthcare settings[3].

Medication errors occur more frequently during administration of medications to pediatric patients compared to adults due to physiological differences between adult and pediatric patients including, weight-based dosing requirements, and the need for individualized drug calculations[4-9]. In particular, children aged 0-4 years are reported to be at higher risk for medication administration-related malpractices[10]. Common medication errors in pediatric clinical practice include incorrect dose calculation, improper dilution of medications, incorrect infusion rate, and failure to verify safe dose ranges. Such errors may arise from heavy workload, insufficient staffing, interruptions during medication preparation, lack of standardized protocols, and inadequate double-check practices[5,11-13].

Nurses play a central role in preventing medication errors, especially during the preparation and administration stages of medications. Although physicians prescribe medications, nurses are responsible for verifying correct dose ranges, preparing medications in accordance with hygienic regulations, and ensuring adherence to medication administration principles. Therefore, the implementation of effective strategies that nurses must follow in medication processes is essential for improving patient safety[14-16].

International organizations such as the World Health Organization recommend the use of standardized medication protocols and double-checked procedures, particularly for administration of high-risk medications[17]. However, in many clinical settings, especially where staffing shortages exist, manual double-checks by another healthcare professional may not always be feasible. This limitation highlights the need for alternative technological solutions that support safe administration of medications[15,18-24].

Computerized decision support systems have emerged as promising tools for reducing medication errors by providing automated dose calculations, drug information, and standardized administration protocols. Despite the growing interest in technological interventions, still limited number of studies have evaluated the effectiveness of web-based double-check systems in administration of high-risk medications to pediatric patients[18-23].

Therefore, this study aimed to examine the effect of a web-based double check program developed as a computerized decision support system on preventing high-risk medication errors made by pediatric nurses.

Research Question: Is the "web-based double check program" effective in reducing error rates during the administration of high-risk medications to pediatric patients?

MATERIALS and METHODS

Study Design and Setting

This quasi-experimental study was conducted using a single-group pretest-posttest study design to evaluate the effectiveness of the web-based double check program in improving the safety of high-risk medication administration among pediatric patients. Data were collected using a non-participant observation method, which is considered as an objective approach for detecting medication administration errors.

This study was carried out between November 2017 and June 2018 in the pediatric surgery clinic, pediatric surgery intensive care unit, and neonatal surgery intensive care unit of a university hospital in Türkiye where patients aged 0-18 years were hospitalized.

Study Population and Sample Size

The population of the study consisted of nurses working in the pediatric surgery-related units of the study hospital and administration of the high-risk medications by these nurses was assessed.

In this study, the pediatric population included patients receiving high-risk medications, which were defined as drugs associated with an increased risk of significant harm when administered erroneously. These medications consisted of intravenous antibiotics (such as vancomycin and meropenem), insulin, anticoagulants (e.g., heparin), concentrated electrolytes (e.g., potassium chloride), sedatives, and opioid analgesics, which are widely recognized as high-risk medications also used in pediatric care[1-3].

Eligibility criteria for participation of nurses were as follows:

- administering medications categorized as high-risk drugs for pediatric patients,
- voluntary participation in the study,
- having adequate internet usage skills to use the web-based program.

During the study period, 31 nurses were working in the relevant clinics. Nurses who were not actively involved in medication administration (charge nurse, chief nurse, polyclinic nurse, and training nurse), nurses who were not in duty during the study period, and those who declined participation were excluded. Consequently, 24 nurses were included in the study sample.

All nurses included in the study held a bachelor's degree; two (8.3%) had a master's degree, five (20.8%) were continuing their master's degree program, and one (4.2%) was pursuing her doctoral education. All participants were female, with a mean age of 33.08±6.47 years. The mean duration of pediatric nursing experience was 8.00±5.52 years. No new nurses joined or left the clinics during the study period, ensuring consistency between pre-and post-intervention observations.

Determination of the Sample Size

The research sample consisted of high-risk medications administered by nurses during the observation periods. The sample size was calculated using G*Power (version 3.1.9.4) based on a comparison of two independent proportions (chi-square test). An effect size of 0.3 (medium effect, according to Cohen's conventions), a type I error (α) of 0.05, and a statistical power of 0.95 (1-β) were assumed. The minimum required sample size was determined to be 530 observations. Achievement of a higher statistical power was preferred to increase the sensitivity of detecting clinically significant differences in medication error rates. During the study, 532 administrations of medications were observed before and 538 after the intervention, yielding a total of 1070 medication observations, which exceeded the required sample size. To evaluate the adequacy of sample size and the statistical power of the findings, a post- hoc power analysis was conducted using G*Power 3.1.9.4. Based on the observed effect size (Cohen's w=0.301) calculated from the primary outcome variable (overall medication error rate), and comparing the pre- and post-intervention groups, the statistical power of the study (1-β) was estimated as 1.000. This result indicates that the sample size was sufficient to detect significant differences between groups.

Data Collection

Observation Process

Relevant data were collected using a non-participant observation method to identify medication administration errors. This observation technique was selected because it provides more objective and reliable results compared to incident report analysis or retrospective record review methods. Schnock et al.[6] reported that the use of observation method in determining medication errors would provide objective results and it is a more reliable and effective method compared to the methods of examining erroneous and clinical records.

At the beginning of the observation phase, two observers independently conducted the first 30 medication observations in order to assess the medication observation form. The second observer was a nurse with clinical experience and postgraduate education in pediatric nursing.

Inter-observer agreement was evaluated using Kappa Power Analysis, and the agreement level was found to be 0.95, indicating excellent reliability[25]. After confirming inter-observer consistency, all subsequent observations were conducted by the principal researcher.

Medication administration errors were first recorded before the implementation of the web-based double check program conducted in three separate sessions by the researcher. Following baseline observations, user accounts were created for all participating nurses, and the program was installed on their mobile devices.

Training sessions on the use of the web-based double check program were conducted in three separate sessions by the researcher. After completing the training, a preliminary trial phase was initiated to ensure that all nurses were familiar with the system and able to use it effectively.

Following this preparation phase, the web-based double check program was integrated into routine medication practices in the clinic. During this intervention period, stages of the medication administration processes were again observed, and medication error rates were recorded using the same observational method.

The overall observation process, including the pre-intervention, training, pilot testing, and post-intervention phases, is presented as a flow diagram in Figure 1 to enhance clarity and transparency of the study design.

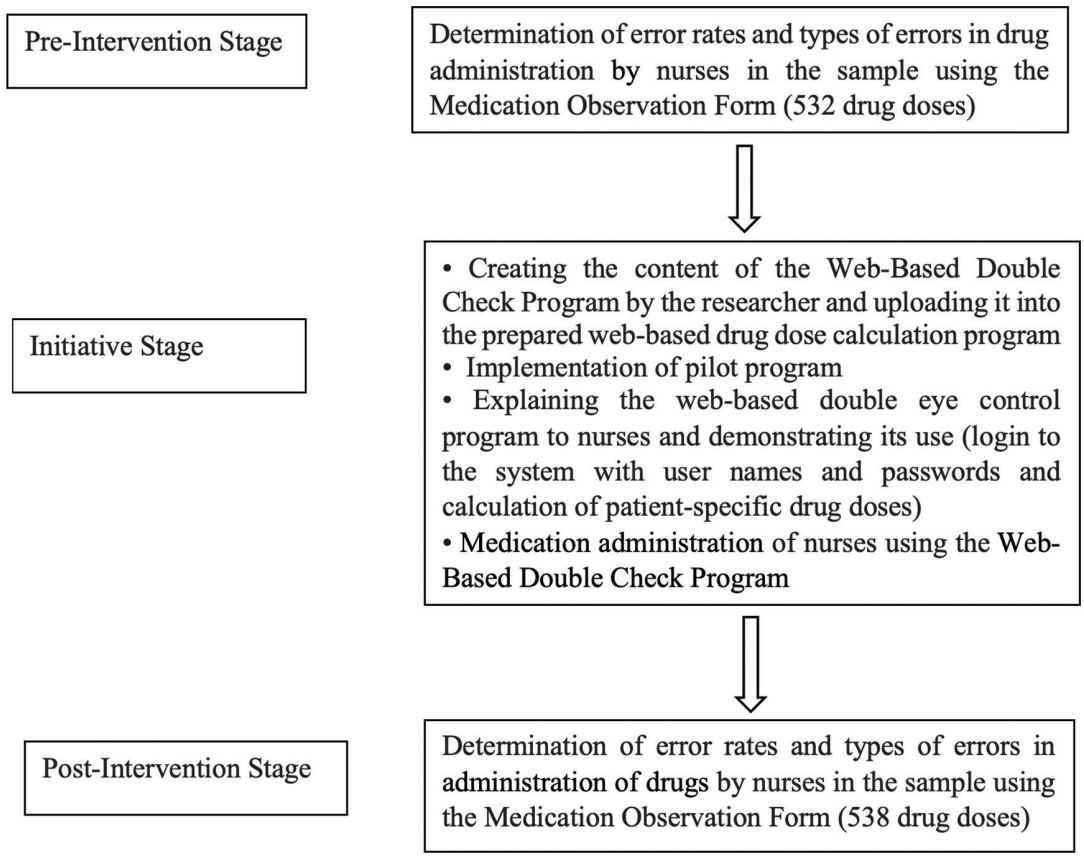

Figure 1. Research flow diagram

Medication Observation Form

Medication administration errors were identified using the medication observation form, which was developed by the researchers based on the relevant literature data[26,27].

This form was designed to evaluate all stages of the medication process including:

- preparation of medications,
- administration of medications,
- patient monitoring,
- documentation and recording.

To ensure content and scope validity, expert opinions were obtained during the development of the form. Based on expert feedback, necessary revisions were made before initiation of the data collection phase.

Medication errors recorded using this form were evaluated according to:

- hospital medication protocols,
- the 10 rights of medical administration (correct medicine, correct dose, correct patient, correct time, correct route of medication, correct medicine form, correct medicine management, correct record, correct response and correct information),
- deviations from standardized medication skill steps defined in the web-based double check program,
- relevant literature-based medication safety standards[26,27].

Web-based Double Check Program

The web-based double check program was developed using a structured multi-stage process.

In the first stage, a web-based platform (www.decpro.net) was created. In the second stage, medication preparation, administration, and follow-up guidelines for the administration of high-risk medications were developed based on a comprehensive literature review[28-30].

In the third stage, expert evaluation was consulted to ensure content validity. Drug-related content included in the program was reviewed by a panel of five experts from pharmacology and pharmacy disciplines. Content validity was assessed using Fleiss' Kappa statistical analysis, and an agreement level of 0.86, indicating excellent agreement, was obtained.

After content validation, the program was pilot-tested for 15 days by 10 pediatric nurses working in pediatric clinics at two different university hospitals outside the study setting.

Feedback obtained from the pilot users was analyzed using thematic analysis, and the results indicated that the program was:

- easy to use,
- provided a practical method for entering patient data,
- helpful in preventing medication errors.

Following the pilot phase, training sessions were conducted for nurses in the clinics where the study was conducted. Each nurse received a username and password, and the system was activated for clinical use.

The program allows nurses to enter patient-specific data, including ages, body weights of the patients, and doses of the prescribed medications. Based on these inputs, the program automatically calculates the appropriate dose for the patient and verifies whether the prescribed dose falls within the safe dose range. In addition, standardized drug administration guidelines are accessible through the program interface.

During the post-intervention phase, this system was used in all observed medication administrations.

Statistical Analysis

Statistical analyses were performed using SPSS software (IBM SPSS Statistics, version 22.0), and a p-value of <0.05 was considered statistically significant.

Descriptive statistics were used to summarize medication error frequencies and percentages observed during the pre-and post-intervention periods. Differences between pre- and post-intervention error rates were analyzed using the chi-square (χ^2) test of independence.

To reduce the increased risk of type I errors associated with multiple hypothesis testing, Holm-Bonferroni correction was applied to all p-values obtained from comparisons of individual medication error types.

The overall medication error rate was calculated as the arithmetic mean of error rates across different stages of the medication administration process (preparation, administration, patient monitoring, and documentation). Although these categories represent heterogeneous components of the medication process, arithmetic averaging was used to provide a composite and interpretable indicator reflecting the general level of medication safety performance. This approach has been used in previous observational medication safety studies to summarize multidimensional error structures and express them as a single outcome measure[31]. However, it is acknowledged that this method assumes equal weighting of error categories and may not fully capture the clinical significance of individual error types.

To ensure consistency in terminology, the term "medication error rate" was used throughout the manuscript to refer to the proportion of observed medication administrations with at least one error. The term "overall medication error rate" specifically refers to the composite indicator calculated from stage-specific error rates. Each stage was given equal weight in the calculation of the overall medication error rate, as no predefined weighting criteria were available for different error types. This approach was selected to provide a simple and interpretable summary measure of overall medication safety performance.

For consistency, the term "dose verification" was used to refer to the process of checking whether the prescribed dose falls within the safe dose range.

This study was derived from the author's doctoral thesis completed in 2018. In the present manuscript, results of the statistical analyses were re-evaluated and updated in accordance with reviewers' recommendations. Specifically, the application of chi-square (χ^2) test of independence and Holm-Bonferroni correction provided a more rigorous control of type I error. In addition, 95% confidence intervals (CIs) were calculated for all observed medication error rates to improve the interpretability and clinical relevance of the findings. Consequently, some p-values differ from those reported in the original thesis.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Ege University Faculty of Medicine Clinical Research Ethics Committee (decision no: 17-11/37, dated: 14.11.2017), and institutional permission was obtained from the hospital where the study was conducted

(decision no: 299596, dated: 21.11.2017). Written informed consent was obtained from all participating nurses. The study was retrospectively registered at ClinicalTrials.gov (NCT06371690; 15.04.2024).

RESULTS

In this quasi-experimental study conducted to reduce the rates of medication administration errors made by nurses, a total of 1070 medication administrations were observed before and after the implementation of the double check program.

Table 1 presents medication error rates according to the stages of the medication administration process. The medication preparation error rate decreased from 92.9% before the intervention to 33.6% after the intervention (χ^2=7.936, p=0.004). The rate of not performing safe dose verification significantly decreased from 92.9% to 17.3% (χ^2=8.557, p=0.003). The rate of not performing medication route verification significantly decreased from 39.3% to 13.2% (χ^2=3.879, p=0.049), and the rate of not evaluating vital signs before and/or after medication decreased from 12.4% to 9.6% (χ^2=7.989, p=0.005). Similarly, the rates of monitoring errors decreased from 61.5% to 22.3%

Table 1. Distribution of medication error rates before and after implementation of the web-based double check program with 95% confidence intervals and Holm-Bonferroni adjustment (n=1070)

Error types	Pre-intervention		Post-intervention		χ^2	p
	n	(95% CI)	n	(95% CI)		
Medication preparation error	494	92.9 (90.7-95.1)	181	33.6 (29.6-37.6)	7.936	**0.004***
Failure to adhere to drug preparation time points	365	68.6 (64.6-72.5)	181	33.6 (29.6-37.6)	0.567	0.452
Failure to use aseptic techniques during preparation of medications	41	7.7 (5.5-10.2)	13	2.4 (1.3-4.1)	1.113	0.291
Dosing error	108	20.3 (17.0-23.9)	58	10.9 (8.4-13.8)	0.180	0.672
Failure to verify safe doses	494	92.9 (90.7-95.1)	92	17.3 (14.2-20.8)	8.557	**0.003***
Drug dilution error	206	38.7 (34.6-42.9)	43	8.1 (6.0-10.8)	3.052	0.081
Using pre-prepared medication	23	4.3 (2.7-6.4)	11	2.1 (1.0-3.7)	0.508	0.476
Failure to label the medication	64	12.0 (9.4-15.1)	20	3.8 (2.3-5.7)	2.842	0.092
Rate of medication error	398	74.8 (71.0-78.4)	239	44.4 (40.2-48.7)	2.466	0.132
Failure to adhere to medication administration times	201	37.8 (33.7-42.0)	138	25.9 (22.3-29.8)	1.430	0.232
Failure to check medication administration route	209	39.3 (35.2-43.5)	70	13.2 (10.5-16.3)	3.879	0.049
Failure to evaluate drug adherence	203	38.2 (34.1-42.4)	31	5.8 (4.0-8.2)	0.486	0.486
Not evaluating vital signs (pre/post)	66	12.4 (9.8-15.5)	51	9.6 (7.2-12.3)	7.989	**0.005***
Failure to use aseptic techniques during administration of medications	22	4.1 (2.6-6.2)	9	1.7 (0.8-3.2)	1.124	0.289
Failure to specify drug infusion rate	225	42.3 (38.1-46.6)	52	9.8 (7.4-12.6)	0.352	0.553
Dose skipping error	28	5.3 (3.5-7.5)	31	5.8 (4.0-8.2)	0.12	0.73
Wrong patient	0	0 (0-0.7)	0	0 (0-0.7)	-	-
Wrong medicine	0	0 (0-0.7)	0	0 (0-0.7)	-	-
Rate of monitoring error	327	61.5 (57.2-65.6)	120	22.3 (18.9-25.9)	3.879	0.030
Rate of recording error	367	69.0 (65.0-72.8)	181	33.6 (29.6-37.6)	0.385	0.554
Overall error rate	523	98.3 (96.7-99.2)	308	57.2 (53.0-61.3)	3.767	0.049

A single medication administration may include more than one error type

*: Holm-Bonferroni correction was applied to adjust for multiple comparisons. After correction, statistically significant differences remained only for preparation errors, failure both to perform safe dose verification, and to evaluate vital signs before and/or after medication administration

Values are presented as numbers (n), percentages (%) and 95% confidence intervals. Confidence intervals were calculated using binomial distribution assumptions

CI: Confidence interval, χ^2: Chi-square test, p: Level of statistical significance

(χ^2=3.879, p=0.030). The overall medication error rate showed a statistically significant reduction, decreasing from 98.3% before the intervention to 57.2% after the intervention (χ^2=3.767, p=0.049).

However, after applying Holm-Bonferroni correction for multiple comparisons, statistically significant reductions remained only in: preparation errors (p=0.004), failure to perform safe dose verification (p=0.003), and failure to evaluate vital signs before and/or after medication administration (p=0.005).

Although reductions were also observed in medication route verification, medication monitoring, and overall medication error rates, these differences did not remain statistically significant after adjustment for multiple comparisons.

Other medication error types, including medication preparation time, drug dilution, infusion rate, and documentation-related errors reduced-though not statistically significantly-following implementation of the web-based double check program.

The overall medication error rate, calculated as the arithmetic mean of error percentages observed across all medication administration stages, including preparation, administration, recording and patient monitoring, is presented in Figure 2. The overall medication error rate, calculated as the arithmetic mean of stage-specific error rates was 47.8% among 532 medication administrations observed before the intervention and 19.4% among 538 medication administrations observed after the intervention, indicating an overall improvement in medication safety performance.

DISCUSSION

In this study, the effectiveness of a web-based double check program in reducing medication errors during administrations of high-risk drug to pediatric patients was evaluated. The findings demonstrated that the implementation of the program resulted in a substantial reduction in medication error rates across stages of the medication administration process.

This composite measure should be interpreted as a summary indicator of overall medication safety performance rather than a direct measure of individual error severity. The observed reduction supports the effectiveness of structured and technology-assisted double-checking strategies in improving medication safety[18-23]. Similar findings have been reported in previous studies demonstrating that structured interventions and decision-support systems significantly reduce medication errors in clinical settings[6,8,18-23,32]. These findings collectively support the role of digital solutions

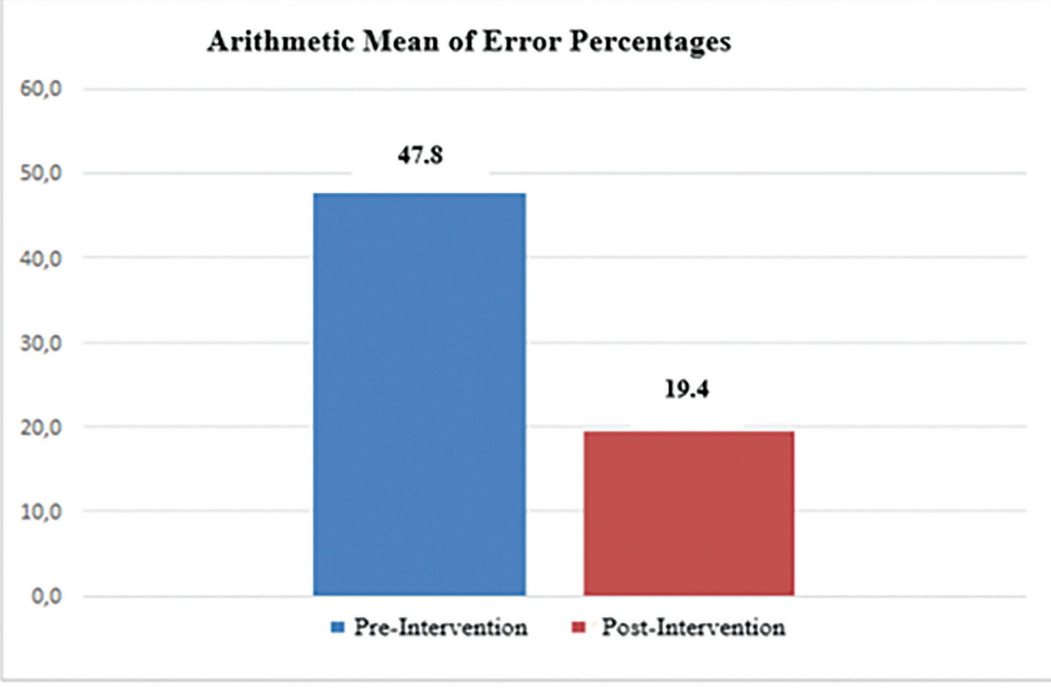

Figure 2. Overall medication error rates calculated as the arithmetic mean of stage-specific error percentages before and after the intervention

in minimizing human-related errors during complex medication processes. A notable strength of this study is that the web-based double check program was available and incorporated into routine medication administration procedures during the post-intervention phase. The system was observed to be used during medication administrations included in the post-intervention period. However, adherence was not systematically quantified using predefined compliance measures. Therefore, the observed reduction in medication errors should be interpreted with this limitation in mind.

After adjustment for multiple comparisons using the Holm-Bonferroni correction, statistically significant reductions were achieved in the rates of preparation errors, failure to perform safe dose verification, and to evaluate vital signs before and/or after administration of medications. These findings indicate that the intervention was particularly effective in improving medication safety practices related to medication preparation accuracy, dose calculation, and patient monitoring procedures. Among individual error types, failure to perform safe dose verification was identified as one of the most frequent errors made before implementation of the intervention, and a statistically significant reduction was obtained after statistical correction. This finding highlights the importance of structured dose calculation and verification systems in preventing dosage-related errors, particularly in pediatric settings where medication doses are frequently calculated based on body weights of the patients. The double check program includes structured dose calculation support based on patient-specific variables such as ages and body weights of the patients, which likely contributed to the observed reduction in dose verification errors. Previous studies have similarly demonstrated that computerized dose verification systems significantly improve medication safety and reduce calculation-related errors[9].

Similarly, the statistically significant reduction observed in preparation errors after adjustment for multiple comparisons suggests improved adherence to safe medication preparation practices. Medication preparation is recognized as a critical step in preventing medication errors, particularly in pediatric care settings where drug dilution and dosage adjustments are commonly required. The integration of structured preparation guidance into the web-based double check program may have contributed to improved compliance with recommended preparation procedures.

Another important finding was the statistically significant reduction in failure rates in the assessment of vital signs before and/or after administration of medications. Patient monitoring, including the assessment of vital signs, is an essential component of safe medication administration, particularly for high-risk medications that may affect cardiovascular or respiratory function. The inclusion of structured reminders and patient monitoring prompts within the double check program likely supported improved compliance with patient monitoring protocols.

Although reductions in medication route verification errors, monitoring errors, and overall medication error rates, were observed these differences did not remain statistically significant after adjustments made for multiple comparisons. These findings suggest that while improvements occurred in these areas, the magnitude of change may not have been sufficient to demonstrate statistical significance after controlling for multiple testing. Similar observations have been reported in previous studies indicating that certain medication safety improvements may require longer implementation periods or additional supportive interventions to achieve statistically significant outcomes[15,18-23,33,34].

Several other medication error types, including medication time, drug dilution, infusion rate, and documentation-related errors, also demonstrated numerical reductions following the intervention; however, these changes did not reach statistical significance. These findings suggest that while technological and procedural interventions can improve safety in specific high-risk steps, some medication errors may remain influenced by environmental and organizational factors such as workload intensity, staffing levels, and time constraints. Previous studies have similarly identified system-level factors as important contributors to medication errors despite the implementation of technological support systems[5,11,13,34,35].

No wrong patient or wrong medication errors were observed during either the pre- or post-intervention periods. This finding may be associated with the routine use of patient identification practices, including wristband verification and cross-checking procedures, which are considered essential components of safe medication administration. The consistent application of patient identification protocols is widely recognized as a critical factor in preventing high-risk medication errors.

When compared with the relevant literature data, medication error rates reported in observational studies vary widely depending on methodology and setting. Previous studies indicated that medication error rates show substantial variability depending on clinical context and methodological approaches[6-11]. Similarly, error rates for specific types such as dosing errors, timing errors, and infusion-related errors also show substantial variability[33,35]. The relatively high pre-intervention error rates observed in this study are consistent with the known vulnerability of pediatric medication processes[9]. However, significant reduction was observed in pre-intervention error rates after the intervention aligned with findings from studies evaluating structured and technology-assisted safety interventions[18-23,32].

Despite these positive findings, the results should be interpreted with caution. Due to the single-group pre–post study design, it is not possible to attribute the observed improvements solely to the intervention used. Alternative explanations such as the Hawthorne effect (increased awareness due to observation), learning effects over time, or increased attention to medication safety during the study period may have contributed to the observed reductions in medication errors. Therefore, causal inferences are limited, and conduction of future studies using randomized controlled designs is recommended.

In addition, since we focused mainly on medication administration events rather than malpractices of nurses, several observations were obtained from the same participants. This repeated-measures structure may have introduced intra-nurse clustering, whereby medication administrations performed by the same nurse could be more similar to each other than to those performed by different nurses. As clustering was not accounted for in the statistical analysis, standard errors may have been underestimated and some p-values may appear more precise than they truly are. Accordingly, the magnitude and statistical significance of the intervention effect should be interpreted cautiously. Future studies should consider analytic approaches such as mixed-effects models or generalized estimating equations to account for correlated observations.

Another important consideration is that medication error rates were not reduced to zero. This indicates that even with advanced decision support systems, residual errors may persist due to human factors, system constraints, and environmental conditions. Understanding these residual risks is essential for designing more comprehensive patient safety strategies.

Overall, the findings suggest that the web-based double check program improved medication safety by transforming key steps of the medication administration process-particularly dose verification, preparation standardization, and administration guidance. The most striking improvements were observed in high-risk and calculation-dependent steps, supporting the role of decision support systems in reducing cognitive burden and enhancing the importance of clinical decision-making process.

The inclusion of 95% CIs enhances the interpretability and clinical relevance of the findings by providing an estimate of the precision of the observed error rates. These findings highlight the importance of integrating digital decision support systems into pediatric clinical practice to enhance medication safety and reduce the rates of preventable errors.

Study Limitations

This study has several limitations that should be considered when interpreting the results.

