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Case Reports

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Original Articles

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Original Article

ChatGPT-4o's performance in detecting diffusion restriction on brain MRI of neonates with hypoxic-ischemic encephalopathy: Does clinical information influence diagnostic interpretation?

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ABSTRACT

Objective: Hypoxic-ischemic encephalopathy is a major cause of neonatal morbidity and mortality. Diffusion-weighted imaging plays a key role in early diagnosis. With the increasing interest in large language models like ChatGPT, it is important to evaluate their potential in radiological interpretation. The aim of this study was to assess the diagnostic performance of ChatGPT-4o in identifying diffusion restriction on neonatal brain Diffusion-weighted imaging (DWI) and to determine whether clinical information (Thompson score) influences its diagnostic responses.

Material and Methods: This retrospective study included 36 neonates (18 with and 18 without diffusion restriction) who underwent brain DWI MRI between postnatal days 4 and 7. For each case, representative DWI and Apparent diffusion coefficient (ADC) images were uploaded to ChatGPT-4o in five separate sessions. The same process was repeated after adding the Thompson score. Performance was evaluated using sensitivity, specificity, Positive predictive value (PPV), Negative predictive value (NPV), Odds ratio (OR), Fleiss Kappa, and McNemar test.

Results: Without clinical information, sensitivity was 56.7%, specificity 90%, PPV 85%, and NPV 67.5% (OR; 11.77). With the Thompson score, sensitivity increased to 72.2%, specificity to 91.1%, PPV to 89%, and NPV to 76.6% (OR; 26.65). Intra-observer agreement was very high (without vs. with Thompson score; κ= 0.825 vs. κ= 0.920). McNemar test showed a statistically significant difference (p=0.045) after clinical data were included.

Conclusion: ChatGPT-4o showed high specificity and moderate sensitivity in detecting diffusion restriction on DWI. Clinical information significantly influenced diagnostic responses, highlighting both the potential and limitations of large language models (LLMs) in radiology.

Keywords: Artificial intelligence, diffusion-Weighted imaging, hypoxic-ischemic encephalopathy, large language models, neonatal MRI

Introduction

Hypoxic-ischemic encephalopathy (HIE), resulting from perinatal asphyxia, is a significant cause of morbidity and mortality in neonatal intensive care units. The incidence of HIE is approximately 2.5 per 1000 in term births without abnormalities and around 7 per 1000 in preterm births (1,2). Neuroimaging plays a critical role in the diagnosis, prognosis, and management of HIE. While USG, CT, and MRI are all part of the diagnostic imaging, MRI provides superior sensitivity and specificity compared to the others (3). Diffusion-weighted imaging (DWI), in particular, is more sensitive in detecting acute brain injury and enables early diagnosis and timely intervention (4).

Recent progress in large language models (LLMs) such as ChatGPT has generated interest in their potential application to radiology, a field that heavily relies on visual data. LLMs have been the subject of numerous studies in radiology practice, particularly in areas such as clinical decision-making, workflow optimization, structured report generation, and enhancing patient communication (5-9). Although various studies have evaluated the performance of different LLMs, the majority predominantly focus on different versions of ChatGPT, which is widely used in daily practice. Among these models, ChatGPT-4o (GPT-4 Omni) was developed by OpenAI (San Francisco, California, USA) and publicly released on May 13, 2024. While ChatGPT-

4o has been investigated for its potential in interpreting radiological images across various domains, no study to date has assessed its performance in detecting diffusion restriction on DWI MRI for the diagnosis of HIE. However, prior research has demonstrated that the inclusion of clinical information can significantly influence the image interpretation of LLMs (10-12).

The aim of our study was to evaluate the performance of ChatGPT-4o in detecting diffusion restriction on neonatal brain DWI MRI, as well as to assess how the inclusion of clinical information influences its image interpretation. In this context, the study also explored the potential impact of integrating LLMs into the radiology workflow and investigated how future developments in this field might affect diagnostic processes

Materials and Methods

This retrospective descriptive study included neonates who were admitted to Izmir Tinaztepe University Private Buca Hospital tertiary-level neonatal intensive care unit between January 2023 and December 2024, received wholebody therapeutic hypothermia due to moderate-to-severe HIE, and had diffusion-weighted MRI scans performed between postnatal days 4 and 7. All MRI scans were acquired using a 1.5 Tesla system (GE Healthcare SIGNA HDe). The Thompson scores obtained from all patients were recorded within the first four hours postnatally.

Total 42 brain diffusion MRI scans from patients diagnosed with moderate-to-severe HIE were initially reviewed. Due to image artifacts that adversely affected image quality, 6 scans were excluded. The final sample consisted of 18 patients with normal MRI findings and 18 patients with diffusion restriction consistent with HIE. To minimize the effect of the small sample size, each image was assessed at five different time points, resulting in a total of 90 diffusion MRI images with normal findings and 90 with diffusion restriction being analyzed.The flow chart of the study is shown in Figure 1.