First, the quasi-experimental single-group pretest-posttest design without a control group limits the ability to establish a causal relationship between the intervention and the observed reduction in medication error rates. Although a significant decrease was observed in medication error rates following the implementation of the web-based double check program, alternative explanations such as the Hawthorne effect, increased awareness of medication safety, and learning effects over time cannot be disregarded.

Second, medication administration errors were assessed using a non-participant observational method. While this approach is considered one of the most reliable methods for detecting medication errors[6], the presence of an observer may have influenced nurses' behaviors and led to temporary improvements in their performances.

Third, the unit of analysis in this study was medication administration events rather than individual nurses. Since multiple medication administrations were observed for the same nurses, observations may not have been fully independent. This potential intra-nurse clustering could have resulted in underestimated standard errors and inflated their statistical significance. Since clustering was not accounted for analytically or in the sample size calculations, the precision of the estimated intervention effects should be interpreted with caution.

Fourth, although training and a pilot phase were conducted prior to implementation of the study, detailed adherence data, such as frequency, completeness and duration of use, or deviations from intended use, were not systematically recorded. Therefore, it cannot be fully determined whether all nurses consistently used the system for all eligible medication administrations or whether variations in compliance may have affected the outcomes.

Fifth, the study was conducted in a single center and a relatively small number of nurses working in pediatric surgical units participated in the study which may limit the generalizability of the findings to other clinical settings, specialties, or healthcare systems.

Sixth, some contextual and system-related factors known to influence medication errors—such as nurse-to-patient ratios, workload, interruptions, and organizational conditions—remained unchanged during the study period. These factors may explain why certain types of medication errors were not completely eliminated despite the intervention.

Finally, technical limitations related to the web-based nature of the program should be acknowledged. The system required stable internet access, and potential connectivity issues which may have affected its usability in certain situations.

Despite these limitations, the study provides valuable evidence on the potential of computerized decision support systems to improve medication safety in pediatric settings. Conduction of future studies using randomized controlled designs, multi-center samples, and detailed adherence to patient monitoring is recommended to strengthen the evidence base of the study.

Additionally, the use of arithmetic averaging across heterogeneous error categories may have limited the sensitivity of the overall error rate to reflect clinically significant differences between specific error types.

CONCLUSION

This study demonstrated that the implementation of a web-based double check program, developed as a computerized decision support system, significantly reduced medication error rates in administration of high-risk medications for pediatric patient populations.

The medication error rates decreased from 47.8% before the intervention to 19.4% after the intervention, indicating a substantial improvement in medication safety. Reductions in medication error rates were particularly evident in preparation of medications, patient monitoring, and dose verification processes. These findings suggest that integrating computerized decision support systems into clinical practice can effectively support nurses in critical steps of medication administration and reduce the risk of errors.

This program contributed to patient safety primarily through automated dose control, guidance to standardized drug preparation, administration, and implementation of structured double-check mechanisms. These features helped minimize calculation errors, improve adherence to safe medication practices, and reduce variability in clinical implementations.

However, due to the quasi-experimental single-group design, causal conclusions are limited. Conduction of future studies with controlled and randomized designs is needed to confirm these findings and to evaluate their long-term effectiveness.

In addition, the persistence of certain error types indicates that technological solutions should be complemented with organizational improvements such as workload management, staffing optimization, and workflow redesign.

In conclusion, computerized decision support systems such as the web-based double check program represent a promising and feasible approach to improving medication safety in pediatric settings. Their integration into hospital information systems and wider clinical use may contribute to reducing medication errors and enhancing patient safety outcomes.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ege University Faculty of Medicine Clinical Research Ethics Committee (decision no: 17-11/37, dated: 14.11.2017), and institutional permission was obtained from the hospital where the study was conducted (decision no: 299596, dated: 21.11.2017). The study was retrospectively registered at ClinicalTrials.gov (NCT06371690; 15.04.2024).

Informed Consent: After the necessary explanations were given to the nurses included in the study about the purpose of the research, the method of application and the planned results, written consent was obtained for their participation.

Declaration of AI Use: The authors declare that no generative artificial intelligence (AI) tools were used in the writing of this manuscript or in the analysis or interpretation of the study data.

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This study is based on the author's doctoral thesis completed in 2018. During the preparation of this manuscript, statistical analyses were re-evaluated and updated in accordance with the recommendations of the reviewers. Consequently, some p-values differ from those reported in the original thesis.

Footnotes

This study was based on the doctoral thesis titled "The effects of using the web-based double eye control program on medication of high risk drugs in pediatric patients", registered at the Council of Higher Education Thesis Center, numbered "531551", prepared by Beste Özgüven Öztornacı under the supervision of Prof. Dr. Zümrüt Başbakkal (available from https://tez.yok.gov.tr/UlusalTezMerkezi/tezSorguSonucYeni.jsp).

This study received the third prize for oral presentation at the 2nd International 7th National Pediatric Nursing Congress organized in Türkiye on November 27-30, 2019.

Author Contributions

Concept: B.Ö.Ö., Z.B., Design: B.Ö.Ö., Z.B., Supervising: Z.B., Data Collection and Processing: B.Ö.Ö., Analysis and Interpretation: B.Ö.Ö., Z.B., Literature Search: B.Ö.Ö., Writing: B.Ö.Ö., Z.B.

Conflict of Interest: The authors have no conflict of interest to declare.

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Original Article

High Mobility Group Box 1 Expression in Wilms Tumor: Stage-stratified Survival Analysis in 46 Cases

Wilms Tümöründe High Mobility Grup Box 1 Ekspresyonu: 46 Olguda Evreye Göre Tabakalandırılmış Sağkalım Analizi

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ABSTRACT

Objective: To investigate High Mobility Group Box 1 (HMGB1) expression in Wilms tumors and determine its relationship with clinicopathological factors and overall survival (OS), including stage-stratified survival analyses.

Method: Forty-six Wilms tumor cases were retrospectively evaluated. Immunohistochemical expression of HMGB1 was recorded as the percentage of HMGB1-positive tumor cells. Associations with clinicopathological parameters were tested using chi-square/Fisher's exact and non-parametric tests. OS was assessed with Kaplan-Meier analysis and log-rank testing. Exploratory analyses included HMGB1 tertiles and a simplified "HMGB1-low" vs. "HMGB1-other" grouping. Stage was analyzed as low stage (1-2) vs. high stage (3-5).

Results: HMGB1 dichotomized using 5% and 10% cut-offs showed no significant associations with clinicopathological variables or OS (p-value>0.05). Stage 3-5 cases had significantly worse OS compared with stage 1-2 (log-rank p-value=0.049). In stage 1-2 tumors, very low HMGB1 expression (1-4%) was associated with significantly worse OS compared with HMGB1expression of ≥5% (log-rank p-value=0.024). This association was not observed in stage 3-5 tumors (log-rank p=0.858).

Conclusion: In this study, HMGB1 expression was not an independent prognostic marker in the overall cohort. However, very low HMGB1 expression may identify a subgroup of early-stage Wilms tumor patients with unfavorable survival and deserves validation in larger-scale studies.

Keywords: Wilms tumor, nephroblastoma, HMGB1, immunohistochemistry, prognosis, overall survival, stage-stratified analysis

ÖZ

Amaç: Bu çalışmada, Wilms tümörlerinde High Mobility Group Box 1 (HMGB1) ekspresyonunun araştırılması ve evreye göre tabakalandırılmış sağkalım analizleri de dahil olmak üzere, klinikopatolojik faktörler ve genel sağkalım (OS) ile ilişkisinin belirlenmesi amaçlandı.

Yöntem: Kırk altı Wilms tümörü olgusu retrospektif olarak değerlendirildi. HMGB1 immünohistokimyasal ekspresyonu, pozitif tümör hücrelerinin yüzdesi olarak kaydedildi. Klinikopatolojik parametrelerle ilişkiler ki-kare/Fisher'ın kesin testi ve non-parametrik testler kullanılarak analiz edildi. OS Kaplan-Meier analizi ve log-rank testi ile değerlendirildi. Keşifsel analizler kapsamında HMGB1 tertilleri ve basitleştirilmiş "HMGB1-düşük" ile "HMGB1-diğer" gruplaması kullanıldı. Evre, düşük evre (1-2) ve yüksek evre (3-5) olarak analiz edildi.

Bulgular: %5 ve %10 eşik değerleri kullanılarak dikotomize edilen HMGB1 ekspresyonu ile klinikopatolojik değişkenler veya OS arasında anlamlı ilişki saptanmadı (p-değeri>0,05). Evre 3-5 olguların OS, evre 1-2 olgulara kıyasla anlamlı derecede daha kötü bulundu (log-rank p-değeri=0,49). Evre 1-2 tümörlerde, çok düşük HMGB1 ekspresyonu (%1-4), ≥%5 ekspresyona kıyasla anlamlı derecede daha kötü OS ile ilişkiliydi (log-rank p-değeri=0,024). Bu ilişki evre 3-5 tümörlerde gözlenmedi (log-rank p-değeri=0,858).

Sonuç: Bu çalışmada, HMGB1 ekspresyonu tüm kohortta bağımsız bir prognostik belirteç olarak saptanmadı. Ancak çok düşük HMGB1 ekspresyonu, erken evre Wilms tümörü hastalarında olumsuz sağkalıma sahip bir alt grubu tanımlayabilir ve daha geniş serilerde doğrulanmayı gerektirir.

Anahtar kelimeler: Wilms tümörü, nefroblastom, HMGB1, immünohistokimya, prognoz, genel sağkalım, evreye göre tabakalandırılmış analiz

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INTRODUCTION

Wilms tumor (also known as nephroblastoma) is the most common malignant renal tumor of childhood, typically occurring before the age of five[1]. It arises from persistent embryonal renal tissue and is classically characterized by a triphasic histology composed of blastemal, epithelial, and stromal elements, although monophasic variants may occur[2]. Clinically, patients often present with an asymptomatic abdominal mass, sometimes accompanied by hematuria, hypertension, or abdominal pain. Genetic alterations frequently involve the *Wilms Tumor 1 (WT1)* gene and other loci associated with renal development[1-3]. Prognosis is generally favorable with modern multimodal therapy, including surgery, chemotherapy, and, in selected cases, radiotherapy; however, histological subtype (especially anaplastic type) and stage remain critical determinants of outcome[4,5]. Although outcomes are generally favorable, a subset of patients experience relapses, treatment resistance, and fatal outcomes[1-3]. Therefore, there is ongoing interest in biomarkers that complement established risk factors such as stage and histology[4,5].

High mobility group box (HMGB) proteins are non-histone nuclear proteins that play key roles in multiple cellular processes[6,7]. The HMGB family comprises HMGB1, HMGB2, and HMGB3. Among these, HMGB1 is ubiquitously expressed in the nuclei of most eukaryotic cells, whereas HMGB2 and HMGB3 show more restricted expression patterns[8-10]. HMGB1 is primarily localized in the nucleus, where it participates in chromatin organization, DNA replication, repair, and transcriptional regulation. However, post-translational modifications such as acetylation, phosphorylation, and methylation can induce its translocation from the nucleus to the cytoplasm. In addition, HMGB1 may be released into the extracellular environment under certain conditions such as hypoxia or during chemoradiotherapy, either actively from immune cells or passively from necrotic or apoptotic cells. Extracellular HMGB1 functions as a cytokine-like mediator, signaling tissue injury and promoting inflammatory responses[10-14].

In cancer biology, HMGB1 contributes to tumor progression through several mechanisms. It supports survival and proliferation of tumor cells by enhancing DNA repair and replication, promotes angiogenesis, modulates immune responses to facilitate immune evasion, and increases the invasive and metastatic capacity of tumor cells[8-10]. Clinically, increased HMGB1 expression is often associated with adverse prognostic features, including higher tumor grade and greater metastatic potential. Given these roles, HMGB1 has emerged as a potential therapeutic target, with current approaches focusing on inhibiting its extracellular signaling or downregulating its expression to limit tumor growth and dissemination[15-19].

This study aimed to evaluate HMGB1 expression in Wilms tumor tissue and to assess its association with clinicopathological variables, overall survival (OS) and its utilization in exploratory stage-stratified analyses.

MATERIALS and METHODS

Study Design and Patients

This retrospective study included 46 patients diagnosed with Wilms tumor. Clinical and pathological data were retrieved from institutional records. The Local Ethics Committee of Buca Seyfi Demirsoy Training and Research Hospital Research and Training Hospital approved this project (decision no: 2024/305, dated: 26.06.2024).

Immunohistochemistry (IHC)

HMGB1 IHC was performed on representative formalin-fixed paraffin-embedded tumor sections using standard staining protocols. Positive and negative controls were included in the analyses. Archival slides stained with hematoxylin and eosin were reassessed for detecting the viable tumor regions and selecting suitable paraffin blocks. IHC was then carried out using diluted monoclonal rabbit antibodies against HMGB1 (Atlas, ATL-HPA049521, USA) at a dilution of 1:500. The pathologists blinded to the patients' clinical characteristics analyzed the slides, and classified staining patterns based on their staining intensities. Diffuse nuclear and/or cytoplasmic staining of the tumor cells was considered HMGB1 positivity, and the number of positive cells was recorded (Figure 1). Furthermore, we assessed whether inflammatory cells that were HMBG1-positive had invaded the tumors and whether HMGB1 was expressed extracellularly.

HMGB1 Scoring

HMGB1 expression was recorded as the percentage of positive tumor cells. HMGB1 was analyzed (i) as a continuous variable, (ii) dichotomized using 5% and 10% cut-offs, and (iii) categorized into tertiles based on its distribution. Exploratory analyses suggested an early-stage survival signal among tumors with very low HMGB1 expression; therefore, tertiles were additionally simplified into HMGB1-low (1-4%) versus HMGB1-other (≥5%).

Follow-up and Outcome Definition

OS was defined as the time from diagnosis to death or last follow-up, expressed in months. Death was considered an event?, Patients alive at last follow-up or lost to follow-up were censored.

Statistical Analysis

Categorical variables were compared using chi-square or Fisher's exact test, as appropriate. Continuous variables were compared using Mann-Whitney U or Kruskal-Wallis tests. OS was analyzed using Kaplan-Meier estimates with log-rank testing. Cox proportional hazards regression models were used for univariate and multivariate analyses. Disease stages were additionally classified as low stage (1-2) versus high stage (3-5) to increase statistical power. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

Clinicopathological Characteristics

A total of 46 patients were included in the study, with an equal sex distribution (23 males and 23 females). The mean age was 3.35±2.07 years. The majority of tumors were unilateral, located on the right side in 47.8% and on the left in 39.1% of the cases, while 13.0% of them were bilateral (Stage V). According to stage distribution, most frequently (37.0%) stage II tumors were detected, followed by stage I (23.9%), stage III (15.2%), stage V (13.0%), and stage IV (10.9%) tumors. When grouped, 60.9% of cases were classified as low stage and 39.1% as high stage. Favorable histology was observed in 76.1% of patients, while 23.9% had unfavorable histology. Clinically, 71.7% of patients had no evidence of relapse, 21.7% experienced relapse, and in 6.5% the outcome was unknown. The average tumor size was 9.13±3.02 cm, and the mean tumor weight was 481.0±321.1 g. The mean overall, and median survival (OS) were 58.76±5.5 and 51.5 months, respectively. There were 11 death events in the cohort.

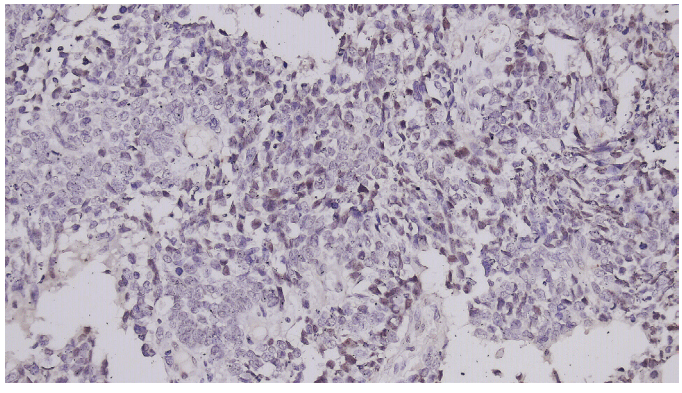

Figure 1. Strong nuclear expression of HMGB1 in some tumor cells (DAB x200)

DAB: 3,3'-diaminobenzidine

HMGB1 Expression and Clinicopathological Correlations

HMGB1 expression detected in tumor cells was limited to the nucleus; no cytoplasmic or extranuclear expression was detected. No difference in HMGB1 expression was found among tumor components. In addition, HMGB1 expression was also present in inflammatory cells in the tumor microenvironment in all tumors. The mean HMGB1 expression level was 15.26±22.21%. Using dichotomized cut-offs of 5% and 10%, HMGB1 expression was not significantly associated with stage grouping, histological subtype, or outcome categories (all p-value>0.05).

Survival Analysis

In Kaplan-Meier analysis, stage 3-5 tumors demonstrated significantly worse OS compared with stage 1-2 tumors (log-rank p-value=0.049) (Figure 2). HMGB1 expression dichotomized at 5% and 10% did not show a significant association with OS (p-value>0.05).

Exploratory tertile-based survival analysis suggested that very low HMGB1 expression (1-4%) might be associated with worse survival. Therefore, tertiles were simplified to HMGB1-low (1-4%) versus HMGB1-other (≥5%) categories. In stage 1-2 tumors, HMGB1-low cases had significantly worse OS compared with HMGB1-other cases (log-rank p=0.024) (Figure 3). This association was not observed in stage 3-5 tumors (log-rank p-value=0.858). The findings of stage-stratified survival analysis for HMGB1-low vs. HMGB1-other are shown in Table 1.

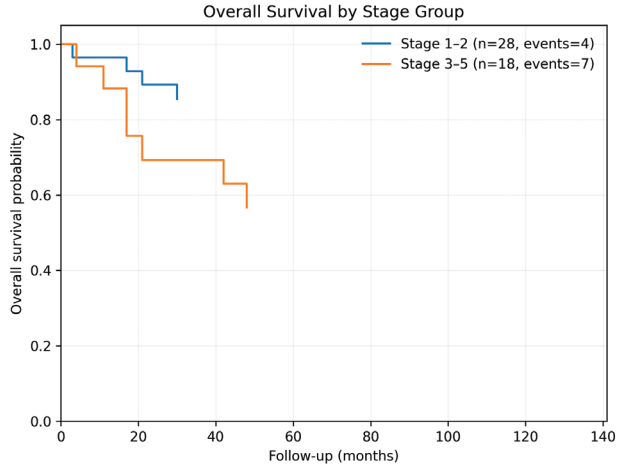

Figure 2. Kaplan-Meier OS curves by stage groups (1-2 vs. 3-5)

OS: Overall survival

Cox Regression Analysis

In multivariate Cox regression analyses of HMGB1 expression (log-transformed), age, stage group (3-5 vs. 1-2), and histology, HMGB1 expression was not independently associated with OS, whereas the stage group showed a borderline association with OS, consistent with the limited number of events.

DISCUSSION

In this retrospective series of 46 Wilms tumor cases with a median survival of 51.5 months also including 11 death events, we evaluated the prognostic impact of HMGB1 immunohistochemical expression using multiple analytic approaches, including conventional dichotomization, tertile categorization, and exploratory stage-stratified survival analyses. The key findings of this study can be summarized as follows: (i) in the overall cohort, HMGB1 expression was not significantly associated with clinicopathological variables or OS when analyzed using 5% and 10% cut-offs; (ii) stage remained a dominant clinical determinant of survival, as stage 3-5 tumors demonstrated significantly inferior OS compared with stage 1-2 disease (log-rank p-value=0.049); and (iii) notably, within early-stage tumors (stage 12), very low HMGB1 expression (1-4%) was associated with significantly worse OS compared with ≥5% expression (log-rank p-value=0.024), whereas this association was not observed in advanced-stage tumors (log-rank p-value=0.858). Collectively, these results suggest that HMGB1 is unlikely to serve as a universal prognostic biomarker across all Wilms tumor patients; however, very low expression may identify a biologically distinct subgroup of early-stage cases with unfavorable survival. Recognizing this subgroup may have clinical implications, as these patients—despite presenting at an early stage—could be considered for the implementation of more intensive and tailored therapeutic strategies[20,21].

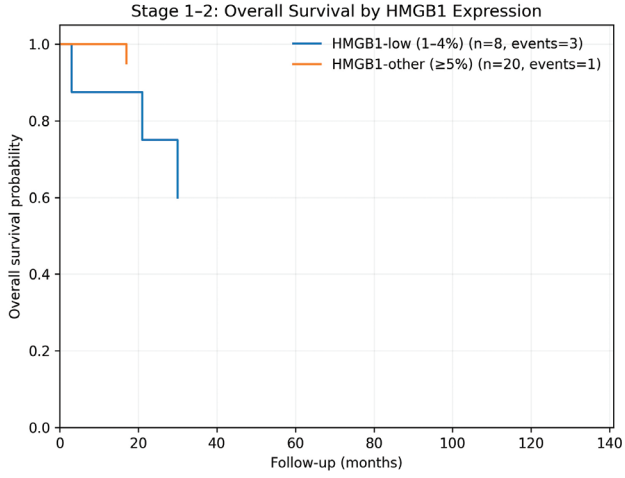

Figure 3. Kaplan-Meier OS curves in stage 1-2 tumors by HMGB1-low vs. HMGB1-other

OS: Overall survival, HMG1: High Mobility Group Box 1

Wilms tumor remains the most common malignant renal tumor of childhood and, despite excellent overall outcomes in contemporary treatment protocols, a clinically meaningful proportion of patients still experience relapse, treatment resistance, and fatal outcomes. Current management is guided by risk-adapted strategies shaped by Children's Oncology Group (COG/NWTS) and International Society of Paediatric Oncology (SIOP) approaches[22]. Although these protocols differ in the timing of surgery and the use of preoperative chemotherapy, both emphasize the prognostic relevance of stage and histologic risk group, together with surgical factors such as tumor spill, margin status, and lymph node evaluation. In agreement with this established framework, the present study confirmed that stage retains significant prognostic importance. The observed survival disadvantage in stage 3-5 patients (log-rank p-value=0.049) reinforces that tumor burden, local extension, nodal involvement, and metastatic spread remain major determinants of outcome even in the modern multimodal treatment era. Importantly, modern treatment protocols of Wilms tumor increasingly seek to balance cure rates with minimization of late toxicities. This has led to treatment de-escalation attempts in clearly

Table 1. Stage-stratified survival analysis for HMGB1-low vs. HMGB1-other

Stage group	HMGB1 group	n	Deaths (events)	Censored
Stage 1-2	HMGB1-low (T1: 1-4%)	8	3	5
Stage 1-2	HMGB1-other (T2+T3: ≥5%)	20	1	19
Stage 3-5	HMGB1-low (T1: 1-4%)	7	3	4
Stage 3-5	HMGB1-other (T2+T3: ≥5%)	11	4	7

Log-rank p-values: Stage 1-2: p-value=0.024; Stage 3-5: p-value=0.858
HMG1: High Mobility Group Box 1

favorable subgroups; however, a persistent challenge is that a small fraction of "clinically favorable" early-stage patients may still relapse or die. Therefore, biomarkers capable of refining prognosis within early-stage disease—where baseline survival is expected to be high—could be clinically meaningful. Our stage-stratified findings support this concept by suggesting that very low HMGB1 expression may identify a subset of stage 1-2 patients with unexpectedly unfavorable OS[20-22].

HMGB1 is a multifunctional non-histone chromatin-binding protein involved in transcriptional regulation, chromatin remodeling, and DNA damage response (DDR). Beyond its nuclear role, HMGB1 can be actively secreted or passively released and acts extracellularly as a damage-associated molecular pattern, thereby modulating innate immune responses and shaping the tumor microenvironment through inflammatory signaling. This dual intracellular-extracellular biology has driven considerable interest in HMGB1 as both a prognostic biomarker and a therapeutic target in multiple tumor types. However, the direction of HMGB1-prognosis association varies widely across cancers, likely reflecting differences in tumor context, immune microenvironment, treatment exposures, and especially HMGB1 compartmentalization and post-translational modifications. A critical interpretative aspect is HMGB1 localization. Physiologically, HMGB1 is predominantly nuclear; however, cancer-related stress responses may drive nuclear-to-cytoplasmic translocation and/or extracellular release. Cytoplasmic accumulation is frequently interpreted as a proxy for HMGB1 mobilization and active inflammatory signaling. Conversely, decreased nuclear HMGB1 (or low overall expression) levels in certain contexts may reflect altered chromatin states, impaired DDR programs, or dedifferentiation-related transcriptional changes. In the present study, HMGB1 expression was consistently observed in association with nuclear localization in tumor cells, and evaluation was based on this nuclear positivity. Therefore, the absence of distinct nuclear-cytoplasmic expression patterns reported in the literature may partly explain the lack of a significant association in the overall cohort[20-22].

In the overall cohort, HMGB1 expression did not show prognostic relevance when dichotomized at 5% and 10%. This negative finding suggests that HMGB1 is not a strong standalone prognostic marker across unselected Wilms tumor cases, and it also highlights an important methodological issue namely HMGB1 biology may not be adequately captured using simple percent-positivity scoring alone. In addition, Wilms tumor is heterogeneous in both histologic composition and molecular drivers; thus, biomarker effects may be context-dependent and clinically visible only in selected subgroups rather than uniformly across all stages[5,14].

The most clinically notable observation of this study is the early-stage survival signal. Among stage 1-2 tumors, HMGB1-low cases (1-4%) demonstrated significantly worse OS than HMGB1-other tumors (≥5%). Interestingly, this association was absent in stage 3-5 tumors. One plausible explanation is that in advanced-stage disease, the adverse prognostic impact of stage dominates outcomes and may obscure smaller biomarker effects. In contrast, early-stage disease provides a "low-noise" prognostic setting where biological differences can emerge more clearly. Therefore, expression of low levels of HMGB1 may represent a hidden biological risk factor that is clinically detectable only for early-stage disease. Several mechanistic hypotheses may be considered. First, very low HMGB1 expression might correlate with unfavorable molecular programs affecting DDR, potentially contributing to treatment resistance or genomic instability. Second, HMGB1 deficiency may influence the immunologic contexture of the tumor microenvironment, reducing immunogenic signaling and limiting immune surveillance. Third, HMGB1 expression could reflect broader differentiation status and embryonal programs within Wilms tumor. Importantly, these mechanistic interpretations remain speculative in the present study and should be validated by future studies combining HMGB1 scoring with molecular profiling and assessment of immune micro environment[6-10].

In multivariable Cox regression models analyzing HMGB1 expression (log-transformed), age, stage group, and histology, HMGB1 did not retain independent prognostic significance, whereas stage showed a borderline association with OS. This result is expected given the limited number of death events (n=11), which constrains statistical power and increases the risk of imprecise hazard estimates in multivariate models. Therefore, while the Kaplan-Meier stage-stratified findings are compelling, they should be interpreted as hypothesis-generating data which should be subjected to external validation[6].

Study Limitations

The present study has limitations. The retrospective single-center design may introduce selection bias and restrict completeness of treatment and molecular data? The sample size is modest and event number limited, reducing power for subgroup analyses and multivariate modeling.

Treatment protocol variables (e.g., COG vs. SIOP-based risk-adapted strategies, radiotherapy exposure, intensity of chemotherapy) were not incorporated which could modify observed associations. In addition, unfortunately the HMGB1 scoring method relied only on percent-positivity without detailed evaluation of staining intensity or intensity of different tumoral components which are key determinants of HMGB1 functional biology. Finally, the HMGB1-low cut-off (1-4%) was derived through exploratory tertile analyses and should not be considered as definitive criteria prior to validation. Despite these limitations, this study provides stage-stratified evidence suggesting that very low HMGB1 expression may be clinically relevant in early-stage Wilms tumor. Future multi-institutional studies with standardized HMGB1 staining/scoring (including localization-based assessment) and integration of molecular risk factors are warranted. If confirmed, HMGB1-low expression may represent a practical biomarker for identifying a small subgroup of early-stage Wilms tumor patients who may require closer surveillance or therapy adjustment[15-19].

CONCLUSION

In conclusion, HMGB1 expression did not emerge as an independent prognostic marker in the overall Wilms tumor cohort; however, very low HMGB1 expression (1-4%) was associated with inferior OS in stage 1-2 tumors, suggesting a potential subgroup effect. This finding supports the broader concept that biomarker discovery in Wilms tumor may benefit from stage-specific evaluation, and that selected early-stage patients may harbor adverse tumor biology not captured by stage alone.

Ethics

Ethics Committee Approval: The Local Ethics Committee of Buca Seyfi Demirsoy Training and Research Hospital Research and Training Hospital approved this project (decision no: 2024/305, dated: 26.06.2024).

Informed Consent: Retrospective study.

Declaration of AI Use: ChatGPT (OpenAI) was used solely to assist in drafting the Main Points section requested by the journal.

Footnotes

Author Contributions

Surgical and Medical Practices: G.D., S.A., Concept: G.D., S.A., R.O., Design: G.D., S.A., Data Collection or Processing: G.D., S.A., R.O., Analysis or Interpretation: G.D., R.O., Literature Search: G.D., Writing: G.D., S.A.

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

Financial Disclosure: The authors declared that this study has received no financial support.

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Original Article

Dental Caries Management Patterns in Pediatric Patients with Chronic Medical Conditions: A Natural Language Processing Approach

Kronik Tıbbi Durumları Olan Pediyatrik Hastalarda Diş Çürüğü Yönetim Örüntüleri: Doğal Dil İşleme Yaklaşımı

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ABSTRACT

Objective: Chronic childhood diseases present significant challenges for dental caries management, yet the intellectual structure of the research domain remains poorly mapped. This study systematically characterizes the knowledge structure, thematic evolution, and citation dynamics at the intersection of pediatric chronic diseases and dental caries management.

Method: A total of 545 abstracts from the Web of Science (1990-2026) were analyzed using natural language processing. K-means clustering and principal component analysis identified intellectual groupings while Latent Dirichlet allocation enabled topic modeling. Temporal evolution and citation impact were assessed, and co-occurrence network analysis revealed conceptual linkages.

Results: Three distinct knowledge clusters emerged: Cluster 0 (specialized studies, average number of citations =27), Cluster 1 (mainstream paradigm, average number of citations =80), and Cluster 2 (emerging research, average number of citations =19). Five optimal research themes were identified (coherence =0.365): General pediatric oral health epidemiology, childhood caries risk factors, patient-centered disease-dental health relationships, comparative methodological studies, and asthma-focused research. Temporal analysis revealed four phases: latent (1990-2000), awakening (2000-2006), initial growth (2006-2015), and accelerated expansion (post-2020). Patient-centered topics peaked at 18-19 publications annually by 2026. Disease-specific analysis showed concentration on diabetes (124 publications), asthma (82), and cerebral palsy (59), with notable underrepresentation of sickle cell anemia and juvenile arthritis. Network analysis identified "oral health," "disease," and "caries" as central nodes, linking clinical outcomes to quality-of-life concepts.

Conclusion: The domain has shifted from descriptive epidemiology toward patient-centered and community-oriented approaches. Persistent thematic and disease-specific gaps highlight the need for integrative, interdisciplinary research addressing neglected chronic pediatric conditions.

Keywords: Dental caries, chronic diseases, children, natural language processing, topic modeling

ÖZ

Amaç: Kronik çocukluk çağı hastalıkları, diş çürüğü yönetimi açısından önemli zorluklar ortaya koymaktadır. Ancak araştırma alanının tematik yapısı yeterince araştırılmamıştır. Bu çalışma, pediyatrik kronik hastalıklar ile diş çürüğü alanının bilgi yapısını, tematik evrimi ve atıf dinamiklerini sistematik olarak araştırmıştır.

Yöntem: Web of Science'tan (1990-2026) toplam 545 özet, doğal dil işleme kullanılarak analiz edilmiştir. K-means kümeleme ve temel bileşenler analizi tematik gruplandırmada, Gizli Dirichlet ayırımı ise konu modelleme amacıyla kullanılmıştır. Zamansal evrim ve atıf etkisi değerlendirilmiş, sosyal ağ analizi ise kavramsal bağlantıları göstermiştir.

Bulgular: Analizler sonucunda üç farklı bilgi kümesi ortaya çıkmıştır: Küme 0 (uzmanlaşmış çalışmalar, ortalama atıf =27), Küme 1 (ana akım paradigma, ortalama atıf =80) ve Küme 2 (gelişmekte olan araştırma, ortalama atıf =19). Beş araştırma teması belirlenmiştir (tutarlılık =0,365): Genel pediyatrik ağız sağlığı epidemiyolojisi, çocukluk çağı çürük risk faktörleri, hasta merkezli hastalık-diş sağlık ilişkileri, karşılaştırmalı

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metodolojik çalışmalar ve astım odaklı araştırma. Zamansal analiz dört aşama ortaya koymuştur: gizil dönem (1990-2000), uyanış (2000-2006), ilk büyüme (2006-2015) ve hızlandırılmış genişleme (2020 sonrası). Hasta merkezli konular 2026 yılına kadar yılda 18-19 yayına ulaşarak zirve yapmıştır. Hastalığa özgü analiz, diyabet (124 yayın), astım (82) ve serebral palsi (59) üzerinde yoğunlaşırken, orak hücreli anemi ve juvenil artrit yetersiz temsil edilmiştir. Sosyal ağ analizi, klinik sonuçları yaşam kalitesi kavramlarına bağlayan merkezi düğümler olarak yer almıştır.

Sonuç: Alan, tanımlayıcı epidemiyolojiden hasta merkezli ve toplum odaklı yaklaşımlara doğru kaymıştır. Kalıcı tematik ve hastalığa özgü boşluklar, ihmal edilmiş kronik pediyatrik hastalıkları ele alan bütünleştirici, disiplinler arası araştırma ihtiyacını vurgulamaktadır.

Anahtar kelimeler: Diş çürüğü, kronik hastalıklar, çocuklar, doğal dil işleme, konu modellemesi

INTRODUCTION

Dental caries is among the most prevalent chronic diseases of childhood, affecting more than 510 million children worldwide through decay of the primary dentition[1]. This burden is particularly pronounced in children living with chronic systemic diseases, where complex, bidirectional interactions between the underlying medical condition(s) and oral health often exacerbate disease severity[2-4]. Children affected by conditions such as cerebral palsy, asthma, diabetes mellitus, cardiovascular anomalies, cystic fibrosis, and neurodevelopmental disorders consistently experience marked oral health disparities compared with their typically developing peers. These disparities commonly present as higher rates of dental caries, periodontal disease, developmental enamel defects, and a reduced oral health-related quality of life[5-9]. In cerebral palsy, for instance, motor limitations and orofacial dysfunction can make daily oral hygiene difficult to maintain, increasing susceptibility to dental disease(s)[2]. Similarly, children with asthma are exposed to a more cariogenic oral environment as a result of long-term inhaled corticosteroid use, habitual mouth breathing, and reduced salivary flow (hyposalivation)[8]. Children with chronic kidney disease also face oral health challenges, as salivary hypofunction and biochemical alterations disrupt normal oral homeostasis and relevant protective mechanisms[7].

The therapeutic implications of dental caries in children with medical complexities extend well beyond disease prevalence. These patients often require invasive restorative procedures, including pulp therapy, preformed metal crowns, or tooth extractions. In young children or those with behavioral and cognitive challenges, such interventions frequently necessitate pharmacological support through conscious sedation or general anesthesia[10,11]. Delivering anesthesia to children with chronic systemic diseases is particularly demanding due to preexisting medical instability, airway and anatomical variations, cardiorespiratory compromise, and the need for multidisciplinary preoperative assessment. As a result, treatment planning is often constrained by medical contraindications, limited access to hospital-based dental services, and heightened safety requirements, which may lead to delayed care, compromised treatment decisions, or unnecessarily aggressive interventions[12,13].

These clinical challenges are reflected in the current research landscape, which remains notably fragmented. Much of the existing literature focuses on individual chronic conditions in isolation, with limited integration of findings into broader, cross-cutting frameworks for managing dental caries in pediatric populations with medical complexities[2-4,6-8,14]. This compartmentalized approach restricts synthesis of interdisciplinary knowledge and hinders the development of unified clinical guidelines and health policies. Although individual studies provide valuable insights, still scarce number of comprehensive analyses mapped the intellectual structure and temporal evolution of this domain.

Advances in natural language processing (NLP) and bibliometric methods offer powerful tools for systematically synthesizing large bodies of medical literature[15]. By enabling automated extraction of themes, identification of research clusters, and visualization of scholarly relationships, these approaches help uncover emerging trends, shifts in research focus, and underexplored areas within complex domains[16]. Applying such methods to pediatric dental research allows for a more integrated understanding of how knowledge has developed and where critical gaps persist. Despite the growing body of literature on pediatric oral health, the intellectual structure of research on dental caries management in children with chronic diseases remains poorly characterized. It is still unclear which thematic clusters dominate this field, how research priorities have evolved over time, and where critical knowledge gaps persist particularly at the intersection of specific chronic conditions and caries prevention or treatment strategies. Traditional narrative reviews have addressed isolated aspects of this topic but fall short of providing a comprehensive, data-driven mapping of the field's conceptual landscape. To address these gaps, the present study employed an NLP-based analytical framework to systematically map the intellectual structure, thematic evolution, and emerging research priorities in dental caries management among children with chronic diseases.

MATERIALS and METHODS

This study applied an integrated NLP framework to analyze the thematic structure, temporal evolution, and conceptual relationships in the literature on dental caries management in children with chronic diseases. By combining text preprocessing, machine learning-based clustering, topic modeling, temporal dynamics and network analysis, the methodology enables a comprehensive and data-driven exploration of research patterns and trends in this domain.

Data Collection and Preprocessing

This study analyzed 545 peer-reviewed scientific publications retrieved from the Web of Science (WoS) database on January 15, 2026 concerning management of dental caries in children with chronic diseases. The literature search was conducted using a comprehensive strategy combining four main conceptual blocks: chronic diseases, pediatric populations, dental caries, and management or preventive approaches. The following search queries were applied:

("chronic disease" OR "chronic illness" OR "chronic condition" OR "children with special health care needs" OR "diabetes" OR "asthma" OR "epilepsy" OR "congenital heart disease" OR "cerebral palsy" OR "chronic kidney disease" OR "cystic fibrosis") AND ("child" OR "children" OR "pediatric" OR "adolescent") AND ("dental caries" OR "tooth decay" OR "early childhood caries") AND ("management" OR "prevention" OR "treatment" OR "oral health care" OR "dental care" OR "caries management" OR "fluoride therapy" OR "fissure sealants" OR "preventive dentistry" OR "minimally invasive dentistry" OR "behavior management" OR "special care dentistry" OR "oral health" OR "pediatric dentistry").

The full search string included terms such as chronic disease, diabetes, asthma, child, pediatric, dental caries, and oral health management, and was limited to English-language articles indexed in Science Citation Index Expanded, Social Sciences Citation Index, and Emerging Sources Citation Index (ESCI) databases, in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA 2020) guidelines[17]. Peer-reviewed original research articles focusing on management, prevention, or treatment of dental caries in pediatric populations with chronic diseases were analytically reviewed. Relevant studies involving children and adolescents, published in English, and providing empirical data were considered eligible. Review articles, systematic reviews, meta-analyses, editorials, letters, conference abstracts, non-peer-reviewed publications, studies not directly addressing dental caries or not involving children with chronic conditions were excluded. The study selection process is illustrated in Figure 1.

A total of 1,389 records were identified through the WoS database. After the removal of 187 duplicates,

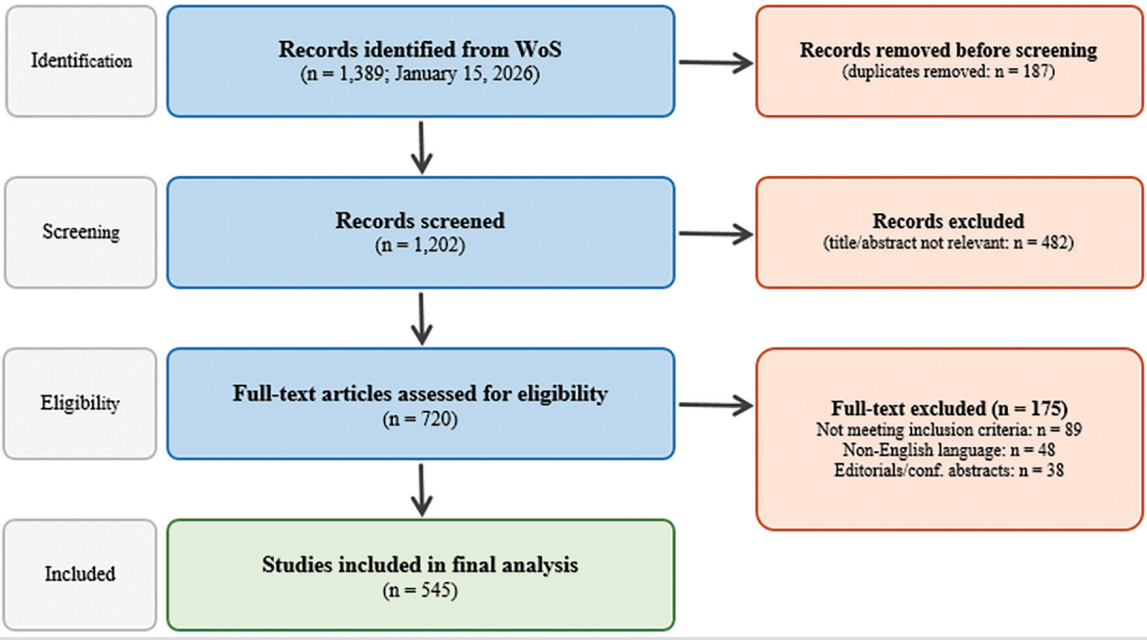

Figure 1. PRISMA flow diagram of the study selection process

PRISMA: Preferred reporting items for systematic reviews and meta-analyses, WoS: Web of Science

1,202 records remained for screening, of which 482 were excluded based on title and abstract. Subsequently, 720 full-text articles were assessed for eligibility, and 175 of them were excluded from the analyses due to not meeting the inclusion criteria i.e. articles published in non-English languages, or being editorials or conference abstracts. Ultimately, 545 studies were included in the final analysis.

The final dataset comprised three core variables: abstract, citation count, and publication year. Text preprocessing was performed exclusively on the abstract. The preprocessing pipeline consisted of: (1) conversion to lowercase for standardization, (2) removal of punctuation marks and numerical expressions using regular expressions, (3) elimination of English stop-words using the Natural Library Toolkit (NLTK) library, and (4) lemmatization using the WordNetLemmatizer to reduce words to their root forms. The cleaned and standardized texts were stored in a new variable, forming the textual input for subsequent NLP and modeling analyses[18-20].

Semantic Analysis with Word2Vec

A Word2Vec model was trained using the Gensim library on the preprocessed abstracts to learn contextual semantic representations of words as 100-dimensional vectors[21]. Document-level numerical representations were created by calculating the arithmetic mean of word vectors within each abstract. These document vectors, stored in the document vector column, served as input for subsequent clustering and dimensionality reduction analyses[22].

Optimal Cluster Number Determination

The optimal number of clusters was determined using the Elbow method[23]. K-means clustering was performed on document vectors with varying numbers of clusters (k=2 to k=10), and inertia values (sum of squared distances from each point to its cluster center) were calculated for each k[24]. The elbow point, where the marginal decrease in inertia diminished substantially, was identified through visual inspection of the inertia plot[23]. Based on this analysis, k=3 was selected as the optimal cluster number, balancing model complexity with explanatory power.

Clustering Analysis

K-means clustering was applied to the document vectors with k=3 clusters. Citation counts were incorporated as weighting factors in the clustering process, allowing highly cited articles to exert greater influence on cluster center determination. This approach ensured that influential or impactful publications shaped the cluster structure. Each article was assigned a cluster label representing its thematic group.

Citation Analysis

For each cluster, average citation counts were calculated to assess scientific impact and visibility. This bibliometric analysis revealed differences in citation performance across clusters, indicating varying levels of influence and recognition within the scientific community. Results were visualized using bar charts to facilitate comparisons.

Optimal Topic Number Determination

To identify the optimal number of topics for LDA (Latent Dirichlet Allocation) modeling[25] coherence score analysis was conducted[26]. Using Gensim's CoherenceModel, coherence scores were calculated for topic numbers ranging from 2 to 10. Coherence scores measure the semantic similarity between high-scoring words in topics, with higher values indicating more interpretable and meaningful themes[26]. The coherence scores were plotted, and the optimal number of topics yielding the highest coherence score was selected. Based on this analysis, 5 topics were determined to provide the best thematic representation of the literature.

LDA Topic Modeling

LDA topic modeling was implemented using processed abstracts to identify thematic structures in the literature[25]. A dictionary and document-term matrix were constructed using Gensim's Dictionary and corpus functions[27]. The LDA model was trained with 5 topics (as determined by coherence analysis), extracting the most prominent keywords and their weights for each topic. Topic distributions were calculated for each document, and the dominant topic and its probability were assigned to each article.

Cluster Visualization with Principal Component Analysis PCA

To visualize clustering results, document vectors were reduced to two dimensions using PCA. Technique PCA1 (x-axis) represented the dimension explaining the most variance, while PCA2 (y-axis) captured the second most important variance source. The two-dimensional projections were plotted as scatter plots, with points colored by cluster labels, enabling visual assessment of cluster separation and spatial relationships.

Temporal Dynamics of Clusters and Topics

Temporal trends of the three clusters were analyzed by grouping articles by their publication years. The number

of articles in each cluster was calculated annually from 1990 to 2026. These trends were visualized using line plots with Seaborn[28], revealing how cluster popularity evolved over time and identifying periods of growth, stability, or decline for different research paradigms. Similarly, temporal trends of the five LDA topics were examined by grouping articles by year and dominant topic. Annual article counts for each topic were calculated and visualized using line plots. This analysis revealed the evolution of research themes over time, identifying emerging, stable, and declining topics within the literature.

Topic Word Clouds Analysis

Word clouds were generated for each of the 5 LDA topics using the WordCloud library[29]. Keywords were sized proportionally to their probability weights within each topic, providing intuitive visual representations of thematic content. These visualizations facilitated rapid interpretation of topic characteristics and complemented the quantitative topic modeling results.

Chronic Disease Content Analysis

Keywords related to common chronic pediatric diseases (diabetes, asthma, obesity, cerebral palsy, congenital heart disease, cystic fibrosis, epilepsy, autism, sickle cell anemia, juvenile arthritis) were defined and searched within the processed abstracts. The frequency and percentage of articles mentioning each condition were calculated using named entity recognition model[30], revealing the chronic diseases that were most prominently studied in relation to management of dental caries. Results were ranked in descending order and visualized using bar charts.

Social Network Analysis

A social network was constructed to examine relationships among key concepts related to the management of dental caries, health outcomes, and complications[31]. Keywords representing management strategies (management, prevention, treatment, intervention), health outcomes (oral health, quality of life, outcome, wellbeing), and clinical complications (pain, abscess, disease, complication, infection, inflammation) were identified. A co-occurrence matrix was created by calculating how frequently each keyword pair appeared together in abstracts. Using NetworkX package for the Python programming language, this matrix was transformed into a network graph where nodes represented keywords and edges represented frequencies of co-occurrences, with edge thickness proportional to co-occurrence strength. The network was visualized using Matplotlib library[32] to reveal conceptual relationships and thematic clusters within the literature.

Statistical Analysis

All computational analyses were performed using Google Colaboratory[33]. Python platform was used as the primary programming language throughout the analysis process[34]. The computational workflow was supported by various libraries commonly used in scientific research. These include NumPy[35] for numerical operations, Pandas[36] for data processing and table analyses, Matplotlib[32] and Seaborn[28] for visualization, Scikit-learn[37] for ML operations, Statsmodels[38] for time series modeling, and WordCloud[29] for word cloud visualizations.

To enhance language quality, AI tools were utilized during manuscript preparation. Specifically, OpenAI's ChatGPT[39] facilitated English translation, and Anthropic's Claude AI[40] was employed for linguistic review and stylistic refinement.

RESULTS

This study employed an integrated NLP framework to examine the thematic structure, temporal evolution, and conceptual relationships in the literature on the management of dental caries among children with chronic diseases. Through the combined use of text preprocessing, machine learning-based clustering, topic modeling, temporal analysis, and network analysis, the findings provide a comprehensive, data-driven overview of research patterns and emerging trends in this domain. The findings of optimal number of clusters, clustering analysis, citation performance, and coherence scores are presented in Figure 2.

At k=2, the inertia value reached approximately 19,600, indicating insufficient granularity and excessive within-cluster variance (Figure 2). A dramatic reduction to approximately 15,000 was observed at k=3, representing a marginal improvement of 4,600 units-the most substantial decrease across all iterations. This inflection point constituted a distinct elbow, beyond which incremental cluster additions yielded diminishing returns, primarily fragmenting existing structures rather than revealing novel patterns. Consequently, 3 clusters were determined as optimal for subsequent analyses.

PCA reduced the multidimensional feature space to two principal components (PC1 and PC2), capturing the dominant variance axes within the corpus. Cluster 0 (turquoise; n≈50-70) exhibited spatial isolation on the negative PC1 axis, demonstrating tight cohesion

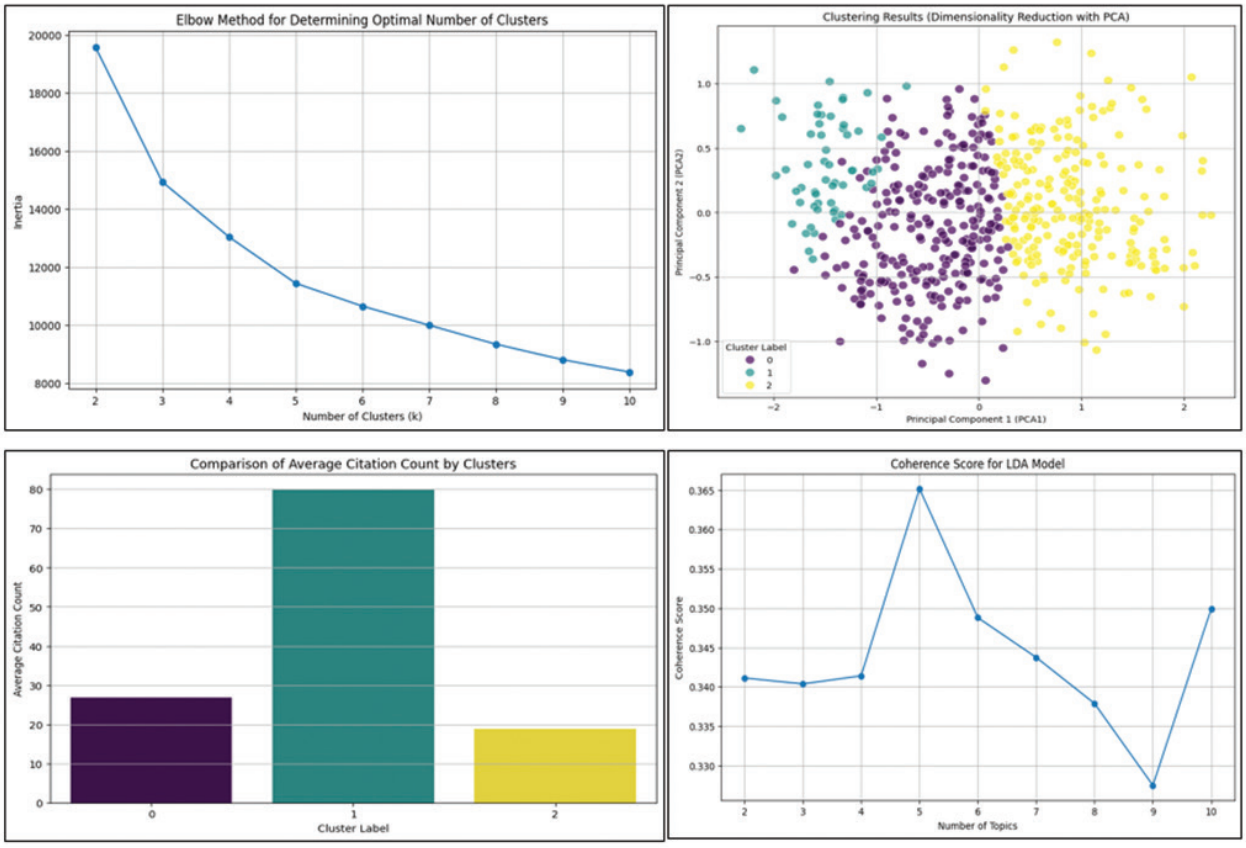

Figure 2. Optimal number of clusters, clustering analysis, citation performance, and coherence scores

indicative of methodological homogeneity and potentially representing a specialized research niche or disease-specific focus. Cluster 1 (purple; n>200) occupied the central region with substantial overlap zones, suggesting its role as the disciplinary mainstream and a transitional bridge between research paradigms. Cluster 2 (yellow; n≈150) displayed greater dispersion along the positive PC1 axis, potentially reflecting thematic heterogeneity or emerging research trajectories. The pronounced separation along PC1 indicated this component as the primary discriminator between clusters, while boundary overlaps suggested continuous epistemological transitions rather than discrete categorical divisions.

Citation performance demonstrated marked heterogeneity across clusters. Cluster 1 achieved the highest mean citation count (M=80), consistent with its central positioning and substantial size, indicative of an established, well-integrated research paradigm. Cluster 0 exhibited moderate impact (M=27), approximately one-third that of Cluster 1, suggesting specialized but recognized scholarly contributions. Cluster 2 recorded the lowest mean citations (M=19), potentially reflecting its emergent nature or peripheral positioning within the intellectual structure of the domain. These differential citation patterns underscore the stratified maturity levels across research clusters: Cluster 1 representing canonical knowledge, Cluster 0 denoting specialized expertise, and Cluster 2 signifying nascent or exploratory research domains.

Coherence score analysis across 2-10 topics identified the optimal LDA configuration. The coherence metric peaked at 0.365 for k=5 topics, representing the optimal balance between thematic granularity and interpretability. Coherence degradation beyond five topics suggested model overfitting and excessive fragmentation, while lower values indicated inadequate capture of the corpus's thematic complexity. The 5-topic model was therefore adopted for subsequent semantic analysis. The findings related to the temporal dynamics of the clusters are presented in Figure 3.