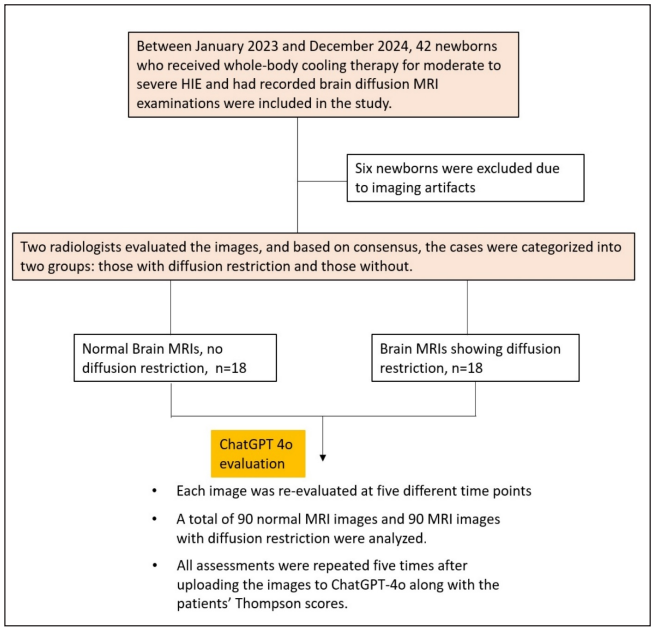

Figure 1: The flowchart of the study.

MRI scans were independently reviewed by two radiologists to determine the presence of diffusion restriction. As both radiologists obtained identical results for all patients, an interobserver agreement analysis was not performed. Based on these evaluations, the infants were divided into two groups: those with diffusion restriction and those without diffusion restriction. Since all patients with diffusion restriction demonstrated lesions in the periventricular white matter, the most representative slices from this region were selected for the diffusion restriction group. To ensure methodological consistency, slices including both lateral ventricles and the periventricular white matter were also selected in the group without diffusion restriction. All images were automatically saved in JPEG format by the hospital's PACS system.

First, the prepared DWI trace images were uploaded to ChatGPT-4o with the question "Can you tell me which MR sequence is this?" to evaluate its ability to recognize the sequence (Figure 2A). Then, the ADC map of the same patient was uploaded with the question "I am sending the ADC map of the same patient. Are there any diffusion restrictions in the images? If so, in which location of the brain?" to assess whether it could detect diffusion restriction (Figure 2B). The following prompt was entered into ChatGPT-4o for the evaluation conducted after providing the clinical information: 'I will send the Thompson score, which is an indicator of the neurological status, along with the diffusion MRI and ADC maps of the newborn patient. Could you please indicate whether there is diffusion restriction?' (Figure 2C, D). For each patient, a separate session was initiated to avoid any influence from previous image assessments. The images of each patient were evaluated five times at one-week intervals. All assessments were repeated five times after uploading the images to ChatGPT-4o along with the patients' Thompson scores. The results obtained with the clinical information included were recorded.

Based on the collected data, sensitivity, specificity, positive predictive value, negative predictive value, and odds ratio were calculated to evaluate the performance of ChatGPT-4o in detecting diffusion restriction. Intra-observer agreement across the five repeated responses provided by ChatGPT-4o for each case was assessed using the Fleiss Kappa method. The McNemar test was used to determine whether there was a significant difference between the responses given before and after the inclusion of the Thompson score. All statistical analyses were performed using IBM SPSS Statistics version 26.

Results

In the first task, which involved identifying the uploaded MR sequence, ChatGPT-4o correctly recognized all