Longitudinal analysis revealed divergent temporal trajectories across clusters. Cluster 0 demonstrated sustained growth post-2005, with pronounced acceleration after 2020, culminating in peak activity in

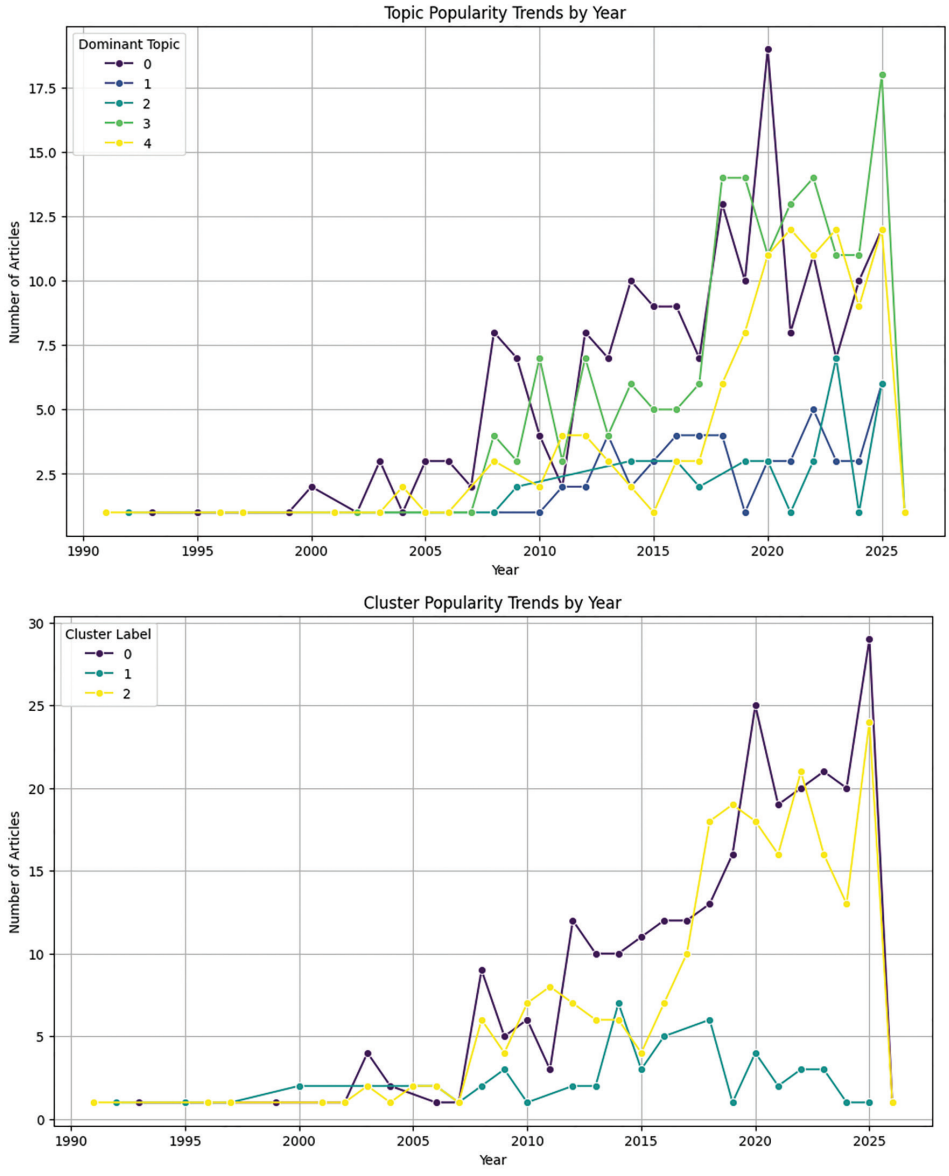

Figure 3. Temporal dynamics of clusters and topics

2026. Cluster 2 exhibited episodic expansion with distinct peaks in 2018 and 2026, suggesting periodic surges in scholarly attention. Conversely, Cluster 1 showed modest growth followed by substantial decline post-2020, potentially indicating paradigmatic saturation or domain reorientation. The temporal distribution of LDA topics spanning 1990-2026 revealed distinct evolutionary phases. The pre-2000 period constituted a latent phase characterized by minimal publication activity. Progressive intensification commenced post-2000, with Topic 0 and Topic 2 demonstrating particularly robust growth after 2006 and accelerated expansion during 2015-2020. Post-2020, Topic 0 emerged as the dominant research theme, accompanied by substantial increases in Topics 2 and 4. These patterns reflect the domain's increasing prioritization of dental caries management in pediatric populations with chronic disease(s), with accelerating research momentum in recent years. Word clouds representing the clustered terms under each topic are presented in Figure 4.

LDA-derived word clouds illuminated the semantic architecture of five distinct research themes.

Topic 0: General Pediatric Oral Health Epidemiology

Represents the domain's foundational dimension. High-frequency terms including child, health, oral, dental, and caries indicate predominance of epidemiological and descriptive investigations. Co-occurring terms (prevalence, disease, care, study, and result) suggest focus on quantification of disease burden and assessment of population-level health status.

Topic 1: Risk Factors for Childhood Dental Caries

Adopts an analytical-etiological orientation. Prominence of caries, dental, health, risk, and age reflects research examining risk determinants, age-stratified patterns, and impact of chronic diseases on the pathogenesis of caries through predictive modeling and risk stratification frameworks.

Topic 2: Patient-Centered Chronic Disease-dental Health Interface

Embodies a holistic, patient-oriented paradigm. Central positioning of patient, health, caries, dental diseases, and particularly diabetes indicates examination of chronic disease-oral health relationships through experiential, care process, and community intervention lenses. Terms as community and care underscore public health and multidisciplinary perspectives.

Topic 3: Comparative Methodology and Controlled Research

Constitutes the strongest methodological theme. Prominence of group, control, index, study, and child reflects high-evidence designs employing control groups, comparative frameworks, and standardized metrics (e.g., Decayed, Missing, Filled Teeth: DMFT index), focusing on efficacy and comparative effectiveness of the intervention.

Topic 4: Disease-specific Approaches and Asthma

Reflects condition-targeted research. The salience of asthma indicates concentrated investigation of asthma-caries relationships, while risk, dental, caries, child, and patient highlight focused analyses of specific risk populations and targeted dental management in defined chronic disease cohorts. Cross-topic analysis revealed that while core concepts (child, dental, caries, health, and oral) permeate all themes, each topic maintains distinctive keyword profiles reflecting unique research questions and methodological orientations. Temporal dynamics indicated particularly robust recent growth in Topic 2, highlighting the ascending importance of patient-centered, holistic approaches in contemporary pediatric dental research. Collectively, these five topics demonstrate the multidimensional, interdisciplinary, and evolutionary nature of dental caries management research in chronic diseases in pediatric populations. The findings related to chronic diseases highlighted in the dental health literature are presented in Figure 5.

Analysis of representation of chronic disease revealed substantial heterogeneity. Diabetes dominated with 124 publications, followed by asthma (n=82) and cerebral palsy (n=59). Obesity, congenital heart disease, cystic fibrosis, and epilepsy received moderate scholarly attention. Autism appeared in limited investigations, while sickle cell anemia and juvenile arthritis emerged as notably underrepresented conditions. This distribution pattern indicates concentrated research interest in

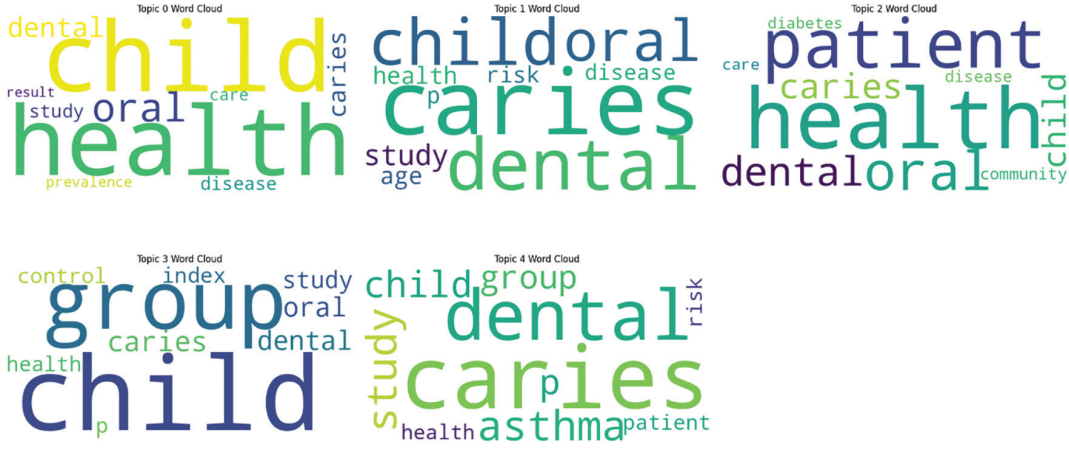

Figure 4. Word clouds of topics

specific chronic conditions, with significant knowledge gaps persisting across numerous populations with pediatric chronic diseases. The findings of the social network analysis of keyword "co-occurrence" in the pediatric dental literature are presented in Figure 6.

Social network analysis of keyword co-occurrence patterns revealed complex semantic relationships within the corpus. Network architecture featured nodes (keywords) connected by edges (co-occurrences), with node size reflecting term frequency and edge thickness indicating co-occurrence strength. The network core comprised three dominant nodes-oral health, disease, and caries-establishing the domain's conceptual foundation.

Within the clinical outcomes cluster, exceptionally strong linkage between abscess and pain reflected the clinical reality of manifestation of pain in advanced carious lesions with abscess formation. Pain functioned as a bridging construct connecting clinical symptomatology to patient-reported outcomes including impact, quality of life, and wellbeing. The proximal positioning of quality of life and wellbeing underscored the growing emphasis on patient-centered outcome assessment in pediatric research, signaling progression beyond purely clinical endpoints toward comprehensive evaluation of child wellbeing.

The management strategies in cluster projects demonstrated management as a hub connected to treatment, prevention, intervention, and outcome, representing research on therapeutic and preventive approaches to dental caries in chronic disease populations. The prominence of prevention emphasized proactive strategies (fluoride therapy, dietary modification, oral hygiene education), while intervention encompassed both clinical and educational modalities.

Regarding pathogenesis and complications, nodes including infection, inflammation, complication, and severity represented dimensions of disease process. The node status encompassed both dental status (e.g., DMFT indices) and general health status. Notably, disease burden appeared relatively isolated, suggesting limited integration of disease burden frameworks within mainstream research discourse.

Network topology analysis demonstrated non-random keyword distribution organized according to semantic proximity. Robust connections characterized the oral health-disease-caries triad and the quality of life-wellbeing dyad, while weak or absent linkages appeared between semantically distant terms (burden-abscess). The multi-centered network structure indicated that distinct conceptual clusters maintained dense internal

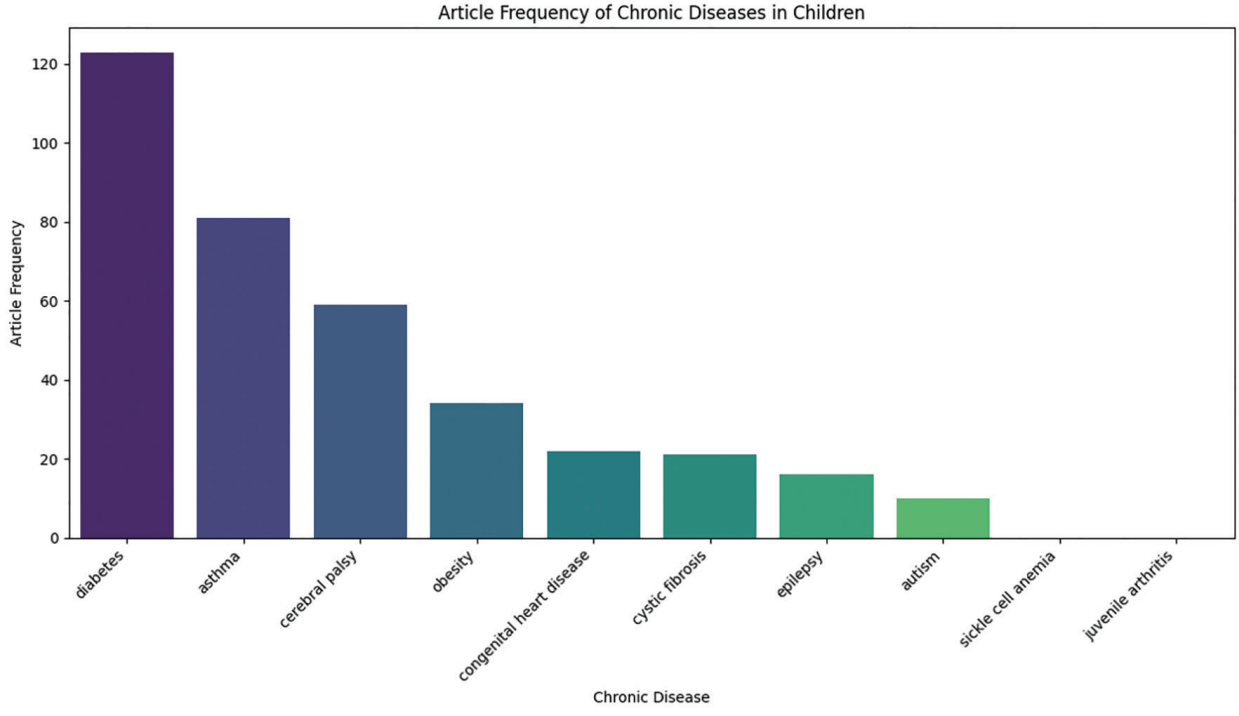

Figure 5. Chronic diseases identified in the pediatric dental health literature

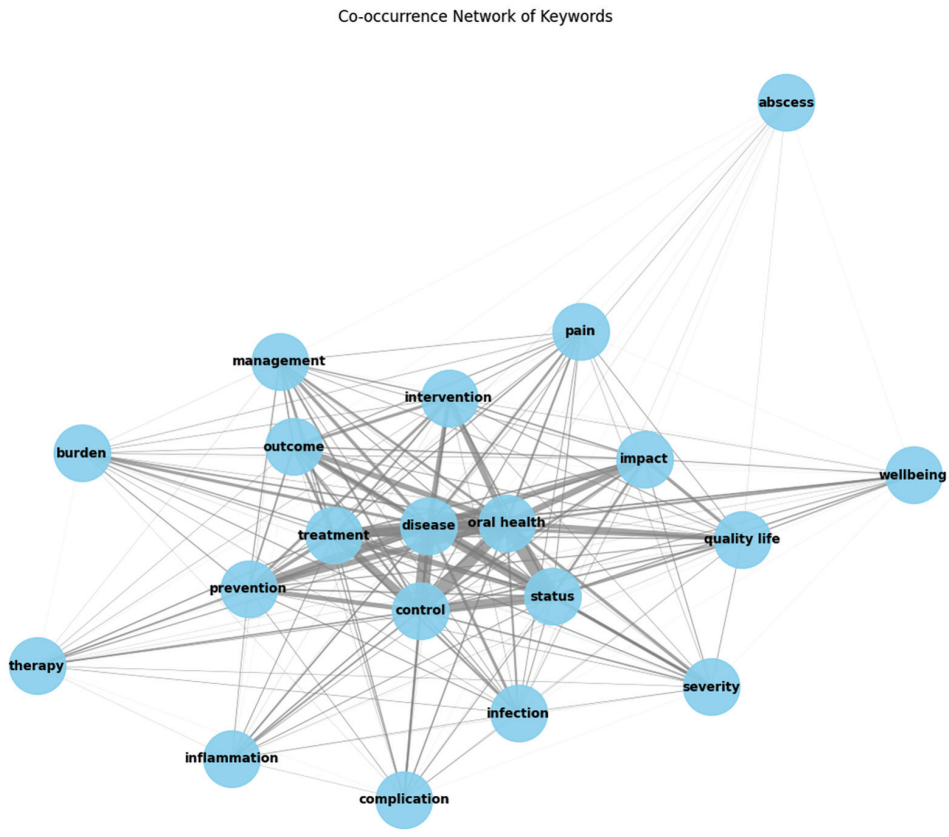

Figure 6. Social network analysis of pediatric dental literature

connectivity while bridging nodes facilitated inter-cluster integration. This complex topological architecture underscores that management of dental caries in pediatric populations with chronic disease constitutes a multifactorial, multidisciplinary, and holistic research domain requiring integrated approaches across clinical, preventive, and patient-centered dimensions.

DISCUSSION

This study provides a comprehensive overview of the scientific literature on the management of dental caries in children with chronic diseases and highlights important patterns in how this domain has evolved over time. The findings suggest that research in this area is heterogeneous, with varying thematic emphases and uneven attention across chronic disease groups. Collectively, the literature reflects both growing recognition of oral health as a component of chronic disease care and persistent gaps that may have implications for clinical practice and health equity.

The identification of three distinct research clusters suggests that the existing literature remains largely structured around disease-specific perspectives rather than integrated models of care. The body of work with the highest citation iimpact reflects the established research foundation documenting the disproportionate burden of oral disease among children with chronic conditions. Seminal studies, including that of Thikkurissy and Lal[5], consistently report higher prevalence of dental caries, periodontal disease, and developmental enamel defects in medically complex children compared with their healthy peers. The strong scholarly impact of this literature likely reflects both its clinical relevance and its methodological rigor, particularly in elucidating the bidirectional relationship between systemic disease and oral health. Previous investigations have demonstrated how chronic conditions such as cerebral palsy and metabolic disorders influence oral hygiene capacity, salivary function, inflammatory responses, and disease susceptibility, while untreated oral infections may further compromise systemic health[2-4].

Highly specialized investigations have focused on specific chronic conditions, most notably cerebral palsy and chronic kidney disease. These studies contribute important condition-specific insights, such as the effects of motor impairment and orofacial dysfunction on oral hygiene practices in children with cerebral palsy, and the role of reduction in salivary flow (hyposalivation) and biochemical alterations in increasing susceptibility to caries among children with chronic kidney disease[2,7]. Although clinically relevant, this body of work often remains embedded within subspecialty frameworks, which may limit its integration into broader pediatric oral health strategies and interdisciplinary care models.

In contrast, a growing body of literature reflects a shift toward patient-centered and integrated approaches to oral health care in children with chronic diseases. While this research has not yet achieved the same level of scholarly visibility as more established studies, its marked expansion after 2020 suggests increasing awareness that effective caries management must extend beyond disease-specific outcomes. Recent studies have emphasized quality of life, functional capacity, and psychosocial wellbeing as integral components of oral health, particularly for children living with complex medical conditions[6]. The relatively limited citation impact of this emerging literature likely reflects the inherent delay between conceptual innovation and its widespread incorporation into clinical practice. It is also worth noting that the comparatively lower citation counts observed for publications from 2021 onward should be interpreted with caution. While there is a natural lag between conceptual innovation and clinical integration, it must equally be recognized that more recently published studies have had substantially less time to accumulate citations relative to earlier works. This temporal citation bias is an inherent characteristic of bibliometric analyses and does not necessarily reflect the actual scientific impact or clinical relevance of recent publications. Accordingly, citation-based comparisons across different time periods should be approached with this limitation in mind, and the apparent underperformance of post-2020 publications in citation metrics is likely, at least in part, a methodological artifact rather than a true indicator of diminished scholarly influence.

Disease-specific analysis demonstrated substantial imbalances in research focus across chronic pediatric conditions. Diabetes mellitus and asthma account for a large proportion of the existing literature, which is consistent with their high prevalence and their well-documented effects of metabolic dysregulation, inhaled medications, and alterations in salivary flow rate on oral health[3,8]. In contrast, conditions such as sickle cell anemia, juvenile idiopathic arthritis, and autism spectrum disorder remain notably underrepresented, despite their well-recognized clinical complexity and potential impact on the delivery of oral health care. This disparity is concerning, as children affected by these conditions often face additional barriers to dental care, including pain crises, functional limitations, behavioral challenges, and increased need for sedation or hospital-based treatment. The relative absence of focused research in these populations suggests not only gaps in scientific knowledge but also potential inequities in the development of evidence-based preventive and therapeutic strategies for vulnerable pediatric groups.

The temporal evolution identified in this study mirrors broader trends in pediatric healthcare. The sharp increase in publications after 2020 likely reflects heightened awareness of healthcare access barriers during the coronavirus disease-2019 pandemic, which disproportionately affected children with chronic diseases requiring hospital-based dental care[12,13]. While this surge signals growing interest in integrated care, sustained efforts will be required to translate emerging evidence into routine clinical practice.

Overall, this analysis highlights both progress and persistent limitations within the domain. Although research activity has increased and patient-centered perspectives are gaining momentum, the lack of integrated frameworks continues to hinder equitable and effective dental care for children with chronic diseases. Addressing these gaps will require interdisciplinary collaboration, targeted research investment in neglected conditions, and policies that support coordinated, preventive, and child-centered oral health care.

Study Limitations

The present study has several limitations that should be acknowledged. The literature search was confined to the WoS database. Although WoS is widely regarded as a rigorous and high-quality source for bibliometric analyses, relying on a single database may not capture the full spectrum of relevant publications indexed exclusively in other repositories such as Scopus or PubMed. Consequently, some studies that could have contributed to the corpus may have been overlooked. Future research is encouraged to replicate or extend this analysis by incorporating multiple databases to enhance the comprehensiveness and generalizability of the findings. Another limitation concerns the temporal coverage of the dataset. Although the analysis encompasses publications up to the year 2026,

it is important to clarify that data were extracted from the WoS database on January 15, 2026. Therefore, only publications indexed up to this specific date were included, and the 2026 data represent a partial rather than a complete annual record. As bibliographic databases may experience indexing delays, some publications from late 2025 and early 2026 might not yet have been indexed at the time of data retrieval. Readers are advised to interpret temporal trend analyses for the most recent period-particularly 2025 and 2026-with this caveat in mind, as the apparent decline or plateau in publication output may partly reflect incomplete indexing rather than a genuine shift in research activity. Future studies updating this analysis after full indexing of 2026 records would provide a more complete picture of recent trends. Methodological limitations inherent to bibliometric and NLP approaches should also be acknowledged. Analytical outcomes are influenced by text preprocessing choices, clustering assumptions, and topic modeling parameters, which may affect the interpretation of thematic structures. Topic identification relied on abstract-level data and keyword-based disease classification, which may have resulted in missed studies or misclassification due to variations in terminology. Moreover, co-occurrence network analysis reflects term proximity rather than causal or clinical relationships.

CONCLUSION

Finally, this analysis describes patterns within the published literature and does not assess study quality, clinical effectiveness, or patient outcomes. As such, the findings provide insight into research trends and gaps rather than providing direct guidance for clinical decision-making.

This NLP-based analysis provides a comprehensive overview of the intellectual structure and thematic evolution of dental caries management research in children with chronic diseases. The findings reveal significant disparities in disease representation, methodological limitations, and insufficient integration of oral health within chronic pediatric care. Addressing these gaps will require more disease-specific, longitudinal, and multidisciplinary research approaches, alongside stronger alignment between dental and medical services. Improving preventive dentistry and effective caries management should be considered an essential component of comprehensive care for children living with chronic diseases.

Ethics

Ethics Committee Approval: This study was based exclusively on publicly available publication data retrieved from bibliometric databases. The analysis did not involve any human subjects, primary data collection, or interventions. Since all data used in this research were already in the public domain and freely accessible, and no identifiable personal information or sensitive data were processed, ethical approval from an institutional review board was not required for this bibliometric analysis.

Informed Consent: Not applicable.

Declaration of AI Use: All authors made substantial contributions to the manuscript. AI assistance was used for language editing, including OpenAI's ChatGPT for English translation and Anthropic's Claude AI for linguistic review and professional refinement. The authors retain full responsibility for the content.

Footnotes

Author Contributions

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Original Article

Ultrasound-guided Hydrostatic Reduction in Pediatric Intussusception: Factors Associated with Treatment Success

Pediyatrik İnvajinasyonda Ultrasonografi Eşliğinde Hidrostatik Redüksiyon: Tedavi Başarısı ile İlişkili Faktörler

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ABSTRACT

Objective: This study aimed to assess demographic and sonographic factors associated with successful ultrasound-guided hydrostatic reduction in pediatric patients with intussusception.

Method: This retrospective, single-center study included children with ultrasonographically confirmed intussusception who underwent ultrasound-guided hydrostatic reduction. Demographic characteristics, intussusception location, intussuscepted segment length, mesenteric lymphadenopathy, free intraperitoneal fluid, and increased mesenteric echogenicity were evaluated. The optimal cut-off value for intussuscepted segment length was determined using receiver operating characteristic (ROC) curve analysis.

Results: A total of 132 patients were included; 79 were male (59.8%), and the median age was 2 years. Hydrostatic reduction was successful in 109 (82.6%) patients. No procedure-related perforation or major complication occurred. Surgical treatment was required in 23 patients (17.4%); manual reduction was achieved in 18, whereas 5 patients with bowel ischemia underwent segmental resection and primary anastomosis. The mean intussuscepted segment length was shorter in the successful reduction group than in the failed reduction group (48.4±17.9 mm vs. 68.8±23.4 mm; p<0.001). ROC curve analysis identified 70 mm as the optimal cut-off for predicting failed reduction, with an area under the curve of 0.762. Free intraperitoneal fluid and increased mesenteric echogenicity were associated with failed reduction (p=0.002 and p=0.037, respectively). Age, sex, intussusception location, and lymphadenopathy were not significantly associated with hydrostatic reduction success.

Conclusion: Ultrasound-guided hydrostatic reduction is safe and effective for pediatric intussusception. Longer intussuscepted segment length, free intraperitoneal fluid, and increased mesenteric echogenicity may help predict failed reduction and the need for surgery.

Keywords: Hydrostatic reduction, ileocolic, intussusception, pediatric intestinal obstruction, ultrasonography

ÖZ

Amaç: Bu çalışmada, pediyatrik invajinasyon hastalarında ultrasonografi eşliğinde hidrostatik redüksiyon başarısı ile ilişkili demografik ve sonografik faktörlerin değerlendirilmesi amaçlandı.

Yöntem: Bu retrospektif, tek merkezli çalışmada ultrasonografi ile invajinasyon tanısı doğrulanan ve ultrasonografi eşliğinde hidrostatik redüksiyon uygulanan çocuk hastalar değerlendirildi. Demografik özellikler, invajinasyon lokalizasyonu, invajine segment uzunluğu, mezenterik lenfadenopati, peritoneal serbest sıvı ve mezenterik ekojenite artışı incelendi. Bu değişkenler ile hidrostatik redüksiyon başarısı arasındaki ilişkiler istatistiksel olarak analiz edildi. İnvajine segment uzunluğu için optimal eşik değer, alıcı işletim karakteristiği (ROC) eğrisi analizi ile belirlendi.

Bulgular: Çalışmaya toplam 132 hasta dahil edildi. Hastaların 79'u erkekti (%59,8) ve medyan yaş 2 yıldı. Hidrostatik redüksiyon 109 hastada başarılı oldu (%82,6). İşleme bağlı perforasyon veya majör komplikasyon

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izlenmedi. Cerrahi tedavi 23 hastada gerekli oldu (%17,4); 18 hastada manuel redüksiyon sağlanırken, iskemi saptanan 5 hastaya segmental rezeksiyon ve primer anastomoz uygulandı. Ortalama invajine segment uzunluğu, hidrostatik redüksiyonun başarılı olduğu grupta başarısız olduğu gruba göre daha düşüktü (48,4±17,9 mm'ye karşı 68,8±23,4 mm; p<0,001). ROC eğrisi analizi, başarısız redüksiyonu öngörmede optimal eşik değerin 70 mm olduğunu gösterdi (eğri altında kalan alan: 0,762). Peritoneal serbest sıvı ve mezenterik ekojenite artışı, başarısız hidrostatik redüksiyon ile ilişkiliydi (sırasıyla p=0,002 ve p=0,037). Yaş, cinsiyet, invajinasyon lokalizasyonu veya lenfadenopati ile redüksiyon başarısı arasında anlamlı ilişki saptanmadı.