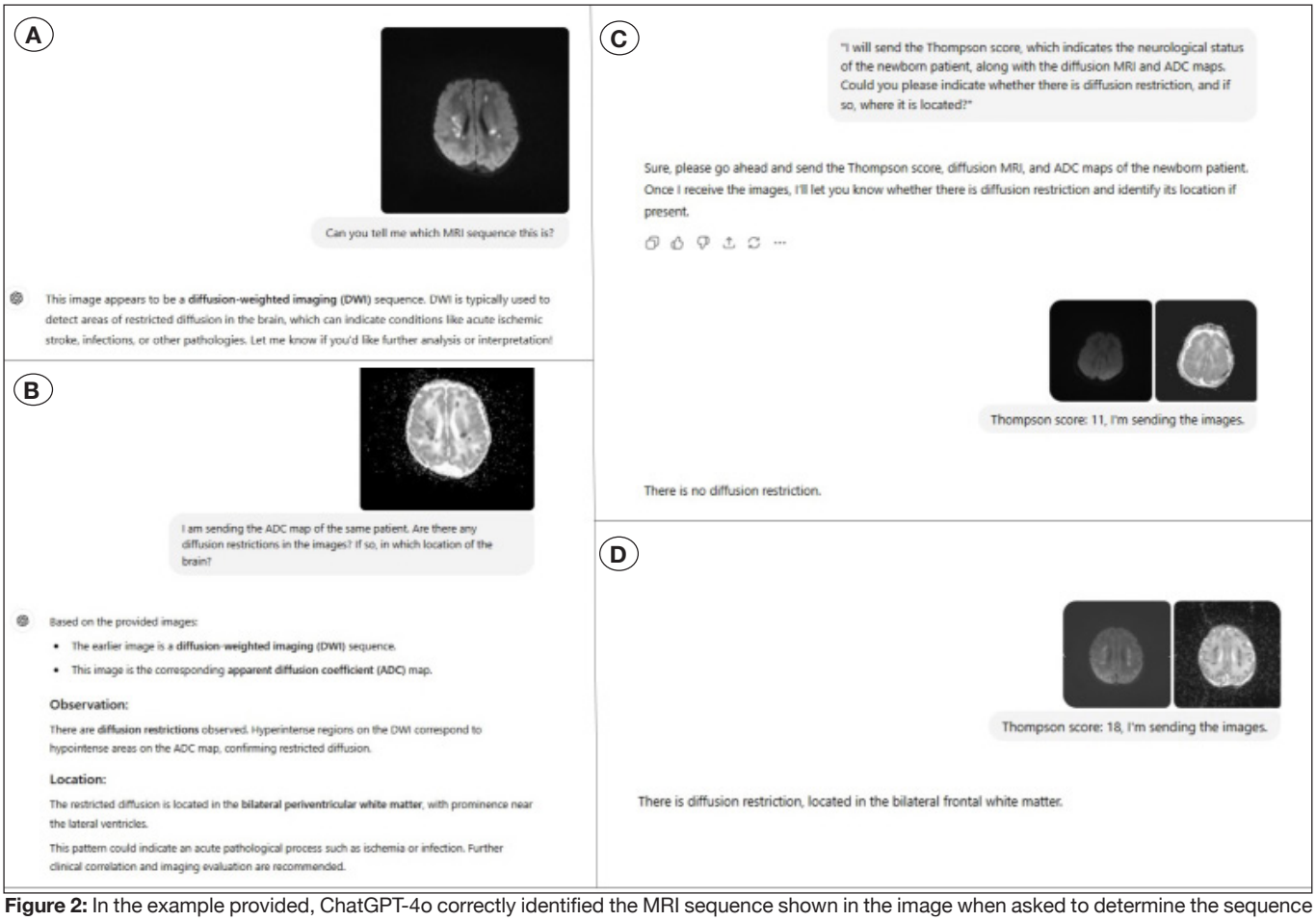

Figure 2: In the example provided, ChatGPT-4o correctly identified the MRI sequence shown in the image when asked to determine the sequence type **(A)**. In the second question directed to ChatGPT-4o, the model correctly identified diffusion restriction in the periventricular white matter **(B)**. Example case without **(C)** and with **(D)** diffusion restriction evaluated by ChatGPT-4o using the prompt provided with the Thompson score.

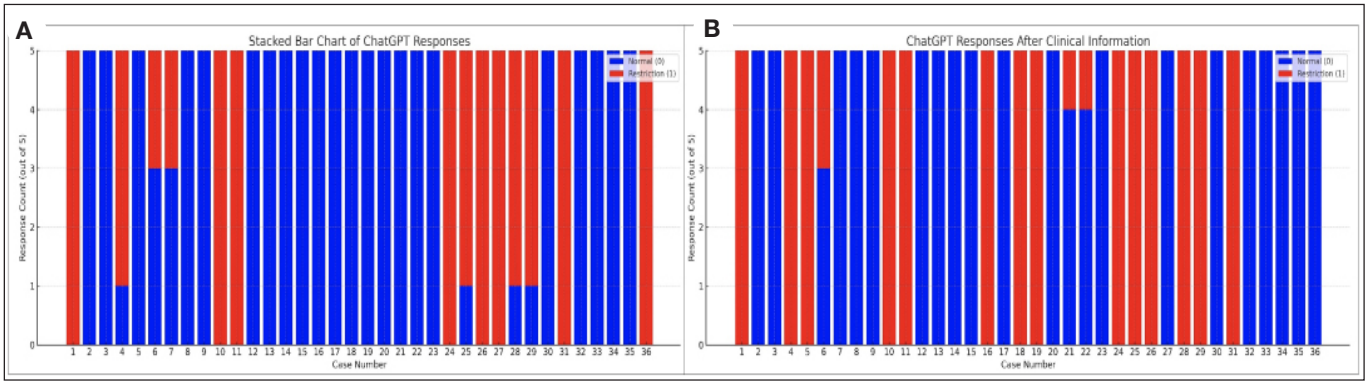

Figure 3: The responses provided by ChatGPT-4o across five repetitions for each case, without **(A)** and with **(B)** Thompson scores.

sequences. For the evaluation of diffusion restriction, ChatGPT-4o identified 51 out of 90 images with diffusion restriction as true positives, and 81 out of 90 normal images as true negatives. However, 9 normal images were classified as false positives, and 39 images with diffusion restriction were classified as false negatives. Based on the evaluation results, the sensitivity of ChatGPT-4o was found to be 56.7% (CI: 46%–67%). The specificity was determined as 90% (CI: 84%–96%). The positive predictive value (PPV) was 85% (CI: 76%–94%), and the negative predictive value (NPV) was 67.5% (CI: 59%–76%). The calculated odds ratio (OR) was 11.77.

After re-evaluating all images with the addition of Thompson scores, the model's sensitivity was found to be 72.2% (CI: 62%–81%). Specificity was determined as 91.1% (CI: 84%–97%). PPV was 89.0% (CI: 81%–96%), and the NPV was 76.6% (CI: 68%–85%). The calculated OR was 26.65 (Table I).

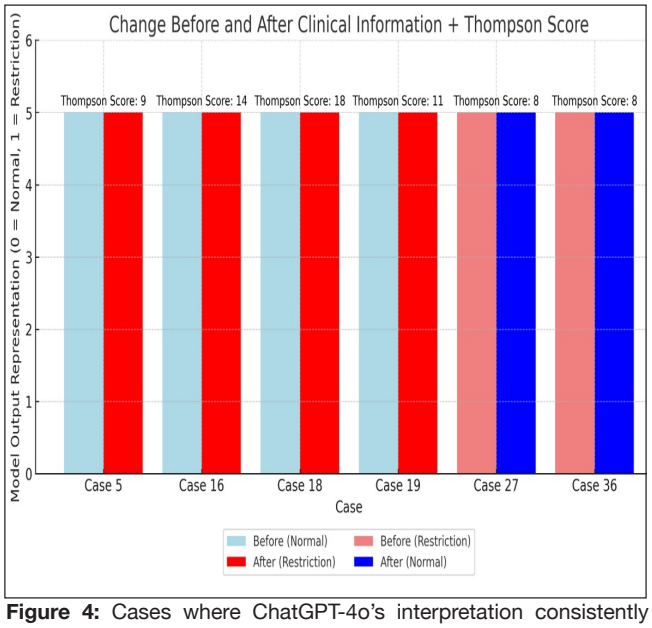

Figure 4: Cases where ChatGPT-4o's interpretation consistently changed in all five repeated evaluations after the inclusion of Thompson scores.

The responses before and after the inclusion of the Thompson scores were compared using the McNemar test. The responses provided by ChatGPT-4o showed a statistically significant change after clinical information was added (p=0.045).

The intra-observer agreement of ChatGPT-4o was assessed using the Fleiss Kappa test. When evaluations were performed based solely on imaging, the agreement was calculated as 0.825 (95% CI: 0.765–0.885), indicating a very high level of consistency (Figure 3A). After the addition of clinical information in the form of Thompson scores, the agreement further increased to 0.920 (95% CI: 0.880–0.960), reflecting a high level of level of consistency (Figure 3B). Cases with responses that changed after the clinical information was provided are shown in Figure 4.

Discussion

The main findings of this study indicate that ChatGPT-4o demonstrates moderate sensitivity (56.7%) and high specificity (90.0%) in detecting diffusion restriction on DWI MRI images. When clinical information (Thompson score) is incorporated, the model's sensitivity increases significantly to 72.2%, while specificity remains high at 91.1%. These results suggest that ChatGPT-4o is substantially influenced by the clinical context during image interpretation.

Although LLMs such as ChatGPT have only been publicly available for a few years, they have already become the focus of numerous studies in the field of radiology due to the wide variety of imaging modalities and the ease of access to data. In a study by Kuzan et al. (13), which evaluated diffusion restriction in the diagnosis of acute stroke, ChatGPT-4 achieved an accuracy rate of 79.5%. In a study conducted by Zhang et al. (14), aiming to evaluate intracranial hemorrhages on brain CT scans, ChatGPT-4 demonstrated an overall detection accuracy of 79.6% across all hemorrhage types, reaching up to 89% specifically in cases of epidural hematoma. In a study by Ozenbas et al. (15) which evaluated the performance of ChatGPT-4o in identifying MRI characteristics and making differential diagnoses of brain tumors the model achieved accuracy rates ranging from 79.5% to 88.3% for certain characteristic features including signal properties, perilesional edema and contrast enhancement. However its performance was found to be low in determining lesion localization and in distinguishing between intra-axial and extra-axial lesions. In a study conducted by Lacaita et al. (16), ChatGPT-4o detected pathologies with an accuracy of 72% on abdominal X-ray images and 66.1% on chest X-ray images. In recent studies, the relatively high diagnostic accuracy achieved by LLMs is considered promising for the future. The continual emergence of new applications and the ongoing updates of existing ones will inevitably further enhance these success rates. In addition to this positive outlook, there are also studies indicating that the integration of LLMs into clinical practice is not yet realistic. In a study by Hager et al. (17), which included 2400 real patient cases and a dataset covering four common abdominal pathologies, it was demonstrated that large language models performed significantly worse than physicians in making diagnoses, failed to follow diagnostic and treatment algorithms, and were unable to interpret laboratory results accurately. In addition, studies have shown that LLMs can generate incorrect yet convincing information and may produce potentially harmful outcomes such as ethical, legal, and privacy concerns, as well as hallucinations (18,19). However, it is important to remember that the LLMs evaluated in these studies were not originally designed for diagnostic purposes; rather, they were initially developed as text-based language models. In the field of radiology, in addition to AI programs specifically developed for diagnostic purposes, we believe that LLMs, given their wide accessibility and lower financial barriers, may also serve as valuable supportive tools within the diagnostic process.