Sonuç: Ultrasonografi eşliğinde hidrostatik redüksiyon, pediyatrik invajinasyonda güvenli ve etkili bir tedavi yöntemidir. Artmış invajine segment uzunluğu, peritoneal serbest sıvı ve mezenterik ekojenite artışı, başarısız redüksiyonu ve buna bağlı cerrahi tedavi gereksinimini öngörmede yardımcı olabilir.

Anahtar kelimeler: Hidrostatik redüksiyon, ileokolik, invajinasyon, pediyatrik intestinal obstrüksiyon, ultrasonografi

INTRODUCTION

Intussusception is the leading cause of bowel obstruction during infancy and early childhood. Approximately 80% of intussusception cases occur in patients younger than 2 years[1,2]. Intussusception most commonly involves the ileocolic region. Clinical presentation is usually characterized by non-specific symptoms such as vomiting, diarrhea, and fever[2]. Given the young age of affected patients, clinical diagnosis may be challenging; therefore, radiological evaluation is frequently required. Diagnosis is usually established by ultrasound (US)[3]. Early diagnosis and treatment are important because delays may lead to intestinal ischemia, necrosis, or perforation[4].

Treatment options for intussusception include pneumatic reduction, hydrostatic reduction, and surgery[2,5]. Pneumatic reduction is performed under fluoroscopic guidance, whereas hydrostatic reduction is performed under US guidance. Since pneumatic and hydrostatic reduction techniques are associated with lower morbidity and mortality rates compared to surgery, they are preferred as first-line treatment options. US-guided hydrostatic reduction has been reported to have a higher success rate than pneumatic reduction[6]. In addition, because US-guided hydrostatic reduction does not involve ionizing radiation and is easy and inexpensive to perform, it is considered a first-line treatment method[7]. The reported success rates of hydrostatic reduction range from 82% to 92.9%[8-10]. Surgery is indicated in cases of failed reduction, shock, peritonitis, or intestinal perforation[2].

Clinical factors such as age, time from symptom onset to treatment, presence of rectal bleeding, and vomiting may affect the success of hydrostatic reduction[11,12]. In addition, radiological findings such as intussuscepted segment length, presence of enlarged intra-abdominal lymph nodes, air-fluid levels, and a pathological lead point have also been shown to be associated with procedural success of hydrostatic reduction[13-15].

This study aimed to assess the associations of demographic and sonographic factors with hydrostatic reduction success in pediatric intussusception. Identifying these factors may reduce the need for surgical treatment and the related morbidity and mortality.

MATERIALS and METHODS

Patient Selection

Approval for this retrospective study was obtained from the local ethics committee of University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital with decision no: 2026/05-08, dated: 12.03.2026. The study population included children who were diagnosed with intussusception by US and underwent US-guided hydrostatic reduction at a single tertiary pediatric center between September 2020 and February 2026. In our center, all patients with suspected intussusception were routinely evaluated by US, and US-guided hydrostatic reduction was attempted in all patients when the diagnosis of intussusception was confirmed. No patient was referred directly to surgery without a prior attempted hydrostatic reduction during the study period. Patients with spontaneously reduced intussusception (n=4) and patients who underwent surgery after failed hydrostatic reduction but had no intraoperative evidence of intussusception (n=1) were excluded.

Radiological Evaluation

Diagnosis of intussusception was established using US by a single radiologist. A high-frequency linear probe (Toshiba, Aplio 500) was used for diagnosis and treatment. Cases of intussusception were categorized as ileocolic, ileoileal, or colocolic according to the involved bowel segment. In all US examinations, the length of the intussuscepted segment was measured along the long axis and recorded. The presence of lymphadenopathy, free intraperitoneal fluid, and increased mesenteric echogenicity was also noted. Increased mesenteric echogenicity was defined as subjectively increased echogenicity of the mesenteric fat adjacent to the

intussuscepted segment compared with the surrounding mesenteric fat. Mesenteric lymph nodes with a short-axis diameter of 6 mm or greater were considered lymphadenopathy.

Considering transient intussusception as a possibility, patients with an intussuscepted segment length of <20 mm on US were managed conservatively. These patients were observed for 1-6 hours and re-evaluated by US. If the finding persisted, an evacuation enema was performed. These patients then underwent repeat US examinations performed by the same radiologist. Patients in whom reduction was not achieved based on follow-up US images and those with an intussuscepted segment length of ≥20 mm underwent hydrostatic reduction.

Hydrostatic Reduction Procedure

After insertion of a 16-18 Fr catheter in the rectum, the balloon of the catheter was inflated to maintain catheter stability. Saline solution was administered through the catheter by gently compressing the suspended saline bag. During administration of saline solution, colonic distension was monitored simultaneously with US. Colonic expansion was allowed up to a maximum diameter of 40 mm. If the luminal diameter exceeded 40 mm, administration of saline solution was stopped because of the risk of perforation.

Hydrostatic reduction was considered successful when saline solution passage proximal to the intussuscepted segment was observed, at which point the procedure was terminated. If passage of saline solution proximal to the intussuscepted segment was not observed, reduction was attempted with the patient first in the right and then in the left lateral decubitus position. If proximal passage of saline solution still could not be achieved, hydrostatic reduction was considered unsuccessful, and the patient was referred for surgery. The reduction procedure lasted approximately 10 minutes.

All patients who underwent reduction procedures were hospitalized for at least 24 hours and underwent at least one follow-up US examination. Recurrent intussusception was detected in two patients during the 24 hour observation period. Both patients were successfully treated with repeat US-guided hydrostatic reduction. No pathological lead point was suspected on US in either patient.

Surgical Reduction

During intraoperative evaluation, bowel viability was assessed in terms of color, peristalsis, and mesenteric circulation. The bowel and mesentery were explored for a possible pathological lead point, such as an associated mass or space-occupying lesion. Enlarged lymph nodes were resected for sampling.

The primary surgical approach was laparotomy and manual reduction. During this procedure, the intussuscepted segment was gently and carefully reduced from distal to proximal using the milking technique. Manual reduction was adopted as the standard approach because it allows preservation of intestinal continuity. The affected bowel segment was resected, and primary anastomosis was performed when manual reduction failed or when irreversible ischemia, necrosis, or perforation was present. Patients were hospitalized for at least 48 hours postoperatively and underwent US 24-48 hours after surgery to evaluate for complications.

Statistical Analysis

A two-tailed p-value below 0.05 was accepted as indicating statistical significance. Data analyses were conducted with Statistical Package for the Social Sciences (SPSS) software, version 20.0 (IBM Corp., NY, USA).

The association between hydrostatic reduction success and age was evaluated using the Mann-Whitney U test, whereas the association with sex was assessed using the chi-square test. The association between intussusception location and hydrostatic reduction success was analyzed using the likelihood-ratio chi-square test. Preprocedural intussuscepted segment length was compared between the successful and failed reduction groups using the independent-samples t-test. Receiver operating characteristic (ROC) curve analysis was performed to determine the intussuscepted segment length cut-off with the best discriminatory ability for predicting failed reduction. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the area under the ROC curve (AUC) were calculated for the identified cut-off. The associations between hydrostatic reduction success and lymphadenopathy, free intraperitoneal fluid, and increased mesenteric echogenicity were evaluated separately using Fisher's exact test.

RESULTS

The study included 132 patients, of whom 79 were male (59.8%) and 53 were female (40.2%). The median age was 2 years [interquartile range (IQR), 1-4 years; minimum age, 3 months; maximum age, 12 years]. Intussusception was ileocolic in 117 patients (88.6%), colocolic in 8 patients (6.1%), and ileoileal in 7 patients (5.3%). Intussusception was successfully reduced by hydrostatic reduction in 109

(82.6%) patients. Recurrent intussusception was observed on follow-up US in two patients during the 24-hour observation period after initially successful hydrostatic reduction. Both patients were successfully treated with repeat US-guided hydrostatic reduction. No pathological lead point was suspected or identified in these patients.

Reduction was achieved surgically in 23 (17.4%) patients. Among these 23 patients, successful manual reduction was achieved in 18 patients. Small bowel resection and anastomosis were performed in 5 patients (3.8%) because of irreversible bowel ischemia. A pathological lead point was identified in 8 patients (6.1%): Meckel diverticulum in 3 patients, acute appendicitis in 2 patients, hemangioma in the adjacent mesentery in 1 patient, adenomyoma in 1 patient, and adhesion in 1 patient. Lymph node resection was performed in 9 patients, and all resected lymph nodes were reported as lymphoid hyperplasia. All patients who underwent surgical treatment were discharged without complications. The demographic findings are summarized in Table 1.

In all patients, the mean intussuscepted segment length was 52.0±20.4 mm. Lymphadenopathy was observed in 87 (65.9%), free intraperitoneal fluid in 32 (24.2%), and increased mesenteric echogenicity in 5 (3.8%) patients. The median short-axis diameter of the lymph nodes was 8 mm (IQR, 6-9 mm).

No significant association was found between reduction success and age or sex (p=0.118 and p=0.721, respectively). The reduction success rates were 84.6% for ileocolic, 75.0% for colocolic, and 57.1% for ileoileal intussusceptions. Intussusception location was not significantly associated with reduction success (p=0.213).

The mean intussuscepted segment length was 48.4±17.9 mm in patients who underwent successful reductions and 68.8±23.4 mm in patients with failed reduction. Intussuscepted segment length was significantly associated with hydrostatic reduction success (p<0.001) (Figure 1). ROC curve analysis identified 70 mm as the optimal cut-off for predicting failed reduction. At this cut-off, sensitivity was 60.9%, specificity was 85.3%, PPV was 46.7%, NPV was 91.2%, and the AUC was 0.762.

Lymphadenopathy was observed in 65.1% of patients who underwent successful reduction and in 69.6% of patients in whom reduction attempts failed. The association between lymphadenopathy and successful hydrostatic reduction was not significant (p=0.81). Free intraperitoneal fluid was more frequent in the failed reduction group than in the successful reduction group (52.2% vs. 18.3%) and was significantly associated with failed hydrostatic reduction (p=0.002). Increased mesenteric echogenicity was also more common in the failed reduction group (13.0% vs. 1.8%) and was significantly associated with failed hydrostatic reduction

Table 1. Demographic, sonographic, and treatment-related findings

Parameters	
Male/female, n	79/53
Median age (yrs)	2 years (IQR, 1-4 years)
Intussusception location, n (%)	
Ileocolic	117 (88.6)
Colocolic	8 (6.1)
Ileoileal	7 (5.3)
Hydrostatic reduction	
Success rates, n (%)	109 (82.6)
Surgical treatment, n (%)	
Manual reduction	18 (13.6)
Resection	5 (3.8)
Pathological lead point	8 (6.1)
Ultrasonographic findings	
Intussuscepted segment length, mean (±SD)	52 (±20.4) mm
Lymphadenopathy, n (%)	87 (65.9)
Free intraperitoneal fluid, n (%)	32 (24.2)
Increased mesenteric echogenicity, n (%)	5 (3.8)

IQR: Interquartile range, SD: Standard deviation

(p=0.037) (Figure 2). The comparative statistical results are summarized in Table 2.

DISCUSSION

In this study, we evaluated demographic and sonographic factors associated with hydrostatic reduction success in pediatric intussusception. The hydrostatic reduction success rate was 82.6%, and no complications occurred during the procedure. The likelihood of successful hydrostatic reduction decreased as intussuscepted segment length increased. The optimal cut-off value for the length of the intussuscepted segment in terms of differentiating successful and failed reduction attempts was calculated as 70 mm. In addition, free intraperitoneal fluid and increased mesenteric echogenicity were significantly associated with failed reduction.

Hydrostatic reduction is a first-line treatment option for pediatric intussusception. In the meta-analysis by Kim et al.[9], the pooled reduction success rate was 82%. In the large series of 543 patients reported by Ntoulia et al.[10], the reduction success rate was 86.7%, and 72 patients required surgery. Among the surgically treated patients,

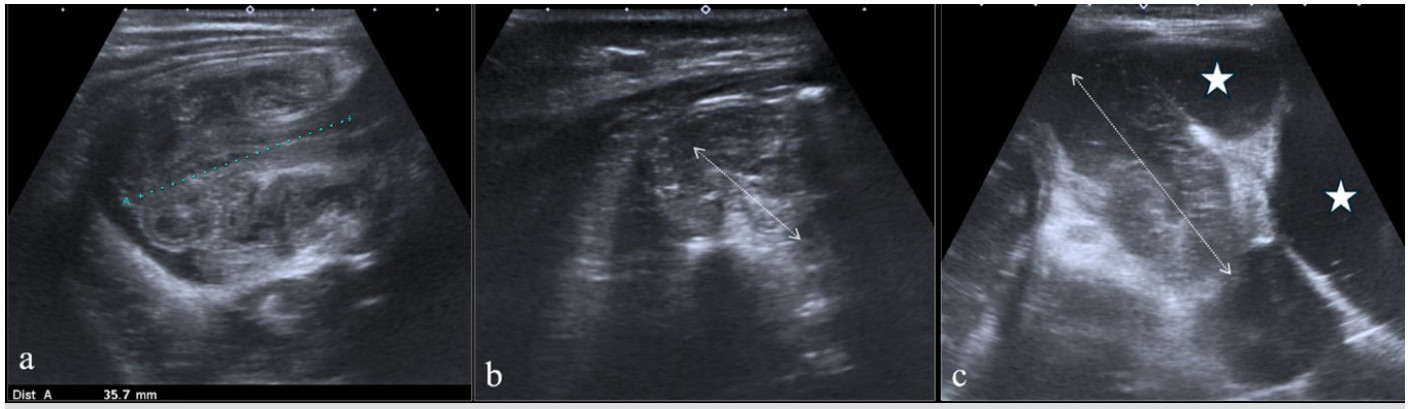

Figure 1. Representative examples of intussusception. a) Ileocolic intussusception measuring 36 mm in length in a 6-month-old female patient. Hydrostatic reduction was successful in this patient. b) A 30-mm intussusception of the ileocecal valve into the cecum in a 2-year-old male patient (dashed arrow). Hydrostatic reduction was successful in this patient. c) Long-segment ileocolic intussusception measuring 75 mm in a 1-year-old male patient (dashed arrow). Diffuse wall thickening of the intussuscepted segment and distension of the proximal small bowel loops are present (stars). Hydrostatic reduction failed, and the patient underwent manual reduction at surgery

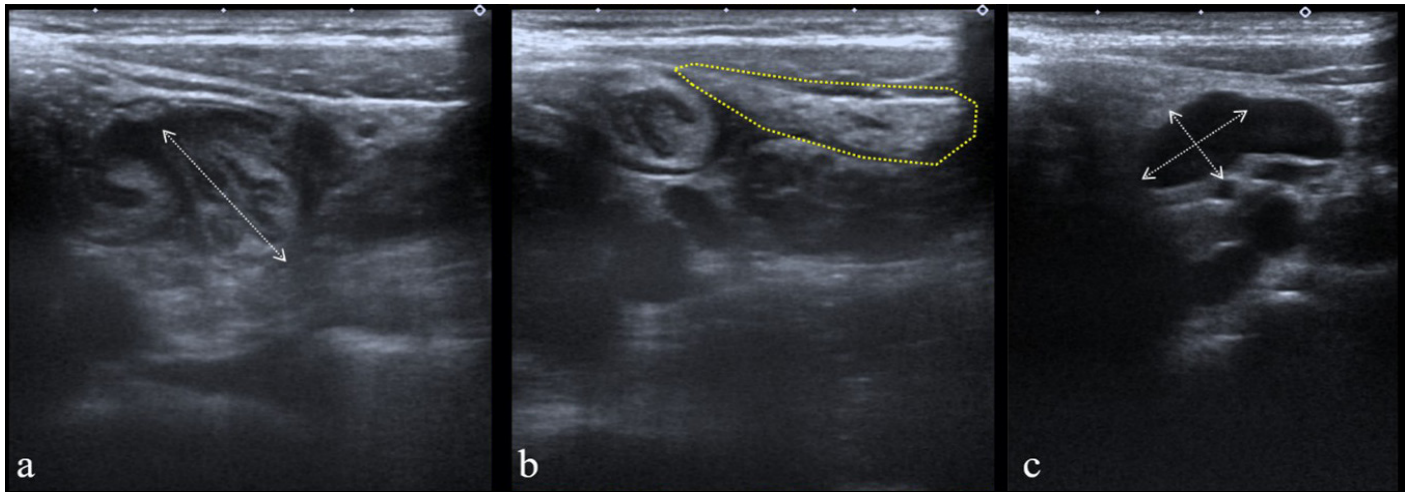

Figure 2. Ultrasonographic findings of a 7-month-old female patient. a) Ileocolic intussusception measuring 35 mm in length (white dashed arrow) and b) increased inflammatory echogenicity in the adjacent mesentery (yellow shaded area). c) Adjacent mesenteric lymph nodes are seen near the intussuscepted segment. The larger lymph node measures 8×13 mm in size (white dashed arrows). Hydrostatic reduction was successful in this patient

Table 2. Comparative statistical results			
Demographic and sonographic findings	**Hydrostatic reduction**		**p-value**
	Successful	**Failed**	
Median age	2 years	3.25 years	0.118
Sex (male/female)	66/43	13/10	0.721
Intussuscepted segment length, mean (± standard deviation)	48.4 (±17.9) mm	68.8 (±23.4) mm	<0.001
Lymphadenopathy, %	65.1	69.6	0.81
Free intraperitoneal fluid, %	18.3	52.2	0.002
Increased mesenteric echogenicity, %	1.8	13	0.037

spontaneous or manual reduction was achieved in 68%, whereas small bowel resection and ileocecal resection were performed in 19.4% and 12.5%, respectively. A pathological lead point was identified in 25% of patients requiring surgery, including lymphoid hyperplasia (9.7%), Meckel diverticulum (4.2%), Burkitt lymphoma (4.2%), enteric duplication cyst (2.8%), juvenile polyp (2.8%), and adenoviral appendicitis (1.4%)[10]. In the series by Yang et al.[16], which included 3086 pediatric patients treated using two different protocols, surgical treatment was required in 19.9% of patients, and bowel resection was performed in 2.6% of all patients. In the meta-analysis by Sadigh et al.[5], the perforation rate during hydrostatic reduction was 0.43%. In our study, 17.4% of patients required surgery after failed hydrostatic reduction. Manual reduction was achieved surgically in 13.6% of patients, whereas small bowel resection was performed in 3.8% because of irreversible bowel ischemia. A pathological lead point was identified in 6.1% of patients, with Meckel diverticulum being the most common finding (2.3%). No perforation occurred during hydrostatic reduction in any patient.

Pediatric intussusception reduction success may be affected by demographic and clinical factors. In the study by Zhuang et al.[11], clinical, laboratory, and imaging parameters were evaluated together, and a nomogram was developed to estimate the need for surgery. Symptom duration, bloody stool, white blood cell count, creatine kinase isoenzyme (CK-MB), intussuscepted segment length, and mental status were identified as independent risk factors[11]. In the series of 290 patients reported by Alsinan et al.[12], female sex, age younger than 1 year, and symptom duration longer than 48 hours were associated with failed reduction. That study included patients aged between 1 and 36 months. Similarly, Elrouby et al.[17] reported that younger age, low body mass index, longer symptom duration, bloody stool, a palpable abdominal mass, left-sided intussusception, and increased air-fluid levels on radiography were associated with failed reduction. However, that study included only patients aged between 6 months and 3 years[17]. In the review by Hwang et al.[18], left-sided colocolic intussusceptions were suggested to have a lower likelihood of successful reduction. In our study, neither age nor sex was significantly associated with hydrostatic reduction success. The success rates were 84.6% for ileocolic, 75.0% for colocolic, and 57.1% for ileoileal intussusceptions. Although the success rate appeared higher for ileocolic intussusceptions, intussusception location was not significantly associated with reduction success. The differences between our findings and those reported in previous studies may partly reflect the relatively small number of patients, particularly in the failed reduction group.

Several sonographic findings have been reported to be associated with hydrostatic reduction success in pediatric patients. In the study by Gondek et al.[13], which included only patients with ileocolic intussusception, free intraperitoneal fluid and absence of Doppler vascularity in the intussuscepted segment were associated with failed reduction. Ayana et al.[14] reported that intussusceptions shorter than 35 mm were more likely to be successfully reduced. In the series by Wondemagegnehu et al.[15], which included 174 children, free intraperitoneal fluid was observed in 21.8% of patients and enlarged lymph nodes in 54.6%. The mean intussuscepted segment length was 52 mm. In that study, free intraperitoneal fluid and the presence of a pathological lead point or associated mass were significantly associated with reduced treatment success[15]. In our study, the likelihood of successful hydrostatic reduction decreased significantly as intussuscepted segment length increased. A cut-off of 70 mm showed 60.9% sensitivity and 85.3% specificity for predicting failed reduction. Free intraperitoneal fluid and increased mesenteric echogenicity were also significantly associated with failed reduction.

Study Limitations

This study has several limitations. First, because of its retrospective and single-center design, the possibility of selection bias cannot be completely excluded. Second, the relatively small number of patients in the failed

hydrostatic reduction group may have reduced statistical power, particularly in subgroup analyses. Therefore, the findings should be confirmed in larger patient cohorts. Third, because sonographic evaluations were performed by a single radiologist, interobserver variability analysis could not be performed, which may have made the results operator-dependent. Finally, because the interval between symptom onset and treatment was inconsistently documented in the medical records, symptom duration could not be analyzed in a standardized manner. This represents an important limitation because symptom duration may affect reduction success, bowel ischemia, the need for bowel resection, and the decision to proceed with surgery. In addition, free intraperitoneal fluid was evaluated only as a binary variable according to its presence or absence; its amount and distribution were not analyzed.

CONCLUSION

In conclusion, hydrostatic reduction of pediatric intussusception can be performed safely and successfully under US guidance. The likelihood of successful reduction decreases as intussuscepted segment length increases. Pre-reduction US assessment of intussuscepted segment length, free intraperitoneal fluid, and increased mesenteric echogenicity may be useful for predicting failed reduction and identifying patients who may require surgery.

Ethics

Ethics Committee Approval: Approval for this retrospective study was obtained from the local ethics committee of University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital with decision no: 2026/05-08, dated: 12.03.2026.

Informed Consent: This is a retrospective study.

Declaration of AI Use: The authors used generative AI tools to improve language clarity and organization during manuscript preparation. All content was subsequently reviewed and edited by the authors, who take full responsibility for the final manuscript.

Footnotes

Author Contributions

Surgical and Medical Practices: Y.K.Ç., A.D.P., M.C., Concept: M.C., Design: Y.K.Ç., A.D.P., M.C., Data Collection or Processing: D.S., O.Ç., A.D.P., Analysis or Interpretation: Y.K.Ç., D.S., O.Ç., M.C., Literature Search: Y.K.Ç., D.S., O.Ç., Writing: Y.K.Ç., M.C.

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Original Article

Clinical Course, Management, and the Role of MEFV Mutations in PFAPA Syndrome: A Single-center Experience

PFAPA Sendromunda Klinik Seyir, Yönetim ve MEFV Mutasyonlarının Rolü: Tek Merkez Deneyimi

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ABSTRACT

Objective: Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is a periodic fever syndrome that onsets in early childhood. The precise roles of medical treatments in symptom control have not yet been clarified. This study aimed to evaluate the clinical characteristics, treatment responses, and genetic findings of children diagnosed with PFAPA.

Method: Patients who were followed with a diagnosis of PFAPA between January 2021 and January 2025 were included in the study. Demographic data, clinical and laboratory findings, results of genetic analyses, and responses to corticosteroids, colchicine, and tonsillectomy were retrospectively evaluated.

Results: A total of 22 patients with a mean age of 77.6 months (male cases: 50%) were included in the study. The median duration of attacks was 4 days [interquartile range (IQR): 3-6], and the median interval between attacks was 30 days (IQR: 25-41.3). Mediterranean fever (MEFV) gene mutations were detected in 36.4% (n=8) of the patients. All patients benefited from corticosteroid therapy during attacks; however, an increase in attack frequency was observed in 45.5% of cases. A decrease in attack frequency was observed in 57.1% (4/7) of the patients using colchicine. Tonsillectomy was performed in 63.6% (n=14) of the patients, and no postoperative complications were observed, while complete recovery was achieved in all cases.

Conclusion: Our findings demonstrate that tonsillectomy is an effective treatment method for controlling febrile attacks in PFAPA.

Keywords: Colchicine, MEFV, PFAPA, tonsillectomy

ÖZ

Amaç: Periyodik ateş, aftöz stomatit, farenjit ve servikal adenit (PFAPA) sendromu, erken çocukluk döneminde başlayan bir periyodik ateş sendromudur. Semptom kontrolünde medikal tedavilerin kesin rolleri henüz net olarak aydınlatılamamıştır. Bu çalışmada, PFAPA tanısı alan çocukların klinik özelliklerinin, tedavi yanıtlarının ve genetik bulgularının değerlendirilmesi amaçlanmıştır.

Yöntem: Ocak 2021 ile Ocak 2025 tarihleri arasında PFAPA tanısıyla takip edilen hastalar çalışmaya dahil edildi. Demografik veriler, klinik ve laboratuvar bulguları, genetik analiz sonuçları ve kortikosteroid, kolşisin ve tonsillektomiye verilen yanıtlar retrospektif olarak değerlendirildi.

Bulgular: Ortalama yaşı 77,6 ay olan toplam 22 hasta (%50 erkek) çalışmaya dahil edildi. Medyan atak süresi 4 gün [çeyrekler arası aralık (IQR): 3-6], ataklar arasındaki medyan süre ise 30 gün (IQR: 25-41,3) idi. Hastaların %36,4'ünde (n=8) MEFV mutasyonları saptandı. Tüm hastalar ataklar sırasında kortikosteroid tedavisinden fayda gördü; ancak olguların %45,5'inde atak sıklığında artış gözlendi. Kolşisin kullanan hastaların ise %57,1'inde (4/7) atak sıklığında azalma görüldü. Hastaların %63,6'sına (n=14) tonsillektomi uygulandı ve postoperatif komplikasyon gözlenmezken tüm olgularda tam iyileşme sağlandı.

Sonuç: Bulgularımız, tonsillektominin PFAPA'da ateşli atakların kontrol altına alınmasında etkili bir tedavi yöntemi olduğunu göstermektedir.

Anahtar kelimeler: Kolşisin, MEFV, PFAPA, tonsillektomi

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INTRODUCTION

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome was first described by Marshall et al.[1] in 1987. The most characteristic feature of this syndrome is the regular periodicity of febrile episodes[2]. These febrile attacks usually last 3-6 days and recur at remarkably regular intervals of 3-8 weeks[3].

PFAPA symptoms most often become manifest before the age of 5 years, and the annual incidence in children under 5 years has been reported as 2.3-2.6 per 10,000[4]. Although the pathogenesis of the syndrome has not been fully elucidated, the involvement of palatine tonsils is thought to play a central role[3].