There are several critical issues, such as bias and prejudice, that must be thoroughly investigated before adapting artificial intelligence and LLMs into medical diagnostic processes. In a study by Zack et al. (20), which evaluated biases in GPT-4's diagnostic decision-making, the authors demonstrated that the model's clinical decisions were influenced by race and gender information, and that it may propagate or even reinforce harmful societal biases. Schmidt et al. (21). demonstrated in their study that, when making diagnostic decisions, ChatGPT was more influenced by the patient's medical history compared to resident physicians. In our study, a significant difference was observed between the responses provided by ChatGPT-4o when diagnosing based solely on imaging and when additional clinical information was provided. Among patients with HIE, in some cases with

Tablo I: Comparative presentation of ChatGPT-4o's responses based on imaging alone and after the addition of clinical information (Thompson score) in terms of sensitivity, specificity, positive and negative predictive values (PPV, NPV), odds ratio (OR) and Fleiss Kappa coefficient results

	Sensitivity*	Specificity*	PPV*	NPV*	OR	Fleiss Kappa
Image-Based Evaluation	56.7 (46–67)	90.0 (84–96)	85.0 (76–94)	67.5 (59–76)	11.77	0.825
With Thompson Score	72.2 (62–81)	91.1 (84–97)	89.0 (81–96)	76.6 (68–85)	26.65	0.920

***:** *% (CI %)*

high Thompson scores indicating greater clinical severity, the model reported the presence of diffusion restriction after receiving clinical information. Conversely, in two patients with low Thompson scores, the model indicated no diffusion restriction following the provision of clinical data. Our findings are consistent with studies showing that clinical context can affect LLM interpretations. For example, Huppertz et al.(11) reported better accuracy for ChatGPT-4 when clinical information was provided, and Horiuchi et al. (10). found that ChatGPT-4 performed better with text-based clinical data than with images alone. Our study adds to this evidence by showing measurable changes after including the Thompson score in neonatal DWI for HIE. Although radiologists themselves may sometimes be influenced by clinical information during image interpretation, the detection of diffusion restriction in our study represents a relatively straightforward diagnostic task. The statistically significant difference observed in this limited patient sample raises important concerns regarding the clinical integration of current LLM versions in diagnostic workflows.

An important factor in the diagnostic process is repeatability. In a study by Frangi et al. (22), which evaluated emergency department triage, a 21% variation was observed across 30 repeated runs for each combination, indicating low repeatability. In a study by Khatri et al. (23) investigating medication-related information queries, the authors found that when the same prompts were tested on different days, ChatGPT-3.5 achieved an accuracy ranging from 10% to 30%, while ChatGPT-4 achieved an accuracy ranging from 40% to 60%, demonstrating limited reproducibility. Similarly, in a study by Krishna et al. (24) using a radiology board-style examination, both ChatGPT-3.5 and ChatGPT-4 demonstrated moderate intrarater agreement. By contrast, Lacaita et al.(16) reported a high level of intraobserver agreement in their study evaluating ChatGPT-4o's performance in interpreting chest and abdominal X-ray images. In our study, a high level of intraobserver agreement was observed both in evaluations based solely on imaging and in those where clinical information was provided. The varying results regarding reproducibility reported in the literature may be attributable to factors such as differences in imaging modalities, the complexity of the diagnostic tasks, the extent of the LLMs' prior exposure to the investigated imaging types, and differences between model versions. From the perspective of integrating LLMs into medical decision support systems, reproducibility must be systematically improved to ensure reliability for both patients and healthcare professionals.

The primary limitations of our study include its single-center and retrospective design. Although each image was evaluated at five different time points to increase the total number of assessments, the relatively small patient population may limit the generalizability of the findings. Another limitation is the repeated-measures design. Since each patient's images were evaluated five times, the McNemar test included non-independent observations, which may have led to an overestimation of statistical power. The study focused exclusively on ChatGPT-4o, a widely used and popular LLM, and did not compare its performance with other LLMs or artificial intelligence applications specifically developed for medical imaging. The results, therefore reflect the performance of this particular version, and it should be noted that future updates or emerging developments may influence these outcomes. Furthermore, although the most demonstrative slices were selected for evaluation, the analysis was performed based on single representative images rather than complete imaging series, which may not fully reflect routine radiological practice.

Conclusion

Our study demonstrates that ChatGPT-4o achieved notably high specificity in detecting diffusion restriction on brain DWI scans for the diagnosis of HIE. A key finding of this study is the significant improvement in diagnostic performance following the inclusion of clinical information, which raises important concerns regarding potential bias and prejudice. Despite these concerns, the increasing accessibility and widespread adoption of LLMs suggest that they may hold substantial promise as diagnostic support tools in radiology. However, future studies involving larger and more diverse patient populations, as well as the inclusion of additional influencing factors, are necessary to further evaluate the reliability, objectivity, and clinical utility of LLMs in medical imaging.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Izmir Tınaztepe University (December 5, 2024, reference number: MUKCE2024/79).

Contribution of the authors

Conception: OC - Design: OC; IB - Supervision: IB -Materials: OC; IB - Data Collection and/or Processing: OC; IB - Analysis and/or Interpretation: OC; IB - Literature: OC; IB - Review: OC; IB - Writing: OC- Critical Review: IB. All authors reviewed the results and approved the final version of the article.

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Conflict of interest
The authors declare that there is no conflict of interest.

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Original Article

C-reactive protein as a predictor of complication and hospital stay in pediatric appendicitis: Role of inflammatory biomarkers

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ABSTRACT

Objective: Acute appendicitis (AA) is a leading cause of pediatric abdominal pain requiring surgical intervention. Differentiating simple appendicitis (SA) from complicated appendicitis (CA) preoperatively remains a clinical challenge. This study aimed to evaluate the diagnostic and prognostic utility of routinely available inflammatory markers—including C-reactive protein (CRP), fibrinogen, immature granulocyte (IG) count and percentage, neutrophil-to-lymphocyte ratio (NLR), and mean platelet volume (MPV)—in children with AA.

Material and Methods: This retrospective study included pediatric patients (<18 years) who underwent appendectomy for AA between January 2020 and December 2022. Patients were categorized as having SA or CA based on intraoperative and histopathological findings. Preoperative laboratory parameters were compared between groups. Spearman correlation and regression analyses were performed to assess associations with complication status and hospitalization duration.

Results: A total of 94 patients were included (mean age: 12.1±3.6 years; 63.8% male). CA was identified in 9 patients (9.6%). CRP levels were significantly higher in the CA group (p = 0.043) and independently predicted complications (OR: 1.018, 95% CI: 1.005–1.032, p =0.009). CRP was moderately correlated with both hospital stay (r =0.369, p <0.001) and fibrinogen levels (r =0.525, p <0.001). In multivariate linear regression, CRP remained a significant predictor of prolonged hospitalization (β =0.365, p =0.002), while fibrinogen did not. IG count, IG percentage, NLR, and MPV were not significantly associated with complication status or hospital stay.

Conclusion: CRP is a practical and reliable marker for predicting both complicated appendicitis and prolonged hospitalization in children. Fibrinogen is associated with disease burden but lacks independent predictive value. IG%, NLR, and MPV did not demonstrate clinical utility in this cohort. CRP may aid in preoperative risk stratification and postoperative care planning in pediatric AA.

Keywords: Appendicitis, C-reactive protein, fibrinogen, inflammatory markers

Introduction

Acute appendicitis (AA) is one of the most common causes of abdominal pain and emergency surgical intervention in children (1–3). Although most cases present as simple appendicitis (SA), a significant proportion may progress to complicated appendicitis (CA), characterized by perforation, gangrene, or intra-abdominal abscess formation. Preoperative differentiation between SA and CA is critical for guiding timely surgical intervention, anticipating potential complications, and determining the length of hospital stay (4).

In pediatric patients, where the clinical presentation can often be atypical or nonspecific, reliance on laboratory parameters becomes especially important. Traditional inflammatory biomarkers—such as white blood cell (WBC) count, absolute neutrophil count (ANC), neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein (CRP)—have been widely used to aid diagnosis and assess disease severity (5–7). Among these, CRP is often highlighted for its moderate predictive value in identifying CA, although its diagnostic accuracy may vary depending on the timing of measurement and patient age.

More recently, attention has turned to hematological markers that can be obtained automatically without requiring additional tests or blood draws. One such parameter is the immature granulocyte (IG) count and percentage, which reflects the early release of granulocytic precursors (promyelocytes, myelocytes, metamyelocytes) into the bloodstream during systemic inflammatory responses (8–10). Several studies have suggested that elevated IG values may have diagnostic and prognostic value in infectious and inflammatory diseases such as sepsis, urinary tract infections, and intra-abdominal infections, including appendicitis (9-11).

Despite promising findings in some reports, the diagnostic performance of IG percentage in distinguishing between SA and CA in children remains uncertain. Variation in sample size, patient age, and definition of complication severity may contribute to inconsistent results across studies (11-13). Therefore, there is still a need for further observational data, particularly from real-world, smaller-scale pediatric cohorts.

In this study, we aimed to evaluate the distribution and potential clinical relevance of several inflammatory markers—including CRP, WBC, ANC, NLR, MPV, IG count, and IG percentage—in pediatric patients with AA. In addition, we assessed length of hospital stay as a clinical outcome measure to further explore its association with disease severity. Although the number of complicated cases in our sample is limited, we sought to observe whether meaningful trends could be identified and compared to patterns described in the literature. We hypothesized that CRP and other inflammatory markers could serve as reliable predictors of complicated appendicitis and prolonged hospital stay in children.