The main goal in the management of PFAPA is to control acute febrile episodes, prevent recurrences, or at least reduce the severity and frequency of attacks[5]. Non-steroidal anti-inflammatory drugs and corticosteroids are the main symptomatic pharmaceutical treatment options, while colchicine and cimetidine are the principal prophylactic medical alternatives[2,5]. However, the precise role of these treatments in symptom control remains uncertain and further research is needed.

The beneficial effect of tonsillectomy on the clinical course of PFAPA was first demonstrated by Abramson et al.[6]. During the following years, several studies reported varying complete clinical remission rates after tonsillectomy[5]. In a long-term follow-up study, Lantto et al.[7] reported that tonsillectomy resulted in complete resolution of febrile episodes in most children with PFAPA. Moberg et al.[3] noted that although tonsillectomy had relieved febrile episodes in the majority of children, some patients continued to experience febrile attacks or other PFAPA-related symptoms.

In this retrospective study, we have aimed to evaluate the clinical characteristics, treatment approaches, and genetic features of children diagnosed with PFAPA who were followed at a tertiary pediatric hospital in Türkiye. In addition, we sought to clarify the efficacy of tonsillectomy and the potential effects of Mediterranean fever (MEFV) gene mutations on the disease phenotype.

MATERIALS and METHODS

This retrospective, cross-sectional study was conducted at University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital. All consecutive patients younger than 18 years of age who were diagnosed with PFAPA syndrome and followed in our clinic between January 2021 and January 2025 were screened in terms of eligibility criteria for inclusion in the study. The diagnosis of PFAPA was based on the modified Marshall criteria proposed by Thomas et al.[8]. Patients were included if they fulfilled these diagnostic criteria and had attained regular follow-up visits in our clinic. Patients with incomplete medical records or with an alternative diagnosis that could explain recurrent febrile episodes (such as infectious, autoimmune, or other autoinflammatory diseases) were excluded. The inclusion of consecutive patients during the study period was intended to reduce potential selection bias.

Ethical approval was obtained from the Local Ethics Committee of University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (decision no: 2025/10-04, date: 29.05.2025). Written informed consent was obtained from the parents of all patients. Data collected from medical records included the demographic characteristics, age at symptom onset, and at the time of diagnosis of PFAPA was made, comorbidities, clinical features during attacks, duration of attacks, and attack intervals. Remarkable laboratory findings detected during attacks [white blood cell (WBC) count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)] were also recorded.

Treatment-related data were collected, concerning the use of corticosteroids during attacks, prophylactic colchicine therapy, and surgical interventions (tonsillectomy with or without adenoidectomy) performed. In addition, the type of tonsillectomy, age at surgery, time interval between diagnosis and surgery, duration of postoperative follow-up, complications, and outcomes were documented. Parental satisfaction with treatment outcomes was also noted.

Results of *MEFV* gene analysis were recorded for patients who underwent testing. According to the results, patients were divided into heterozygous mutation-positive and mutation-negative groups. Clinical findings, laboratory parameters, treatment responses, and surgical outcomes were compared according to genetic mutation status.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 software program (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation or median values and interquartile range (IQR), depending on their distribution patterns. Categorical variables were expressed as numbers and percentages. Comparisons of categorical variables were performed

using the chi-square test, while non-normally distributed continuous variables were compared using the Mann-Whitney U test. A two-sided p-value<0.05 was considered statistically significant.

RESULTS

A total of 22 cases comprising 11 (50.0%) female and 11 (50.0%). Male patients diagnosed with PFAPA syndrome were included in the study. The mean age of the patients at the time of evaluation was 77.6±27.4 months. The median age at symptom onset was 21.0 months (IQR: 13.5-36.0), while the mean age at diagnosis was 46.8±22.0 months. A comorbid condition was observed in only one patient (4.5%), who had chronic urticaria. Heterozygous MEFV gene mutations were identified in 8 (36.4%) patients. The distribution of mutations was as follows: M694V in 3 (13.6%), E148Q in 3 (13.6%), R202Q in 1 (4.5%), and V726A in 1 (4.5%) patient, respectively. The demographic and clinical characteristics of the patients are summarized in Table 1.

During attacks, all patients presented with fever. The most frequent accompanying findings were tonsillar exudate in 20 (90.9%), pharyngitis in 15 (68.2%), oral aphthae in 8 (36.4%), and cervical lymphadenopathy in 17 (77.3%) patients. Abdominal pain was reported for 5 (22.7%) and arthralgia for 3 (13.6%) patients, while none of them experienced arthritis or headache. The median duration of attacks was 4 days (IQR: 3-6), and the median interval between attacks was 30.0 days (IQR: 25.0-41.3). Laboratory investigations performed during attacks revealed a mean WBC count of 8461.4±2924.9/mm^3, a mean CRP level of 58.0±26.5 mg/L, and a median ESR of 22.5 mm/h (IQR: 13.8-34.0).

All patients received corticosteroid treatment during attacks, and improvement in clinical findings was observed in all cases. However, despite this acute response, 10 (45.5%) patients experienced an increased frequency of subsequent attacks after corticosteroid treatment, which led to repeated corticosteroid use during recurrent attacks. Colchicine was used by 7 (31.8%) patients of whom 4 (57.1%) showed a reduction in attack frequency. None of the patients experienced colchicine-related adverse effects. Tonsillectomy was performed in 14 (63.6%) patients with a median age of 51.5 months (IQR: 46.5-60.8) at surgery and a median interval between diagnosis and surgery was 4.0 months (IQR: 2.0-8.5). Among these, 13 (92.9%) patients underwent total tonsillectomy, while 1 (7.1%) had partial tonsillectomy. Concurrent adenoidectomy was performed in 6 (42.9%) patients. No postoperative complications were observed, and all patients achieved complete recovery following tonsillectomy. An overview of the therapeutic interventions and clinical responses of the patients is provided in Table 2.

The clinical and genetic characteristics of the patients undergoing tonsillectomy are detailed in Table 3. Among these 14 patients, MEFV gene mutations were identified in 5 cases, including heterozygous M694V (n=2), R202Q (n=1), V726A (n=1), and E148Q (n=1) mutations. Regardless of age at tonsillectomy, gender, type of tonsillectomy, concurrent adenoidectomy, or *MEFV* status, complete recovery was achieved in all patients following surgery. During the postoperative follow-up period, which ranged from 6 to 40 months, none of the patients required corticosteroid therapy, and no attacks were observed within the last 6 months. Moreover, all parents reported a reduction in school or daycare

Table 1. Demographic and clinical characteristics of the patients

Characteristics	
Gender, female, n (%)	11 (50.0)
Age (months), mean ± SD	77.6±27.4
Age at symptom onset (months), median (IQR)	21.0 (13.5-36.0)
Age at diagnosis (months), mean ± SD	46.8±22.0
Clinical findings, and symptoms detected during attacks, n (%)	
Febrile episodes	22 (100.0)
Tonsillar exudate	20 (90.9)
Cervical lymphadenopathy	17 (77.3)
Pharyngitis	15 (68.2)
Oral aphthae	8 (36.4)
Abdominal pain	5 (22.7)
Arthralgia	3 (13.6)
Arthritis	0 (0.0)
Headache	0 (0.0)
Duration of attacks (days), median (IQR)	4 (3-6)
Intervals between attacks (days), median (IQR)	30.0 (25.0-41.3)
Abnormal laboratory findings noted during attacks	
WBC (/mm^3), mean ± SD	8461.4±2924.9
CRP (mg/L), mean ± SD	58.0±26.5
ESR (mm/h), median (IQR)	22.5 (13.8-34.0)
Comorbidities, n (%)	1 (4.5)
Heterozygous MEFV gene mutation, n (%)	8 (36.4)

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, IQR: Interquartile range, MEFV: Mediterranean fever, SD: Standard deviation, WBC: White blood cell

Table 2. Treatment modalities and responses of the patients	
	n (%)
Corticosteroid therapy	22 (100.0)
Response to corticosteroid therapy	22 (100.0)
Increased attack frequency after corticosteroid use	10 (45.5)
Colchicine use	7 (31.8)
Response to colchicine	4 (57.1)
Adverse effects of colchicine	0 (0.0)
Tonsillectomy performed	14 (63.6)
Age at tonsillectomy (months), median (IQR)	51.5 (46.5-60.8)
Interval between diagnosis and surgery (months), median (IQR)	4.0 (2.0-8.5)
Type of tonsillectomy	
Partial tonsillectomy	1 (7.1)
Total tonsillectomy	13 (92.9)
Concurrent adenoidectomy	6 (42.9)
Postoperative complication	0 (0.0)
Outcome after tonsillectomy	
Complete recovery	14 (100.0)
IQR: Interquartile range	

absenteeism and expressed overall satisfaction with the surgical outcomes.

A total of 16 patients underwent *MEFV* gene analysis, of whom 8 had heterozygous mutations and 8 were mutation-negative. The age at symptom onset did not differ significantly between the heterozygous mutation-positive (22 months, IQR: 18-42) and mutation-negative (21 months, IQR: 12-39.8) groups (p>0.05). Similarly, intervals between attacks were comparable (30 days, IQR: 22.5-37.8 vs. 30 days, IQR: 25-30; p>0.05). During attacks, WBC counts (9086.3±3354.7 vs. 7272.5±2060.8/mm^3; p>0.05) and ESR levels (23.5 mm/h, IQR: 22.0-34.0 vs. 21.5 mm/h, IQR: 13.8-33.0; p>0.05) were also comparable between the groups. However, CRP levels were significantly higher in the heterozygous mutation group (76.8±19.5 vs. 47.3±25.1 mg/L; p=0.020). Although an increase in attack frequency following corticosteroid use was observed in 62.5% of heterozygous-mutation and 37.5% of mutation-negative patients, this difference was not statistically significant (p>0.05). Response to colchicine was also comparable, with improvement observed in 50.0% of heterozygous-mutation and 66.7% of mutation-negative patients (p>0.05).

DISCUSSION

Our study has focused on evaluating the clinical, laboratory, and genetic characteristics, as well as the outcomes of therapeutic approaches in patients followed up at a pediatric diseases and surgery training and research hospital with the diagnosis of PFAPA syndrome. Heterozygous MEFV mutations were detected in 36.4% of patients, and this rate increased to 50% in the subgroup who underwent genetic testing. This finding suggests that genetic factors may play a role in the susceptibility to this disease, the pathogenesis of which has not yet been fully elucidated. Corticosteroids, commonly used in the management of PFAPA syndrome were found to increase attack frequency in 45.5% of cases. In addition, tonsillectomy was performed in 63.6% of patients, with no complications reported during follow-up, and complete resolution of febrile attacks was observed.

PFAPA is an autoinflammatory syndrome of unknown etiology, with symptoms typically become manifest during the early childhood[9]. In our study, the median age at symptom onset was 21 months, consistent with the literature data[3]. The attacks exhibit a periodicity that can be easily recognized by parents; however, no standardized treatment protocol exists for their management. Corticosteroids represent the main medical option for relieving symptoms during attacks and have been reported to be effective in 85-95% of the cases[2,5]. In our cohort, all patients received corticosteroid therapy during attacks and showed a clinical response. Although this dramatic response is considered an important finding supporting the diagnosis of PFAPA, corticosteroids do not prevent the emergence of new episodes[5,10]. Furthermore, in 45.5% of our study patients an increased frequency of flare-ups was observed following corticosteroid therapy.

Colchicine has been investigated as a potential prophylactic treatment option in PFAPA patients to reduce corticosteroid use and the frequency of febrile attacks[5]. In the literature, response rates to colchicine treatment have been reported to range between 45% and 95.1%[11]. In our study, a reduction in frequency of attacks was observed in 57.1% of patients receiving colchicine. The treatment was well tolerated, and no colchicine-related adverse effects were detected in our study. In contrast, Welzel et al.[12] reported adverse effects associated with colchicine therapy in PFAPA patients which had not necessitated discontinuation of therapy including mild to moderate gastrointestinal symptoms, asymptomatic mild elevations of transaminases, and leukopenia.

In the Turkish population, the prevalence of *MEFV* gene mutations is approximately 20%, whereas in our study,

Table 3. Clinical and genetic characteristics of patients undergoing tonsillectomy

Patient no.	Gender	MEFV genetic test results	Age at tonsillectomy (months)	Type of tonsillectomy	Concurrent adenoidectomy	Postoperative complications	Outcome after tonsillectomy	Follow-up duration after tonsillectomy (months)	Number of attacks after tonsillectomy (previous 6 months)
1	M	Negative	50	Partial	Yes	None	Complete recovery	12	0
2	F	Heterozygous M694V	89	Total	No	None	Complete recovery	12	0
3	F	Negative	56	Total	Yes	None	Complete recovery	24	0
4	F	Heterozygous M694V	60	Total	No	None	Complete recovery	12	0
5	F	Negative	63	Total	Yes	None	Complete recovery	12	0
6	F	Not analyzed	40	Total	No	None	Complete recovery	6	0
7	F	Negative	53	Total	Yes	None	Complete recovery	6	0
8	F	Heterozygous R202Q	49	Total	Yes	None	Complete recovery	12	0
9	M	Heterozygous V726A	97	Total	No	None	Complete recovery	6	0
10	M	Not analyzed	53	Total	No	None	Complete recovery	6	0
11	F	Not analyzed	40	Total	No	None	Complete recovery	9	0
12	M	Heterozygous E148Q	42	Total	Yes	None	Complete recovery	26	0
13	M	Not analyzed	48	Total	No	None	Complete recovery	40	0
14	F	Not analyzed	50	Total	No	None	Complete recovery	24	0

F: Female, M: Male, MEFV: Mediterranean fever

its prevalence rate (50%) among PFAPA patients who underwent genetic testing was markedly higher than observed in the general population[13]. The impact of MEFV mutations on the disease phenotype in PFAPA, particularly with regard to treatment response, has been investigated[11]. Pehlivan et al.[14] reported that PFAPA patients carrying MEFV mutations exhibited a better response to colchicine, whereas Otar Yener et al.[15] found no significant association between MEFV mutation status and treatment response. Özaslan et al.[11] suggested that M694V carriage was the only predictor of colchicine responsiveness. In our study, patients with MEFV mutations did not differ in terms of age at disease onset or attack frequency. CRP levels during attacks were significantly higher in patients with MEFV mutations; however, this finding did not translate into a distinct disease phenotype. Although an increase in attack frequency following corticosteroid use was observed more frequently in patients with heterozygous MEFV mutations relative to those without, but the difference in incidence rates was not statistically significant. Similarly, no differences were found between groups in terms of response to colchicine therapy.

Although PFAPA is considered a self-limiting disease, it has a substantial negative impact on the health status of both children and their caregivers[5]. Rydenman et al.[4] demonstrated that health-related quality of life deteriorates during febrile episodes and that this effect persists even during afebrile periods. In our study, the median interval between PFAPA diagnosis and tonsillectomy was 4 months, reflecting parents' desire to achieve a curative treatment as soon as

possible despite its potential surgical risks. A Cochrane review published in 2019 reported that children may benefit from tonsillectomy; however, only moderate level of evidence has favoured surgical intervention[9].

To date, only two randomized controlled trials have evaluated the efficacy of tonsillectomy in PFAPA[9]. In the first study, complete resolution of postoperative febrile attacks was reported in 63% of patients (12/19), while in the second study, all 14 patients (100%) had achieved remission[16,17]. In other series, rates of complete clinical remission have been reported to range between 74% and 97%[3,14,18-20]. In our study, tonsillectomy alone was performed in 8 patients, while 6 patients underwent concurrent adenoidectomy. Regardless of the type of tonsillectomy, and concurrent adenoidectomy performed, or *MEFV* mutation status, complete recovery was achieved in all patients following surgery.

Study Limitations

The main limitations of our study are its retrospective design and its single-center design. In addition, MEFV genetic mutation analysis was not performed in all patients. The relatively rare occurrence of PFAPA limited the sample size, thereby restricting the generalizability of the findings, particularly with regard to surgical complications.

CONCLUSION

In conclusion, this study demonstrates that tonsillectomy per se or in combination with adenoidectomy, is an effective treatment for controlling febrile attacks in children with PFAPA. Nevertheless, the potential risks of surgery should be carefully communicated to families. Furthermore, the detection of a high frequency of MEFV mutations among the analyzed patients strengthens our view that advances in genetics may contribute to elucidating the pathogenesis of this syndrome.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Local Ethics Committee of University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (decision no: 2025/10-04, date: 29.05.2025).

Informed Consent: Written informed consent was obtained from the parents of all patients.

Declaration of AI Use: AI tools were used for language correction only.

Footnotes

Author Contributions

Concept: Ç.Ö., Design: Ç.Ö., Data Collection or Processing: Ç.Ö., Ö.A.G., Analysis or Interpretation: Ç.Ö., Ö.A.G., Literature Search: Ç.Ö., Writing: Ç.Ö., Ö.A.G.

Conflict of Interest: The authors declare that they have no conflicts of interest associated with this study.

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Original Article

Clinical Characteristics and Factors Associated with Duration of Inpatient Treatment in Female Adolescents with Eating Disorders

Yeme Bozukluğu Tanılı Kız Ergenlerde Klinik Özellikler ve Yatarak Tedavi Süresiyle İlişkili Faktörler

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ABSTRACT

Objective: This study examined the sociodemographic and clinical characteristics of female adolescents with eating disorders receiving inpatient treatment, compared anorexia nervosa (AN) and non-AN eating disorder groups, evaluated changes in depressive symptoms, and identified factors associated with the duration of inpatient treatment.

Method: This single-center retrospective study reviewed the records of 45 female adolescents with eating disorders treated in a child and adolescent psychiatry inpatient unit between July 2021 and May 2026. Patients were categorized into AN and non-AN eating disorder groups. Sociodemographic data, psychiatric comorbidities, risk behaviors, indications of hospitalization, comorbid medical conditions, pharmacological treatment, depressive symptom severity and duration of inpatient treatment were analyzed.

Results: The mean age of the patients was 15.13±1.71 years, and 48.9% had AN. The AN group had lower body mass index and higher rates of amenorrhea/menstrual irregularity, comorbid medical conditions, need for nutritional support, and hospitalization due to weight loss or medical instability. The non-AN group had higher rates of psychiatric comorbidities, cigarette and alcohol use, non-suicidal self-injury, suicide attempts, and hospitalization due to suicidality or non-adherence to treatment. Depressive symptom severity decreased from admission to discharge in both groups. In an exploratory hierarchical regression analysis, depressive symptom severity at admission and indication for hospitalization were associated with the duration of inpatient treatment, whereas diagnostic group was not.

Conclusion: Female adolescents receiving inpatient treatment for eating disorders presented with substantial clinical complexity. Duration of treatment was associated with severity of depressive symptoms and the indication for hospitalization rather than with diagnostic category. These findings provide real-world data from Türkiye and underscore the need for larger-scale prospective studies examining factors associated with treatment course and prognosis.

Keywords: Eating disorders, adolescents, inpatient treatment, anorexia nervosa, hospitalization duration

ÖZ

Amaç: Bu çalışmada, yatarak tedavi gören yeme bozukluğu tanılı kız ergenlerin sosyodemografik ve klinik özelliklerinin incelenmesi, anoreksiya nervoza (AN) ve AN dışı yeme bozukluğu gruplarının karşılaştırılması, depresif belirtilerdeki değişimin değerlendirilmesi ve yatarak tedavi süresiyle ilişkili faktörlerin belirlenmesi amaçlanmıştır.

Yöntem: Bu tek merkezli, retrospektif çalışmada, Temmuz 2021 ile Mayıs 2026 tarihleri arasında bir çocuk ve ergen psikiyatrisi yataklı servisinde yeme bozukluğu nedeniyle tedavi edilen 45 kız ergenin dosya kayıtları incelenmiştir. Hastalar AN ve AN dışı yeme bozukluğu grupları olarak sınıflandırılmıştır. Sosyodemografik veriler, psikiyatrik eş tanılar, riskli davranışlar, yatış endikasyonları, komorbid tıbbi durumlar, farmakolojik tedaviler, çocuklar için depresyon derecelendirme ölçeği puanları ve yatarak tedavi süresi analiz edilmiştir.

Bulgular: Hastaların yaş ortalaması 15,13±1,71 yıl olup, %48,9'u AN tanısına sahipti. AN grubunda beden kitle indeksi daha düşük; amenore/menstrüel düzensizlik, komorbid tıbbi durumlar, beslenme desteği gereksinimi ve kilo kaybı ya da tıbbi instabilite nedeniyle yatış daha sık saptandı. AN dışı grupta ise psikiyatrik eş tanı, sigara ve alkol kullanımı, kendine zarar verme davranışı, intihar girişimi, suisidalite ya

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da tedavi uyumsuzluğu nedeniyle yatış daha sık görüldü. İki grupta da depresif belirtiler yatış süresince azalma gösterdi. Keşifsel hiyerarşik regresyon analizinde, yatış sırasındaki depresif belirti şiddeti ve yatış başlangıcındaki depresif belirti şiddeti ve yatış endikasyonu yatarak tedavi süresiyle ilişkili bulunurken, yeme bozukluğu tanı grubu ile ilişki saptanmadı.

Sonuç: Yatarak tedavi gören yeme bozukluğu tanılı kız ergenler klinik açıdan karmaşık özellikler göstermektedir. Tedavi süresi, tanı grubundan ziyade depresif belirti şiddeti ve yatış endikasyonu ile ilişkili bulunmuştur. Bu bulgular, Türkiye'den gerçek yaşam verileri sunmakta ve tedavi süreci ile prognozla ilişkili faktörlere yönelik daha geniş örneklemli prospektif çalışmalara duyulan gereksinimi desteklemektedir.

Anahtar kelimeler: Yeme bozuklukları, ergenler, yatarak tedavi, anoreksiya nervoza, yatış süresi

INTRODUCTION

Eating disorders are severe psychiatric conditions that commonly emerge during adolescence and are associated with substantial medical and psychiatric morbidities, impaired psychosocial functioning, reduced quality of life, and elevated risk of mortality[1,2]. According to the diagnostic and statistical manual of mental disorders-fifth edition, feeding and eating disorders include several diagnostic categories, such as anorexia nervosa (AN), bulimia nervosa (BN), binge-eating disorder (BED), avoidant/restrictive food intake disorder, pica, rumination disorder, other specified feeding or eating disorder (OSFED), and unspecified feeding or eating disorder (UFED)[3].

A systematic review of prevalence studies published between 2000 and 2018 reported weighted mean lifetime prevalence estimates of feeding and eating disorders as 8.4% in women and 2.2% in men[4]. However, prevalence estimates vary by age group, diagnostic approach, and time frame. A recent systematic review and meta-analysis focusing specifically on children and young people reported a pooled global point prevalence of 5.23% for any eating disorder, with OSFED identified as the most common diagnostic category[5]. Although adolescence is a critical developmental period for the onset and detection of eating disorders, recent evidence also indicates that eating disorders and associated psychiatric comorbid disorders may be observed in younger children[6].

Eating disorders in young people are rarely limited to eating-related symptoms or weight disturbance alone. Psychiatric and medical comorbidities are common and may increase their clinical severity, impair functioning, and complicate treatment planning[7,8]. Common psychiatric comorbidities and risk-related clinical features include anxiety and mood disorders, trauma-related symptoms, substance use disorders, non-suicidal self-injury (NSSI), and suicide-related behaviors[9-11]. Medical complications of eating disorders are often multisystemic, affecting the cardiovascular, gastrointestinal, metabolic, and reproductive systems[7]. Therefore, clinical assessment in adolescents with eating disorders should not be restricted to evaluation of body weight, body mass index (BMI), or medical stability, but should also include psychiatric comorbidity, self-harm, risk of suicide, and adherence to treatment. Accordingly, treatment planning should be holistic and individualized, integrating medical stability, psychiatric risk, severity of symptoms, and response to treatment[12].

Many children and adolescents with eating disorders may be managed in outpatient or less intensive treatment settings when they are medically stable and psychiatric risks can be safely contained. However, inpatient treatment may be necessary in the presence of severe nutritional compromise, rapid weight loss, refusal of oral intake, cardiovascular or metabolic instability, severe psychiatric comorbidity, suicidality, family conflict, or failure of outpatient treatment[13-15]. Inpatient care provides an intensive setting for medical stabilization, nutritional rehabilitation, psychiatric assessment, symptom management, and maintenance of patient safety.

Adolescents requiring inpatient treatment may represent a more severely affected clinical subgroup of patients with eating disorders[16]. In Türkiye, a recent study described a multidisciplinary outpatient follow-up model for pediatric eating disorders and reported improvements in body mass indices and global clinical severity during follow-up[17]. In addition, a retrospective study from Türkiye involving adolescent girls diagnosed with AN found that more than one-third had a history of suicide attempts and approximately 40% had engaged in NSSI[18]. However, real-world data focusing specifically on adolescents requiring inpatient treatment remain scarce.

Therefore, the present study aimed to retrospectively examine the sociodemographic and clinical characteristics, diagnostic distribution of eating disorders, psychiatric comorbidities, indications for hospitalization, and changes in depressive symptom severity in adolescents with eating disorders admitted to a child and adolescent psychiatry inpatient unit in Türkiye. Secondary aims were to compare patients with AN and non-AN eating disorders and to identify factors associated with duration of hospitalization.

MATERIALS and METHODS

Study Design and Setting

This was a single-center retrospective observational study conducted in the Child and Adolescent Psychiatry Inpatient Unit of Dokuz Eylül University. Clinical records of patients hospitalized with a diagnosis of an eating disorder between July 2021 and May 2026 were retrospectively reviewed. To reduce the potential confounding effect of the acute coronavirus disease-2019 pandemic period on hospitalization patterns and clinical characteristics, the study period was restricted to admissions from July 2021 onward.

Participants

The inclusion criteria were hospitalization in the child and adolescent psychiatry inpatient unit during the study period and a documented clinical diagnosis of AN, BN, OSFED/UFED, or BED. The exclusion criterion was discharge at the patient's own request before termination of treatment. The study sample consisted of 45 adolescents who met these criteria and were hospitalized with a diagnosis of an eating disorder during the study period. For patients with more than one hospitalization during the study period, only data from the most recent hospitalization were included in the analyses. All eligible inpatients identified in the records were female. Ages of the study population were recorded in months, and the age range of the patients varied between 134 and 214 months. Diagnoses of eating disorder and comorbid psychiatric conditions were established by child and adolescent psychiatrists based on routine clinical interviews and documented in the medical records.

Since BN, BED and OSFED/UFED subgroups were too small to allow meaningful diagnosis-specific comparisons, patients were classified into AN and non-AN groups for exploratory analyses. The non-AN group comprised patients with BN, BED, or OSFED/UFED. The groups were then compared with respect to their clinical characteristics, psychiatric comorbidities, indications for hospitalization, and duration of inpatient treatment.

Data Sources and Study Variables

Data were obtained through retrospective review of the hospital information management system and medical records of the patients. For each patient, data relevant to sociodemographic characteristics, clinical features, eating disorder diagnosis, psychiatric comorbidities, indications for hospitalization, results of medical consultations, pharmacological treatment, severity of depressive symptoms, and duration of inpatient treatment were recorded.