Materials and Methods

This retrospective study was conducted in the Pediatrics and Pediatric Surgery units of two tertiary care centers in Tokat, Türkiye. Pediatric patients under the age of 18 who underwent surgery with a preoperative diagnosis of acute appendicitis between January 2020 and December 2022 and were histopathologically confirmed to have acute appendicitis were evaluated using electronic medical records

Patients were included if they had undergone surgery for suspected acute appendicitis and had available preoperative laboratory parameters including complete blood count (CBC), C-reactive protein (CRP), fibrinogen, and immature granulocyte (IG) values. Patients were excluded if they had chronic inflammatory diseases (e.g., inflammatory bowel disease, autoimmune disorders), hematological malignancy, ongoing infection other than appendicitis, or if they had received antibiotics prior to hospital admission. Patients with normal appendix on histopathological examination were also excluded.

Patients were classified into two groups based on intraoperative findings and histopathology reports:

- Simple appendicitis (SA): including catarrhal and phlegmonous appendicitis
- Complicated appendicitis (CA): including perforation, abscess formation, gangrene, or the presence of intra-abdominal fecaliths

Demographic data including age, sex, and length of hospital stay (in days) were recorded. Preoperative laboratory parameters including white blood cell (WBC) count, neutrophil and lymphocyte counts, immature granulocyte (IG) count and percentage, CRP, fibrinogen, mean platelet volume (MPV), and neutrophil-to-lymphocyte ratio (NLR) were collected from hospital records. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.

IG values were measured using an automated hematology analyzer (Sysmex XN-1000, Sysmex Corporation, Kobe, Japan), which detects promyelocytes, myelocytes, and metamyelocytes as part of the IG cluster.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as mean and standard deviation or median (minumum-maximum), depending on the data distribution. Categorical variables were presented as frequency and percentage.

The Mann–Whitney U test was used to compare laboratory parameters between the simple and complicated appendicitis groups. Spearman correlation analysis was used to assess the relationship between inflammatory markers and length of hospital stay. Logistic regression was performed to identify predictors of complicated appendicitis, and linear regression analysis was used to evaluate factors associated with hospitalization duration. A $p < 0.050$ was considered statistically significant.

Results

A total of 94 pediatric patients who underwent surgery for acute appendicitis were included in the study. Of these, 85 patients (90.4%) were classified as having simple appendicitis, and 9 patients (9.6%) as complicated appendicitis. The mean age of the patients was 12.1±3.6 years, with a male predominance (63.8% male, 36.2% female).

When comparing laboratory parameters between the two groups using the Mann–Whitney U test, C-reactive protein (CRP) levels were significantly higher in the complicated appendicitis group ($p = 0.043$). Additionally, the length of hospital stay was significantly longer in the complicated group ($p = 0.001$).

No statistically significant differences were observed between the groups in terms of age ($p = 0.742$), WBC count

Table I: Comparison of laboratory parameters between simple and complicated appendicitis groups

Parameter	Simple Appendicitis*	Complicated Appendicitis*	p†
Age (years)	12.0 (4–18)	12.0 (7–15)	0.742
WBC (10^9/L)	15.3 (4.3–34.2)	16.9 (10.3–21.7)	0.546
ANC (10^9/L)	12.0 (2.65–29.6)	14.6 (9.3–22.1)	0.507
IG	0.07 (0–0.54)	0.08 (0.01–0.22)	0.682
IG (%)	0.50 (0.1–3.6)	0.80 (0.2–1.9)	0.795
NLR	7.34 (1.1–31.7)	9.1 (2.7–16.2)	0.708
Fibrinogen (mg/dL)	333.3 (33.3–586.2)	390.7 (241.0–481.2)	0.419
MPV (fL)	9.20 (7.4–12.8)	8.9 (7.8–10.6)	0.289
CRP (mg/L)	28.5 (0.1–149.0)	115.7 (10.4–149.0)	0.043
Length of Stay (days)	2.0 (1–12)	3.0 (2–7)	0.001

***:** *median (min–max),* **†:** *Mann–Whitney U test.* ***WBC:** white blood cell count, **ANC:** absolute neutrophil count, **IG:** immature granulocyte, **NLR:** neutrophil-to-lymphocyte ratio, **MPV:** mean platelet volume, **CRP:** C-reactive protein*

Table II: Spearman correlation coefficients between laboratory parameters and hospital stay / complication status

Variable	Hospital Stay		Complication Status	
	r	p*	r	p*
CRP	0.369	< 0.001	0.215	0.042
Fibrinogen	0.358	0.001	0.087	0.422
IG	–0.046	0.669	–0.044	0.684
IG%	–0.059	0.585	0.028	0.797
NLR	0.083	0.432	0.039	0.710
MPV	–0.063	0.548	–0.111	0.292

***:** *Spearman's rho correlation coefficients,* ***IG:** immature granulocyte, **NLR:** neutrophil-to-lymphocyte ratio, MPV: mean platelet volume, **CRP:** C-reactive protein.*

Table III: Logistic regression for complicated appendicitis

Predictor	OR (Exp(B))	95% CI	p
CRP	1.018	1.005–1.032	0.009
Fibrinogen	1.005	0.997–1.013	0.219

***CRP:** C-reactive protein*

Table IV: Linear regression for hospital stay

Predictor	β (Standardized)	B (Unstd.)	p	Model Type
CRP	0.470	0.018	<0.001	Univariate
Fibrinogen	0.360	0.007	0.001	Univariate
CRP	0.365	0.014	0.002	Multivariate
Fibrinogen	0.161	0.003	0.168	Multivariate

***CRP:** C-reactive protein, **Model R^2 (multivariate) =** 0.222, **Adjusted R^2 =** 0.203*

(p =0.546), absolute neutrophil count (p =0.507), immature granulocyte count (p =0.682), IG percentage (p =0.795), NLR (p =0.708), fibrinogen (p =0.419), or MPV (p =0.289). The median values and ranges of each parameter by group are presented in Table I.