Sociodemographic variables included the ages of the patients and their parents. Clinical variables included eating disorder diagnosis number of comorbid psychiatric diagnoses, specific psychiatric comorbidities, including major depressive disorder, anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), post-traumatic stress disorder, borderline personality traits, conduct disorder, obsessive-compulsive disorder, and intellectual disability, as well as NSSI, history of suicide attempt, cigarette, alcohol, and substance use, amenorrhea or menstrual irregularity, presence of compensatory behaviors, need for nutritional support during hospitalization, and pre-admission BMI.

The primary indications for hospitalization were classified into four clinical categories as weight loss, medical instability, suicidality, and non-adherence to treatment. Given the limited sample size, these categories were collapsed into a binary variable as weight loss and/or medical instability versus suicidality and/or non-adherence to treatment. Additional medical conditions identified through consultations during hospitalization were also recorded which included electrolyte or acid-base disturbances, endocrine-metabolic conditions, cardiac problems, severe or treatment-resistant malnutrition, and gastrointestinal conditions.

Regarding pharmacological treatment, antidepressant and antipsychotic use during hospitalization were recorded. Antidepressant doses were calculated as fluoxetine-equivalent doses, and antipsychotic doses were calculated as chlorpromazine-equivalent doses.

Assessment of Depressive Symptoms

Severity of depressive symptoms was assessed using admission and discharge scores recorded on the children's depression rating scale-revised (CDRS-R)[19]. Both raw CDRS-R and CDRS-R T-scores were included in the analyses. Changes in depressive symptoms from admission to discharge were examined in the total sample and separately according to diagnostic groups. In addition, the association between changes in depressive symptoms and the duration of hospitalization was evaluated. Change in CDRS-R scores was calculated as admission score minus discharge score; therefore, higher change scores indicated greater reductions in the severity of depressive symptoms during inpatient treatment.

Outcome Measures

Study measures included sociodemographic and clinical characteristics, indications for hospitalization, changes in depressive symptoms, and duration of inpatient treatment. Exploratory analyses compared the AN and non-AN groups and examined factors associated with the duration of inpatient treatment. For this purpose, diagnostic groups, number of comorbid psychiatric diagnoses, indications for hospitalization, and admission CDRS-R raw scores were included in the regression analysis model.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation, and categorical variables as numbers and percentages. Comparisons between the AN and non-AN eating disorder groups were performed using independent-samples t-tests for continuous variables, and chi-square test or Fisher's exact test for categorical variables as appropriate. Non-normally distributed continuous variables and ordinal/count variables were presented as median [interquartile range (IQR)] and compared between groups using the Mann-Whitney U test.

Changes in CDRS-R raw scores and CDRS-R T-scores between admission and discharge were evaluated using paired-samples t-tests. A 2×2 mixed-design analysis of variance was conducted to examine whether changes in depressive symptoms differed according to diagnostic groups. The association between change in CDRS-R scores and duration of the hospitalization was assessed using Pearson correlation analysis.

Hierarchical multiple linear regression analysis was performed to identify factors associated with the duration of inpatient treatment. Diagnostic group and number of comorbid psychiatric diagnoses were entered in the first step, indication for hospitalization in the second step, and admission CDRS-R raw scores in the third step. Due to missing data, the regression analysis was conducted with 43 participants. The level of statistical significance was set at $p<0.05$. Given the exploratory nature of the analyses, p-values were not adjusted for multiple comparisons and should be interpreted cautiously. Effect sizes were reported where appropriate using Cohen's d, partial eta squared and explained variance. Regression assumptions, including multicollinearity, linearity, and residual distribution, were examined before interpreting the final model.

A post-hoc power analysis was conducted for the final multiple regression model using Cohen's f^2, calculated from the model's R^2. In addition, a sensitivity analysis was performed to estimate the minimum detectable effect size for 80% power, given the available sample size, α level, and number of predictors.

Ethical Considerations

This study was conducted as a retrospective chart review. Ethical approval was obtained from the Dokuz Eylül University Non-Interventional Research Ethics Committee (approval number: 2026/08-01, dated: 23.02.2026). Patient data were retrospectively reviewed and anonymized before analysis. The study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.

RESULTS

Sample Characteristics

A total of 45 female adolescents hospitalized with a diagnosis of an eating disorder were included in the study. The mean age of the participants was 15.13±1.71 years, with an age range of 11.17-17.83 years. The mean maternal age was 44.54±6.36 years, and the mean paternal age was 49.24±5.49 years.

Regarding diagnostic distribution, 22 participants were diagnosed with AN, 6 with BN, 16 with OSFED/UFED, and 1 with BED. Accordingly, 22 patients were classified into the AN group, whereas 23 patients into the non-AN eating disorder group.

Additional medical conditions identified through consultations performed during hospitalization were present in 14 patients (31.1%). The most common of them were electrolyte or acid-base disturbances (n=5), endocrine-metabolic disorders (n=4), and cardiac problems (n=3). Other conditions included severe or treatment-resistant malnutrition (n=2) and gastrointestinal conditions (n=1). The demographic and diagnostic characteristics of the total sample are summarized in Table 1.

Comparisons According to Diagnostic Groups

When the AN and non-AN eating disorder groups were compared, no significant difference was found in terms of age. The number of comorbid psychiatric diagnoses was significantly higher in the non-AN eating disorder group than in the AN group [median (IQR): 2.0 (1.0) vs. 0.5 (1.0); Mann-Whitney U=93.00, z=-3.816, $p<0.001$]. The mean pre-admission BMI was significantly lower in the AN group than in the non-AN eating disorder group, 16.42±2.48 versus 26.19±5.00, respectively ($t(27.85)=-7.83$, $p<0.001$).

Table 1. Demographic and diagnostic characteristics of the total sample

Variables	Total sample (n=45)
Sex, female, n (%)	45 (100.0)
Age, years, mean ± SD	15.13±1.71
Maternal age, years, mean ± SD	44.54±6.36[a]
Paternal age, years, mean ± SD	49.24±5.49[a]
Family structure, n (%)	
Intact family	29 (64.4)
Separated/divorced parents	11 (24.4)
Parental loss	3 (6.7)
Unknown	2 (4.4)
Maternal education, n (%)	
Primary/secondary school	7 (15.6)
High school	12 (26.7)
University degree or higher	15 (33.3)
Unknown	11 (24.4)
Paternal education, n (%)	
Primary/secondary school	6 (13.3)
High school	10 (22.2)
University degree or higher	18 (40.0)
Unknown	11 (24.4)
Family history of eating disorders, n (%)	2 (4.4)
Types of eating disorders, n (%)	
AN	22 (48.9)
BN	6 (13.3)
OSFED/UFED	16 (35.6)
BED	1 (2.2)
Indications for hospitalizations, n (%)	
Medical instability	2 (4.4)
Weight loss	16 (35.6)
Suicidality	18 (40.0)
Non-adherence to treatment	9 (20.0)
Additional medical conditions identified during hospitalizations, n (%)	14 (31.1)
Electrolyte/acid-base imbalance	5 (11.1)
Endocrine-metabolic conditions	4 (8.9)
Cardiac problems	3 (6.7)
Severe/treatment-resistant malnutrition	2 (4.4)
Gastrointestinal conditions (gastritis etc.)	1 (2.2)

Data are presented as n (%) or mean ± standard deviation. Percentages were calculated based on the total sample. [a]: Data were available for 41 patients. Because more than one additional medical condition could be present in the same patient, the sum of the subcategories may exceed the total number of patients with additional medical conditions. AN: Anorexia nervosa, BN: Bulimia nervosa, BED: Binge-eating disorder, OSFED/UFED: Other specified or unspecified feeding or eating disorder

Amenorrhea or menstrual irregularity, pre-admission compensatory behaviors, additional medical conditions identified during hospitalization, and the need for nutritional support during hospitalization were also significantly more frequently detected in the AN group

Use of cigarette and alcohol use cigarette and alcohol use NSSI, and a history of suicide attempts were significantly more common in the non-AN group. Substance use did not differ significantly between the groups. Indications of hospitalizations differed significantly between the groups. In the AN group, hospitalization was more commonly due to weight loss and/or medical instability, whereas in the non-AN eating disorder group, suicidality and/or non-adherence to treatment was the predominant indication for hospitalization. Among comorbid psychiatric diagnoses, major depressive disorder, ADHD, and borderline personality traits were significantly more common in the non-AN eating disorder group than in the AN group. No significant intergroup differences were found for anxiety disorders, post-traumatic stress disorder, conduct disorder, obsessive-compulsive disorder, or intellectual disability.

No significant differences were observed between the groups regarding duration of symptoms, age at treatment initiation, time to hospitalization, number of hospitalizations, admission CDRS-R raw scores, or admission CDRS-R T-scores. Similarly, fluoxetine-equivalent antidepressant doses and chlorpromazine-equivalent antipsychotic doses, and duration of inpatient treatment did not differ significantly between the diagnostic groups. Clinical and treatment characteristics according to diagnostic groups are summarized in Table 2.

Changes in Depressive Symptoms from Admission to Discharge

At admission, CDRS-R raw scores were comparable in the AN and non-AN eating disorder groups (54.33±15.73 and 52.55±14.25, respectively). At discharge, mean CDRS-R raw scores decreased to 39.50±14.02 in the AN group and 37.14±13.81 in the non-AN eating disorder group. Similarly, CDRS-R T-scores decreased from 71.05±11.81 to 59.65±12.23 in the AN group and from 70.09±11.25 to 56.73±12.46 in the non-AN eating disorder group.

Among participants with both admission and discharge CDRS-R data (n=42), CDRS-R raw scores decreased significantly from admission to discharge, $t(41)=8.46$, $p<0.001$, Cohen's $d=1.31$. CDRS-R T-scores showed a comparable and significant decrease, $t(41)=8.59$,

Table 2. Clinical and treatment characteristics by eating disorder group				
Variables	**Total (n=45)**	**AN (n=22)**	**Non-AN ED (n=23)**	**p-value**
Clinical characteristics				
Age, years, mean ± SD	15.13±1.71	14.75±1.55	15.49±1.81	0.151
Number of comorbid psychiatric diagnoses, median (IQR)	1 (2.0)	0.5 (1.0)	2.0 (1.0)	<0.001
Pre-admission BMI, mean ± SD	21.30±6.29	16.42±2.48	26.19±5.00	<0.001
Amenorrhea/menstrual irregularity, n/N (%)	16/44 (36.4)	13/21 (61.9)	3/23 (13.0)	0.001
Pre-admission compensatory behaviors, n/N (%)	27/41 (65.9)	17/20 (85.0)	10/21 (47.6)	0.020
Additional medical condition identified during hospitalization, n (%)	14 (31.1)	11 (50.0)	3 (13.0)	0.011
Need for nutritional support during hospitalization, n (%)	15 (33.3)	15 (68.2)	0 (0.0)	<0.001
Risk behaviors and substance use				
Cigarette use, n (%)	5 (11.1)	0 (0.0)	5 (21.7)	0.049
Alcohol use, n (%)	6 (13.3)	0 (0.0)	6 (26.1)	0.022
Substance use, n (%)	1 (2.2)	0 (0.0)	1 (4.3)	1.000
Non-suicidal self-injury, n (%)	25 (55.6)	8 (36.4)	17 (73.9)	0.017
History of suicide attempt, n (%)	23 (51.1)	5 (22.7)	18 (78.3)	<0.001
Indications for hospitalizations				<0.001
Weight loss/medical instability, n (%)	18 (40.0)	17 (77.3)	1 (4.3)	
Suicidality/treatment non-adherence, n (%)	27 (60.0)	5 (22.7)	22 (95.7)	
Comorbid psychiatric diagnoses				
Major depressive disorder, n (%)	26 (57.8)	9 (40.9)	17 (73.9)	0.036
Anxiety disorders, n (%)	10 (22.2)	3 (13.6)	7 (30.4)	0.284
Attention-deficit/hyperactivity disorder, n (%)	6 (13.3)	0 (0.0)	6 (26.1)	0.022
Post-traumatic stress disorder, n (%)	3 (6.7)	1 (4.5)	2 (8.7)	1.000
Borderline personality traits, n (%)	5 (11.1)	0 (0.0)	5 (21.7)	0.049
Conduct disorder, n (%)	3 (6.7)	0 (0.0)	3 (13.0)	0.233
Obsessive-compulsive disorder, n (%)	1 (2.2)	1 (4.5)	0 (0.0)	0.489
Intellectual disability, n (%)	1 (2.2)	1 (4.5)	0 (0.0)	0.489
Illness course and treatment characteristics				
Symptom duration, months, mean ± SD	16.72±12.55[b]	14.41±13.09	19.56±11.57	0.201
Age at treatment initiation, years, mean ± SD	13.78±1.77	13.62±1.56	13.94±1.98	0.571
Time to hospitalization, months, mean ± SD	12.62±10.99[c]	10.00±9.31	15.67±12.23	0.109
Number of hospitalizations, median (IQR)	1 (0.0)	1.0 (1.0)	1.0 (0.0)	0.521
Admission CDRS-R raw score, mean ± SD	53.42±14.85	54.33±15.73	52.55±14.25	0.698
Admission CDRS-R T-score, mean ± SD	70.56±11.41	71.05±11.81	70.09±11.25	0.787
Fluoxetine-equivalent dose, mg/day, mean ± SD (N=42)	42.76±20.63	42.33±19.98	43.24±21.84	0.888
Chlorpromazine-equivalent dose, mg/day, mean ± SD (n=44)	249.98±179.48	238.31±173.91	260.63±187.67	0.685
Inpatient treatment duration, days, mean ± SD	23.33±7.76	24.73±7.42	22.00±8.00	0.243

Data are presented as n (%), n/N (%), mean ± standard deviation (SD), or median [interquartile range (IQR)], unless otherwise indicated. Independent-samples t-tests or Welch's t-tests were used for normally distributed continuous variables, Mann-Whitney U tests were used for non-normally distributed/count variables. Chi-square tests or Fisher's exact tests were used for categorical variables, as appropriate. The p-value for indication for hospitalization refers to the overall comparison of the two collapsed indication categories. Data were missing for 1 patient for amenorrhea/menstrual irregularity and for 4 patients for pre-admission compensatory behaviors. [b]: Data were available for 40 patients. [c]: Data were available for 39 patients. AN: Anorexia nervosa, non-AN ED: Eating disorders other than anorexia nervosa, BMI: Body mass index, CDRS-R: Children's depression rating scale-revised, ADHD: Attention-deficit/hyperactivity disorder, NSSI: Non-suicidal self-injury, PTSD: Post-traumatic stress disorder, OCD: Obsessive-compulsive disorder

$p<0.001$, Cohen's d =1.33. A 2×2 mixed-design analysis of variance was conducted to determine whether changes in depressive symptoms differed by diagnostic groups. For CDRS-R raw scores, the main effect of time was significant, $F(1,40)=69.56$, $p<0.001$, $\eta p^2 =0.64$; however, the interaction between time and diagnostic group was not significant, $F(1,40)=0.007$, $p=0.933$. Similarly, for CDRS-R T-scores, the main effect of time was significant, $F(1,40)=72.02$, $p<0.001$, $\eta p^2 =0.64$, whereas the interaction between time and diagnostic group was not significant $F(1,40)=0.36$, $p=0.552$. These findings indicate that depressive symptoms decreased significantly, and comparably during inpatient treatment of both the AN and non-AN eating disorder groups. Change in CDRS-R raw scores was calculated as admission scores minus discharge scores; thus, higher values indicated greater symptom reduction. A moderate positive Pearson correlation was found between reduction in CDRS-R raw scores and the duration of hospitalization, $r=0.413$, $p=0.007$.

Factors Associated with Duration of Inpatient Treatment

Hierarchical multiple linear regression analysis was conducted to identify factors associated with the duration of inpatient treatment. Diagnostic group and the number of comorbid psychiatric diagnoses were entered in the first step, indication for hospitalization in the second step, and admission CDRS-R raw score in the third step. Due to missing data, the analysis was conducted with 43 participants.

The first model, which included the diagnostic groups and number of comorbid psychiatric diagnoses, did not significantly predict the duration of inpatient treatment, $F(2,40)=0.76$, $p=0.476$, $R^2=0.036$. After indication for hospitalization was included in the model in the second step, the total explained variance increased to 10.4%; however, this increase was not statistically significant, $\Delta R^2=0.068$, $p=0.094$. In contrast, the inclusion of admission CDRS-R raw scores in the third step made a significant contribution to the model, $\Delta R^2=0.181$, $p=0.004$. The final model explained statistically significant variance of 28.6% in the duration of inpatient treatment, $F(4,38)=3.80$, $p=0.011$, $R^2=0.286$.

In the final model, admission CDRS-R raw scores were positively associated with the duration of inpatient treatment, B =0.205, standard error (SE) =0.066, 95% confidence interval (CI) (0.07, 0.34), $\beta=0.429$, $p=0.004$. Indication for hospitalization was also significantly associated with the duration of inpatient treatment, B =-6.98, SE =3.16, 95% CI (-13.37, -0.59), $\beta=-0.492$, $p=0.033$. Since the indication for hospitalization was coded as 0= weight loss/medical instability and 1= suicidality/ treatment non-adherence, the negative B coefficient indicated that hospitalization due to suicidality and/or non-adherence to treatment was associated with a shorter duration of inpatient treatment than hospitalization due to weight loss and/or medical instability. No evidence of problematic multicollinearity was observed in the final regression model, with variance inflation factor values ranging from 1.015 to 2.768.

Based on the final model R^2 of .286, the observed effect size was Cohen's $f^2=0.40$. With 43 participants, four predictors, and $\alpha=0.05$, the post-hoc power analysis indicated adequate power to detect the observed large overall model effect. However, sensitivity analysis showed that the available sample size provided 80% power only for relatively large effects, indicating that smaller but clinically meaningful associations may not have been detected.

The results of the hierarchical regression analysis are summarized in Table 3.

DISCUSSION

The present study characterized a clinically severe and heterogeneous sample of female adolescents with eating disorders admitted to a child and adolescent psychiatry inpatient unit. Patterns of clinical complexity differed across diagnostic presentations. Patients with AN showed greater nutritional and medical compromise, including lower pre-admission BMIs, higher rates of menstrual irregularity and medical comorbidities, and a greater need for nutritional support. In contrast, the heterogeneous non-AN group showed a greater burden of psychiatric comorbidity and higher rates of smoking, alcohol use, NSSI, and previous suicide attempts. Despite these differences, the groups did not differ significantly in terms of admission CDRS-R scores or duration of inpatient treatment. In the exploratory regression model, duration of inpatient treatment was associated with severity of depressive symptoms at admission and indication for hospitalization, but not with diagnostic group or number of comorbid psychiatric diagnoses.

The contrast between the groups may reflect both differences in diagnostic phenotypes and diagnosis-specific pathways leading to psychiatric hospitalization. In AN, low body weight, recent weight loss, nutritional compromise, and physiological abnormalities may make the need for hospitalization more apparent.

Table 3. Hierarchical regression analysis of factors associated with duration of inpatient treatment								
Model/variable	**R^2**	**ΔR^2**	**F**	**B**	**SE**	**95% CI**	**β**	**p-value**
Model 1	0.036	0.036	F(2,40)=0.76					0.476
Diagnostic group				-0.88	2.69	(-6.32, 4.57)	-0.063	0.745
Number of comorbid psychiatric diagnoses				-1.10	1.44	(-4.00, 1.81)	-0.147	0.450
Model 2	0.104	0.068	F(3,39)=1.51					0.226
Diagnostic group				3.11	3.51	(-3.98, 10.20)	0.222	0.381
Number of comorbid psychiatric diagnoses				-0.58	1.43	(-3.49, 2.32)	-0.078	0.686
Indication for hospitalization				-5.96	3.47	(-12.98, 1.05)	-0.421	0.094
Model 3	0.286	0.181	F(4,38)=3.80					0.011
Diagnostic group				4.19	3.19	(-2.27, 10.65)	0.300	0.197
Number of comorbid psychiatric diagnoses				-0.53	1.30	(-3.16, 2.10)	-0.071	0.685
İndication for hospitalization				-6.98	3.16	(-13.37, -0.59)	-0.492	0.033
Admission CDRS-R raw score				0.205	0.066	(0.07, 0.34)	0.429	0.004

The dependent variable was the duration of the hospitalization. The analysis was conducted with 43 participants. Diagnostic group and number of comorbid psychiatric diagnoses were entered in Model 1; hospitalization indication was added in Model 2; and admission CDRS-R raw score was added in Model 3. Diagnostic group was coded as 1= AN and 2= non-AN eating disorder. Hospitalization indication was coded as 0= weight loss/medical instability and 1= suicidality/treatment non-adherence. In Model 2, the addition of hospitalization indication resulted in a non-significant increase in explained variance, ΔR^2=0.068, p=0.094. In Model 3, the addition of admission CDRS-R raw score resulted in a significant increase in explained variance, ΔR^2 =0.181, p=0.004. According to the direction of coding, hospitalization due to suicidality and/or treatment non-adherence was associated with a shorter inpatient treatment duration compared with hospitalization due to weight loss and/or medical instability. AN: Anorexia nervosa, CDRS-R: Children's depression rating scale-revised, SE: Standard error, CI: Confidence interval

Adolescents with non-AN eating disorders, however, may not be underweight and may be hospitalized primarily for indications such as severe depression NSSI, suicide attempts, alcohol or cigarette use, behavioral dysregulation, or non-adherence to treatment. The non-AN inpatient group may therefore represent a particularly high-risk inpatient subgroup rather than the broader population of adolescents with non-AN eating disorders.

Consistent with this interpretation, the non-AN group had higher rates of major depressive disorder, ADHD, borderline personality traits, NSSI, and previous suicide attempts. Previous research has similarly linked ADHD and borderline personality pathology to bulimic and binge-eating presentations[20-22]. However, since the study did not include a comparison group of psychiatric inpatients without an eating disorder, the additional contribution of eating disorder pathology to the need for inpatient treatment could not be determined.

Eating disorders are not clinically homogeneous, and transitions between diagnostic categories may occur over time[23]. Although previous studies have examined shared and diagnosis-specific clinical patterns, their findings have not yielded a consistent account of transdiagnostic similarities and differences[24,25]. OSFED represents the most frequently reported diagnostic group of eating disorders in children and adolescents, also evidenced by recent data from Türkiye[5,26]. Consistent with these reports, OSFED/UFED accounted for most of the non-AN group in the present study (16/23, 69.6%). However, combining BN, BED, and OSFED/UFED into a single group may have concealed clinically relevant differences among these diagnostic groups.

The findings have implications for assessment in general psychiatric settings. Symptoms of eating disorders may be overlooked when adolescents present with depression, anxiety, self-harm, or other psychiatric concerns, particularly in the absence of marked weight loss. Pehlivanturk-Kizilkan et al.[27] found that approximately two-thirds of eating disorder cases among adolescent psychiatric inpatients were not identified during routine clinical interviews and were detected only through systematic screening. Clinicians should therefore assess restrictive eating, binge eating, compensatory behaviors, body-image concerns, and recent weight changes regardless of BMI or presenting complaint.

Duration of inpatient treatment did not differ significantly between the AN and non-AN groups, but this finding should not be interpreted as evidence of equivalent treatment needs. In AN, inpatient care may focus primarily on nutritional rehabilitation, weight restoration, monitoring for refeeding-related complications, and physiological stabilization. In non-AN presentations, greater attention

may be required for NSSI, suicidality, psychiatric comorbidity, behavioral dysregulation, treatment engagement, and planning of safe discharge. Similar periods of inpatient treatment may therefore reflect different forms of clinical complexity rather than comparable treatment content or resource use.

In the final regression model, the duration of hospitalization for suicidality and/or non-adherence to treatment was approximately seven days shorter than that for weight loss and/or medical instability. One possible explanation is that admissions for nutritional compromise or medical instability may require a longer period of time for physiological stabilization and nutritional rehabilitation, whereas some admissions for the management of acute psychiatric risk may focus on crisis containment, safety planning, and transition to outpatient care. This result should nevertheless be considered exploratory. The CI was relatively wide, and clinically distinct indications were combined because of the limited sample size. In addition, indication of hospitalization was not statistically significant before admission CDRS-R score was entered into the model and became significant only in the final step. The estimate may therefore have been influenced by overlap or suppression effects involving severity of depression and indication for admission, as well as instability arising from the modest sample size. Replication in larger samples using more specific hospitalization categories is needed.

Depressive symptom scores were lower at discharge than at admission, with similar levels of improvement in the AN and non-AN groups. This may reflect the combined effects of crisis stabilization, nutritional and psychiatric treatment, and the structured inpatient environment. However, without a comparison group, the improvement cannot be attributed directly to hospitalization or any specific intervention. Higher admission CDRS-R raw scores were associated with longer duration of inpatient treatment, possibly reflecting greater need for psychiatric stabilization among adolescents with more severe depressive symptoms. However, this association may also reflect unmeasured dimensions of clinical severity and therefore should not be interpreted causally.

Eating disorders manifesting firstly in childhood or adolescence may follow persistent or relapsing courses. A recent meta-analysis has reported that approximately 40% of eating disorders identified during adolescence persisted into early adulthood and that relapses occurred in approximately one-quarter of cases[28]. Early recognition and timely treatment may reduce the duration of untreated illness and improve the likelihood of recovery[29]. Longitudinal and transdiagnostic research is needed to identify the clinical, psychiatric, and treatment-related factors associated with prognosis.

Several strengths of the study should be noted. It provides real-world data from a child and adolescent psychiatric inpatient setting in Türkiye, incorporates both medical and psychiatric dimensions of clinical severity, and examines an understudied population requiring intensive treatment. The availability of admission and discharge CDRS-R assessments allowed evaluation of within-admission changes in depressive symptoms. In addition, duration of inpatient treatment was examined using a model that incorporated diagnosis, psychiatric comorbidity, indication for hospitalization, and severity of depressive symptoms rather than relying solely on diagnostic comparisons.

Study Limitations

However, this study has several limitations. The retrospective, single-center design limited control over the completeness and consistency of routine clinical documentation and precluded causal inference. The sample included only female adolescents receiving psychiatric inpatient care, limiting generalizability of the results to male and gender-diverse adolescents, outpatients, and less severely affected clinical populations. Since each the BN, BED, OSFED, and UFED subgroups consisted of small number of patients, they were combined into a heterogeneous non-AN group. Although this strategy enabled us to conduct planned analyses, it may have obscured diagnosis-specific differences. The modest sample size also limited statistical power; therefore, non-significant findings should not be interpreted as evidence of equivalence. BMI-for-age Z-scores or percentiles and standardized measures of symptom severity of eating disorders were not available. Symptoms and risk-related characteristics may have been underdocumented or inconsistently recorded, and duration of inpatient treatment may have been influenced by bed availability, discharge procedures, family circumstances, and access to post-discharge care.

CONCLUSION

In conclusion, medical and psychiatric severity took different forms across eating disorder presentations in this inpatient sample. AN was more strongly associated with nutritional and medical compromise, whereas the non-AN group showed higher rates of psychiatric comorbidity, self-injury, previous suicide attempts, cigarette and alcohol use. Assessment and treatment planning should

therefore integrate nutritional status, medical stability, depressive symptoms, suicidality, self-injury, psychiatric comorbidity, and treatment engagement rather than relying primarily on diagnosis or body weight. Greater attention to non-AN presentations in psychiatric settings may facilitate earlier recognition and more appropriately tailored care for high-risk adolescents.

Ethics

Ethics Committee Approval: This study was conducted as a retrospective chart review. Ethical approval was obtained from the Dokuz Eylül University Non-Interventional Research Ethics Committee (approval number: 2026/08-01, dated: 23.02.2026).

Informed Consent: Retrospective study.

Declaration of AI Use: An AI-assisted tool was used only for English language editing. The authors reviewed and approved the final manuscript and are responsible for its content.

Footnotes

Author Contributions

Surgical and Medical Practices: E.S., M.T.Ö., S.A.G., H.B.B., R.O.Ç., Concept: E.S., S.A.G., H.B.B., R.O.Ç., Design: E.S., S.A.G., H.B.B., R.O.Ç., Data Collection or Processing: E.S., M.T.Ö., R.O.Ç., Analysis or Interpretation: E.S., M.T.Ö., R.O.Ç., Literature Search: E.S., R.O.Ç., Writing: E.S., S.A.G., H.B.B., R.O.Ç.

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Invited Review

The Problem of Using Unconsented Pediatric Health Data in Retrospective Studies

Pediyatrik Verinin İzin Alınmaksızın Retrospektif Çalışmalarda Kullanılabilirliği Sorunu

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ABSTRACT

Retrospective studies are considered among the least harmful clinical studies, since they do not require direct contact with patients. However, as a right that has entered our lives relatively recently, the right to the protection of personal data is a fundamental right and is directly related to the protection of privacy. When considering the data on children, who constitute a vulnerable group, privacy is becoming even more important. Although patients' data, which have long been considered as the hospital's data, have not posed significant problems for ethics committees to date. In particular, the growing interest in retrospective research involving artificial intelligence is sparking debates about the protection of personal data, especially for legacy data collected without consent. While regulations on personal data protection permit the use of data for scientific purposes in certain circumstances, the scope of this authorization remains unclear. So this study aims to offer solutions to this problem in light of the global doctrine by explaining the scope of the regulations regarding the right to the protection of data using a definition-based discussion method, and then makes suggestions in comparison with the ethical principles and the laws of other countries.

Keywords: Data protection, children's data, retrospective studies, patient records, legacy data, ethics committee

ÖZ

Hastalarla direkt temas eden çalışmalar olmadıklarından retrospektif çalışmalar, klinik çalışmalar içerisinde en zararsız olanı olarak değerlendirilmektedir. Ancak yakın geçmişte hayatlarımıza giren kişisel verilerin korunması hakkı, temel haklardan birisidir ve gizliliğin korunması ile direkt olarak alakalıdır. Savunmasız bir grup olan çocukların verileri düşünüldüğünde gizlilik daha da önem arz eden bir husus haline gelmektedir. Yasal düzenlemeler öncesinde hasta dosyası, hastanenin verisi olarak değerlendirildiğinden etik kurullar açısından bu denli sorun teşkil etmemekte idi. Ancak yapay zeka ile yapılan retrospektif çalışmalara yönelim artınca kişisel verilere yönelik sorunlar gündeme gelmeye başladı. Bu konu, özellikle yasal düzenlemeler öncesi dönemde, onam alınmaksızın toplanan hasta verileri açısından tartışmalar noktasında önem arz etmektedir. Yasal düzenlemeler, belirli koşullar altında kişisel verinin bilimsel çalışmalarda kullanımına izin verse de bu iznin kapsamı yasal düzenlemelerde net bir şekilde açıklanmamaktadır. Bu çalışma, yabancı doktrin ışığında bu soruna çözüm önerilerinde bulunabilmeyi amaçlamakta ve bu amacı gerçekleştirebilmek adına kişisel verilerin korunması hakkındaki mevzuatı tanım temelli bir tartışma ile ele almayı ve bu konudaki etik ilkelerle birlikte değerlendirerek bu soruna çözüm önerileri sunabilmeyi hedeflemektedir.

Anahtar kelimeler: Verilerin korunması, çocukların verileri, retrospektif çalışmalar, hasta kayıtları, eskiden kalan veri, etik komite

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INTRODUCTION

Whether the legacy data used in the retrospective studies complies with the legal requirements is a matter of concern for ethics committees. When it comes to the use of children's health data, there is a tendency to approach the matter with greater sensitivity. At this point, there is a misconception that the children's data is considered sensitive. On the other hand, there is also a misconception that retrospective studies are harmless and there is no need for an ethics committee's approval for such harmless studies. If the data in question is legacy data, it means the patient data collected before the regulations

on personal data protection and the recognition of the right to personal data protection, then there is also a misconception that it is the hospital's data to be used[1]. These misconceptions lead to errors in practice, and they can even lead to the ethics committees making erroneous decisions. However, in clinical studies, ethics committees' decisions are the most important ethical instruments in research.

When a literature review is conducted on this question, there are almost no studies addressing it. There is only a study from Switzerland, because there is a special provision on waiver consent. However, there is no study that proposes a general solution to this problem in the light of applicable legal text. This study aims to propose a solution to this problem in light of applicable Turkish law, while also examining the relevant international legal texts. So this study will begin with the term 'retrospective research' and its scope to be able to conclude why ethics committee approval required for these studies and we will examine its relation with the personal data protection. Then we will discuss the legal status of health data, especially children's health data, in comparison with the legal status of pre-regulation data. After that, we will discuss the legal status and the availability of unconsented legacy data in the retrospective studies. After discussing the ethical dimension of this situation, we will conclude this study with the suggested legal solutions for this problem.

Retrospective Research

Retrospective studies are conducted by investigating previous patient records already present in the database to achieve a specified outcome[2]. These are purely observational studies and do not alter existing patient records[3,4] or require the acquisition of new data. These studies are quite important in medical research because they help confirm discoveries or facts in medical sciences[5]. In these studies many types of personal health data can be used such as laboratory test results, diagnostic, medications, treatments, demographics, etc.[6]. There are two types of retrospective studies: cohort studies and case-control studies. Cohort studies are made by observing one or more groups' data, while case-control studies are made with the data of those who have the specific diseases or of the "specific cases"[4].

Retrospective Research and Health Data Protection

In short, the right to the protection of personal data as we know it today was fully recognized and detailed in 1995 with the adoption of the European Data Protection Directive (95/46/EC). Then the right evolved into its current form in 2016 with the adoption of the General Data Protection Regulation (GDPR)[7].

Even though Türkiye had signed the European Council Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data in 1981, no action had been taken on this matter until 2010[8]. The right to protection of personal data was recognized in 2010 with the amendment made in Article 20 of the Turkish Constitution, which regulates the right to privacy. During the European Union candidacy process, to meet the harmonization requirements[9], Türkiye adopted the EU's then-current regulation on personal data protection, namely the European Convention for the Protection of Individuals about Automatic Processing of Personal Data (Convention no. 108) dated 1981. Thus, Türkiye enacted the Turkish Law on Protection of Personal Data (Turkish Law no. 6698/ KVKK) in 2016, just before the GDPR was adopted in the EU. However, amendments to the KVKK were made in 2024 to comply with the GDPR. Although both regulations are similar on fundamental issues, it is impossible to say that there are no differences.

As retrospective studies are based on patients' personal health data, they raise questions regarding legal regulations on the protection of personal data[10]. While personal health data are regulated under the special category of personal data in both regulations these data require special protection such as explicit consent of the data subject for processing. However, health data must be used in accordance with the purpose explained to the patient when obtaining consent to collect their health data. In retrospective studies, as we mentioned earlier, stored health data are used. That means many of these records were collected years ago, maybe even before the regulations came into force, and there might be no way to reach the patient to obtain their consent for the usage of their personal health data, which was collected maybe decades ago. In the following sections of this study, we will address these issues in depth.

Legal Framework of Pediatric Health Data Protection

Legal Characteristics of Children's Personal Health Data

Even though there are no specific regulations in either domestic (KVKK) or international law (GDPR) regarding the protection of children's personal data, both regulations include special provisions for the protection of health

data. Both regulations recognize health data as a special category of personal data. That means processing health data requires specific conditions, and these data must be protected more strictly. If one of these specific conditions is not met, personal health data cannot be processed. These specific conditions regulated in KVVK are explicit consent of the data subject, expressly provided for by the laws, necessity for the protection of life or physical integrity of the person himself/herself or of any other person, who is unable to explain his/her consent due to the physical disability or whose consent is not deemed legally valid, processing of personal data of the parties of a contract is necessary, necessity for compliance with legal obligation, data have been made public by data subject, necessity for protection of any right, necessity for the legitimate interests pursued by the data controller. However, the special conditions regulated by the GDPR are not that different from those in the KVKK.

When it comes to children's health data, the main focus is on who has the authority to give consent to its processing. In many legal systems as it is in Türkiye, children cannot take legal action by themselves. So their parents have legal authority to act on behalf of their children. That is why there are no special regulations regarding legal authority to give consent for the children. However, GDPR has a special regulation for the authorization of children at least 16 years old to give consent for the processing of their own personal data. Nevertheless, there are no such exceptions in Turkish law. Nonetheless, parents can access their children's health data according to Turkish law.

Pre-regulation Characteristics of Collection of Personal Health Data

In 1995, the predecessor to the GDPR, Directive 95/46/EC, recognized personal health data as a special category of personal data. Before that, there was no distinction between personal data and personal health data, and both were generally evaluated under the right to privacy of personal life[11]. There is no difference in the pre-regulation period of Turkish law, too. However, health data were collected in accordance with the legal requirements for creating patient records and stored in accordance with the archiving regulations during the pre-regulation period of Turkish law. Nevertheless, there have been some personal data protection crimes regulated in the Turkish Penal Code, such as recording of personal data, illegally obtaining or disclosing data, failure to destroy data, violation of privacy, violation of the confidentiality of communication, and eavesdropping and recording of conversations between people[12]. Besides, when it comes to health data, there are crimes and remedies for violations of the physician's obligation to keep secrets[12].

Applicability of Personal Data Regulations to Previously Collected Data

Non-retroactivity of laws is one of the main principles of Turkish law. This principle is a requirement for legal certainty[13]. However, both KVKK and GDPR do not tend to evaluate pre-regulation data as an acquired right. KVKK has a transitional provision about this matter. According to KVKK's temporary article 1: "Personal data that is processed before the date of publication of this Law shall be rendered compliant within two years following the date of publication of this Law. Personal data that is determined to be contrary to the provisions of this Law shall be immediately deleted, destroyed, or anonymized. However, the consents that are lawfully obtained before the date of publication of this Law shall be deemed lawful in terms of this Law, provided that no declaration of intention to the contrary is made within one year." On the other hand, GDPR has no transitional provision on this matter, but among the recitals, there is a similar provision as "Processing already underway on the date of application of this Regulation should be brought into conformity with this Regulation within the period of two years after which this Regulation enters into force." Where processing is based on consent pursuant to Directive 95/46/EC, the data subject doesn't need to give his or her consent again if the manner in which the consent has been given is in line with the conditions of this Regulation, to allow the controller to continue such processing after the date of application of this Regulation. Directive 95/46/EC shared a similar perspective on this matter, but the Directive's main focus of the adaptation process was on the digitalization of physical data.

When it comes to health data, in the pre-regulation period, these data were collected in compliance with the current legal requirements. For example, article 72 of Turkish law no. 1219 regulates a legal requirement for physicians to maintain patients' records. The Operating Regulations of Inpatient Treatment Institutions of the Turkish Ministry of Health also establish a legal requirement for inpatient treatment institutions to create and store patient files. There are also official instructions from the Ministry of Health on the archival obligations of healthcare institutions. Besides, collecting health data for treatment is also a requirement for the treatment agreement to be performed.

Data Collected Before Personal Data Regulations Without Valid Consent

The main issue with medical retrospective studies is the legitimacy of pre-regulation-collected health data. The main cause of this problem is that data was collected for treatment purposes and not for research. Besides, these data might be collected without consent under the circumstances of that day. In this section, we will address this issue while using the "legacy data" term in a legal context, and we will discuss relevant issues such as re-contacting data subjects for consent, purpose limitation, use of personal health data, and the legal bases for ongoing data processing.

Legal Status of Legacy Data

The term "Legacy Data" may have different meanings across various disciplines[14]. The main definition of the term is the data collected from disused information systems. In the legal context, we can define the term as the data collected before regulations about personal data protection, even before the protection of personal data was recognized as a right, or briefly, data collected in the pre-regulation period. Today, these data are generally still stored due to institutions' legal archiving requirements. However, these data cannot be considered to have been collected in compliance with KVKK because these data were not collected based on the data subject's explicit consent, as we understand it today in the context of KVKK. Nevertheless, explicit consent is not the primary condition for the legality of processing personal health data. The other relevant conditions are: "If it is expressly provided for by law; if it is necessary for the protection of public health, preventive medicine, medical diagnosis, treatment and care services, or the planning, management, and financing of health services, by persons or authorized institutions and organizations who are under an obligation of confidentiality." Under these conditions, legacy health data can be accepted as compliant with the KVKK. However, this matter must be handled with care. If the retention period specified by the regulation has expired, this data cannot be accepted as lawful. Further, there is also a problem with the limited purpose of usage of these data. Because legacy health data were generally collected for the treatment of the patient, they were not collected for academic purposes. So this secondary use would conflict with the KVKK's limited-purpose usage condition. At this point, Article 28 of KVKK comes to the rescue. This article says that: "Processing of personal data for the purposes of official statistics and, through anonymization, research, planning, statistics, and similar purposes, this Law shall not be applied." However, for such use, the data must be anonymized.

The Principle of Processing Data for Specific, Explicit, and Legitimate Purposes and the Fitness for Purpose

Both GDPR and KVKK specify the main principles for personal data processing. Both regulations share similar principles, but the GDPR addresses them in greater detail. In this section, we will not address all of these principles but only the principles that are relevant to this section. These are: the principle of processing data for specific, explicit, and legitimate purposes and the principle of processing data to the purpose for which data are collected.

Lack of Explicit Consent

In accordance with the principle of processing data for specific, explicit, and legitimate purposes, personal data cannot be collected for an undefined purpose. That means data controllers cannot collect personal data just in case it might be needed someday[15]. That's why the data controller must determine certain purposes for the data collection and processing, and this specific purpose must be known clearly to the data subject[16]. When it comes to anonymized data, there is no issue regarding this obligation. However, non-anonymized data cause huge problems in this context. Hence, Turkish law allows researchers to use anonymized health data in their research. Nevertheless, it is not clear whether Turkish law permits researchers using non-anonymized health data. Because Turkish regulation on this matter explicitly allows the use of anonymized data in research, while there is no regulation regarding non-anonymized data. However, there's also a provision which allows "Processing of personal data for the purposes of art, history, and literature or science, or within the scope of freedom of expression, provided that national defense, national security, public safety, public order, economic safety, privacy of personal life or personal rights are not violated." This provision is unclear regarding non-anonymized data. When comparing these two regulations, we can conclude that anonymized health data can be used for scientific research in all cases. In contrast, non-anonymized data can only be used in accordance with the data subject's fundamental rights. However, this conclusion also raises some questions, such as: "What does usage in accordance with fundamental rights mean?", "Does this mean usage with informed consent?". If we must respect the data subject's fundamental rights, obtaining informed consent may be the right path to follow. However, the Council of Europe recommends that "the law may provide for the processing of health-related data for scientific research without the data subject's consent." This recommendation is based on the public interest in the research. However,

this recommendation is being criticized in the doctrine as suggesting that even if consent is not required for the processing of its health data for scientific research, the data subject must be granted the right to request that its data be excluded from research[17].

Swiss law permits explicitly researches using non-anonymized data without consent under some conditions, which are: ethics committee approval, research's precedence over patient confidentiality, impossibility of re-contacting with the patient, patient's awareness that their data may be used for research, and no objections about it, and maintaining strict confidentiality of the patient's data. Nevertheless, Swiss law suggests researchers use anonymized data as possible[18].

Processing Limited to the Purpose (Data Minimization)

Principle of processing limited to the purpose or briefly data minimization principle is actually the second branch of the principle of processing data for specific, explicit, and legitimate purposes[19]. Because first, the data controller must specify the data collection purpose and this purpose must be legal and then this purpose must be explicitly explained to the data subject. After collecting the data, data controller must process this data in accordance with the collection purpose. This principle has quite importance for both regulations (GDPR and KVKK). However, both regulations also allow the data processing for compatible purposes with the specified collection purpose. Yet, the meaning of the term "compatible purposes" is unclear in both regulations[20]. Actually this allowance is grounded in practicality[16]. Therefore the unclarity of the provision brings its own questions of the application. That's why some authors have attempted to make this principle understandable by breaking it down into its components[21].

When it comes to scientific researches, there is an exemption regulated in GDPR as[22]: "Further processing for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes shall, in accordance with Article 89(1), not be considered to be incompatible with the initial purposes ('purpose limitation')." Nevertheless, even though KVKK has not regulated this exception, it has already an exemption provision for scientific researches/purposes.

Ethical Dimension

When it comes to the use of personal health data, compliance with ethical principles is just as important as compliance with legal rules. In this regard, international documents serve as an important reference point. When it comes to ethical principles for medical researches, the main document on this matter is the Declaration of Helsinki of World Medical Association (WMA). This declaration states that ethical principles stated in this document includes "research using identifiable human material or data. "This statement implies that unidentifiable (anonymized) human data is beyond the scope of this declaration. These ethical principles stated in the Declaration as follows: "The primacy of protecting the patient's health, patient's dignity and fundamental rights (such as protection of privacy, physical and mental well-being, etc.); generation of knowledge to understand the causes and the impacts of the illnesses and to develop a treatment and prevention methods and to advance human health; lawfulness; sustainability; research capability; protection of vulnerable people/groups/communities; compensation of the damages; proportionality (a research must be conducted if the importance of its impact has outweighs its risks and burdens); compliance with scientific principles; preparation of a detailed research protocol; ethics committee approval; informed consent based on free will; usage of best-practice methods; research registration and publication."

Another text on this subject is the Belmont Report, which was the result of the topic that drew attention following the Nuremberg trials. This report, emphasizes fundamental ethical principles such as respect for human, beneficence and justice. In addition, the report lists the applications must be done to implement these principles as follows: Informed consent, assessment of risks and benefits and the selection of research subjects.

In addition to the Belmont Report, there are also ethical guidelines for Health-related Research Involving Humans of Council for International Organizations of Medical Sciences in collaboration with the World Health Organization. These guidelines also emphasize general ethical principles on this matter such as; respect for fundamental rights, research's consistency with the community's health needs and priorities, equitable distribution, evaluation of potential risks and benefits of the research, choice of control in clinical trials, caring for participants' health needs, community engagement, collaborative partnership, informed consent, collection, storage and use of biological material and health data, reimbursement and compensation, protection of vulnerable groups, public accountability, establishing research ethical committees. These guidelines support broad informed consent for unspecified future use however, it requires that certain conditions be met as;

patient must be informed that its health data can be used in a future research and if the patient has no objection for the future use then researcher can use the patient's health data in a possible research. Nevertheless, the patient must always be granted the right to withdraw their consent. In addition if these data would be used without consent, then the ethics committee should evaluate the importance of the research and the risks of this situation. Besides, these guidelines allow researchers to use online obtained health-related data too, but under some conditions to be met. First, researcher must contact and obtain the informed consent of the data subject, if it is impossible to access to the data subject then the researcher must obtain the permission of the owner of the online platform. Additionally, researcher must ensure the privacy protection and take measures to prevent the data from being linked to an individual. Finally, the researcher must provide a detailed explanation in the research protocol of how these data will be used and how risks will be managed. These guidelines also address the topic of research involving children and adolescents. According to these guidelines, research involving children and adolescents require the consent of their parents. If the child reach the legal age of maturity, then the child's consent must also be obtained. The researches involving children and adolescents should be conducted only if it will benefit them. Otherwise, the research should primarily focus on adults.

Ethical Justification for Using Legacy Data

According to these international documents which set ethical principles for medical researches, there is no ethical problem for anonymized data to be used in the studies whether it is consented or not. However, the problems arise on using non-anonymized data. When it comes to multicenter retrospective studies, the issue of transfer of patient's data to a third party without the patient's knowledge arise. Thus, respect for fundamental rights and autonomy principles would be infringed[1]. Even if the contact info of the patient's would be shared with the third parties for the purpose of obtaining consent, it would also be an infringement on the respect for privacy[18].

At this point, it is up to the ethics committee to evaluate the ethical conditions are met in this situation. First of all, evaluation of the importance of this study and its benefits given the risks involved must be considered by the ethics committee. The broader consent option must be also considered, that means if the possibility of the future usage of the health data had been told to the patient in that time and the patient had not objected to this situation. These are the acceptable conditions under these ethical principles. However, when it comes to protection of privacy, especially for the multi central studies, re-contacting with the patient option must be seriously considered. If it is impossible to re-contacting with the patient, for example if the patient is deceased in the time of study, then ethics committee shall give authorization which would be considered as "substituted consent"[18]. Otherwise, avoidance of the contacting the patient on the assumption that they would not consent is not an acceptable situation under ethical principles[18] and the ethical committee should not accept this occasion. Nevertheless, to avoid encountering such difficult-to-resolve situations, the use of anonymized data should always be prioritized and encouraged.

Role of Ethics Committees in Retrospective Studies

The origin of the concept of an ethics committee, as we know it today, attributed to the Declaration of Helsinki. According to the declaration, research protocol must be submitted to a transparent, independent and competent research ethics committee for an approval. Apart from the Declaration of Helsinki, there is Directive 2001/20/EC of the European Parliament which took its final form in the light of the Helsinki Declaration. This directive includes the official definition of the 'ethics committee' as "An independent body in a Member State, consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent." Further, the ethics committee's core mission is described as outweighing the risks and anticipated benefits in the following provisions of the directive and also the evaluation of the ethical breaches can be rise during the research[1]. Besides, the directive regulates that a clinical trial can only be initiated with the approval of the ethics committee.

In Türkiye, as a general regulation on ethics committee, there is a Regulation on Clinical Trials. However the retrospective studies are excluded from this regulation and this regulation, regulates ethics committees for interventional clinical trials (including drugs, bioequivalance and other interventional clinical trials). There are non-interventional ethics committees for

non-interventional studies, especially for observational studies in Türkiye[23]. There is also a regulation about non-interventional studies under the name of "Regulation on Clinical Research on Traditional and Complementary Medicine Practices." According to this regulation, the scope of this kind of studies are "clinical research of drugs, medicinal and biological products to be conducted on human beings, clinical research on cosmetic products and their raw materials, observational drug studies, medical device clinical research, observational medical device studies, stem cell clinical research, non-interventional clinical research, and traditional and complementary medicine practices." This regulation specifies the core duty of the non-interventional ethics committee as assessing the anticipated benefits and forecasted risks of the submitted researches and also the compliance of the research with ethical principles. This regulation have a special provision for the studies on children and according to this provision, ethical committee cannot evaluate the research on children without the positive opinion of a pediatrician or a child psychiatrist on the submitted research and without the informed consent of parents of the children and additionally of the children if the children is capable of giving consent. However, the children must be informed about the research too. There is also a prohibition on persuasive incentive or financial offer to ensure the child's participation to the study. Among the general principles of the research regulated in this regulation, there is a principle of publishing only anonymized results of the study.

Suggestions for Legal Compliance of the Usage of Unconsented Legacy Data

When it comes to unconsented legacy data, the usage of anonymized data should always be preferred. While the term anonymization means to remove identifying information from the data[24] and to make the data unidentifiable by all means, the researcher must ensure that the anonymized data cannot be linked to a real person under no circumstances and must take all necessary measures in this regard. However it is worth noting that while AI systems use big data to work, even if the data has been anonymized, there is still a risk that could be link to a real person by matching with other data in the big data[25,26]. So, the researcher makes sure that the anonymized data must be unidentifiable with the real people by all means and must choose a reliable anonymization method for that reason. Additionally, the researcher whose study would include AI technologies, ensure that preferred AI technology might not be able to identify the anonymized data's data subject. Besides, the researcher must explain the anonymization method and the AI technology would be used in the study in detail in the research protocol that would be submitted to the ethics committee. Even if the usage of the anonymized data is a safe heaven from both a legal and ethical standpoint, the research is still requires the approval of ethics committee. There are some guidelines of the Committee on Publication Ethics based on case studies and according to these guidelines while referring to the WMA's Declaration of Taipei, all of the researches involving human beings require an ethics committee approval[27].

When it comes to the usage of unconsented legacy data non-anonymized, it must be the last resort and under some requirements to be met. In this regard, relevant Swiss regulation for waiver of informed consent for research on non-anonymized data, serves as a useful guide. For a lawful and ethical waiver of informed consent, the study must have significant benefits, as exceeding the patient's interests for confidentiality, it would be impossible to reach to the patient and this impossibility must be justified in the research protocol, patient must be informed for the future use of its health data in a potential research when the data were collected and the researcher must ensure the protection for the privacy of the data subject. When it comes to multicentral research, contacting the patient has become even more important, since the personal data would be shared with the third parties. In our view, in that situation, whoever collected the data must contact the patient to obtain permission to share with third parties. These suggestions are also applicable from the perspective of Turkish law. While it is unclear that the usage of the non-anonymized and unconsented legacy data is permitted for scientific purposes according to the Turkish law, the relevant regulation prioritizes the protection of privacy and fundamental rights in such situation. It is also important to remember that Turkish law only permits to anonymized publication of the result of the study.

CONCLUSION

Since the retrospective studies are observational studies, they differ from other types of medical research. Furthermore, because they do not include direct intervention with the patient's body, they are generally considered the least ethically problematic[28]. So that there are some authors that criticize ethical committees to be too strict to discourage conducting retrospective studies[5]. However, this is a misleading assumption. Because the personal data is among the most valuable assets of a person. It is also relates to the person's private

life. A breach of personal data also constitutes a violation of privacy. Such a situation would also cast a doubt on public confidence in the healthcare system.

While the right to personal data protection was recognized as a right in 1995, it took its current form following the regulations introduced in 2016. It is worth noting that while there are some important provisions about health data, there is no special provision on children's data. Since the health data is regulated as special category of personal data under these regulations, protection of health data requires special protection and special conditions to be processed. While processing the health data is subject to strict rules, regulation allows to the usage of the health data in scientific studies. However, while the usage of the anonymized health data in the scientific researches is allowed clearly, there is a lack of clarity in the use of non-anonymized health data in the scientific research. Nevertheless, the regulations prioritize the data subjects' fundamental rights regarding their personal data.

When it comes to legacy data, there is no doubt that the data can be used in retrospective studies as long as the data anonymized. On the other hand, while there is lack of clarity in the usage of the non-anonymized and unconsented legacy health data, there are some ethical principles and some regulations of other countries that might be the guide on this matter. Upon examining these, the following examinations can be drawn: The research must have a significant importance in the light of the risks it poses to the individual's rights; it must be impossible to re-contact to the patient to obtain its consent[1] and it must be justified in the research protocol; while collecting the data, the patient must be informed about the possibility of the future use of their data in scientific purposes, and there should be no objection to this; and there must be the ethics committee approval, which serves as a substituted consent. Besides, it is important to note that if the child had reached the legal maturity age by the time the study was conducted, then the parents' consent is not enough. However, the use of the anonymized data should be the priority, while the use of non-anonymized data should be a last resort. Finally, it should not be forgotten that Turkish law does not allow non-anonymized data to be published as the result of a scientific research.

Declaration of AI Use: This declaration does not apply to the use of basic tools for checking grammar, spelling, or references (such as Mendeley, EndNote, Zotero, and others). If there is nothing to declare, there is no need to add a statement.

Footnotes

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