Spearman correlation analysis showed a moderate positive correlation between CRP and both length of hospital stay (r =0.369, p <0.001) and fibrinogen levels (r =0.525, p < 0.001). Similarly, fibrinogen was moderately correlated with hospitalization duration (r =0.358, p =0.001). A strong positive correlation was also observed between IG percentage and IG count (r =0.897, p <0.001); however, neither showed any significant association with hospital stay or complication status. Other parameters, including NLR and MPV, were also not significantly correlated with clinical outcomes (p >0.050 for all) (Table II).

Univariate logistic regression revealed that CRP was a significant predictor of complicated appendicitis (OR: 1.018, 95% CI: 1.005–1.032, p =0.009), whereas fibrinogen was not (p =0.219) (Table III). Regarding hospitalization duration, both CRP (β =0.470, p <0.001) and fibrinogen (β =0.360, p=0.001) were found to be positively associated in univariate linear regression. In multivariate analysis including both markers, only CRP remained statistically significant (β =0.365, p =0.002), while fibrinogen did not (p =0.168) (Table IV).

Discussion

Acute appendicitis is the most common surgical emergency in children and can progress from a benign inflammatory process to a severe, complicated condition involving perforation, abscess, or gangrene. Identifying markers that accurately predict disease severity is essential for optimizing management and improving outcomes.

In this study, CRP emerged as both the most reliable diagnostic and prognostic biomarker. CRP levels were significantly higher in complicated cases and independently predicted complication status in univariate logistic regression (OR =1.018; 95% CI:1.005–1.032; p=0.009). CRP also showed a moderate positive correlation with hospital stay (r =0.369; p <0.001) and remained an independent predictor of prolonged hospitalization in multivariate linear regression (β = 0.365; p = 0.002). These results are consistent with Beltran

et al. (14), who reported that CRP >80 mg/L predicted perforation with high sensitivity (82%) in children , and Xharra et al. (15), who found CRP >50 mg/L significantly correlated with abscess formation.

The biological context for CRP's predictive power lies in its acute-phase regulation by interleukin6 (IL6), which elevates rapidly after tissue injury or bacterial invasion (16). IL6, along with interleukin1β (IL1β) and tumor necrosis factorα (TNFα), induces hepatocyte synthesis of CRP, which then facilitates complement activation and opsonization (17). In complicated appendicitis, transmural inflammation, neutrophil infiltration, and bacterial translocation accentuate cytokine release, leading to sharply elevated CRP and fibrinogen levels (16,17).

Fibrinogen, another acute-phase reactant, was moderately correlated with both CRP ($r = 0.525$; $p < 0.001$) and hospital stay ($r = 0.358$; $p = 0.001$), reflecting its role in clotting and inflammation. Although it failed to be an independent predictor in logistic regression, its elevation likely represents a response to endothelial activation and systemic inflammation driven by IL6 and IL1β (18). Alvarez et al .(19) similarly reported increased fibrinogen in perforated appendicitis, though its predictive value diminished when adjusted for CRP.

We assessed immature granulocyte (IG) count and percentage as early hematologic markers. IGs surge in the marrow during systemic inflammation and are measurable by modern hematology analyzers (20). Güngör et al. (21) previously demonstrated that elevated IG% could predict complicated appendicitis in children (AUC = 0.78). However, in our cohort neither IG nor IG% correlated with complications or hospital stay—despite their strong internal correlation ($r = 0.897$; $p < 0.001$). This discrepancy may be due to differing analyzer thresholds, sample timing relative to symptom onset, or the small number of complicated cases limiting statistical power.

Neutrophil-to-lymphocyte ratio (NLR) has been studied widely in both adult and pediatric AA, with some series demonstrating NLR >5 as a predictor of perforation (22,23). Mechanistically, stress-induced neutrophilia and lymphopenia produce a high NLR, reflecting systemic inflammation. However, our study did not support NLR as a reliable marker, perhaps due to variability in immune response among children or early presentation before peak leukocyte changes. This lack of correlation may also be explained by the relatively small number of complicated cases, reducing statistical power and masking potential associations.

Similarly, mean platelet volume (MPV) has been proposed as a marker of platelet activation in inflammation (24). High MPV may indicate heightened cytokine-mediated platelet production. Yet, we found no association between MPV and complication status or hospital stay, reinforcing the inconsistent reliability of this marker in AA.

From a pathophysiological standpoint, complicated appendicitis follows a sequence: mucosal ulceration → transmural necrosis → wall perforation → peritoneal contamination. Neutrophil infiltration and bacterial translocation trigger a cytokine cascade dominated by IL1β, TNFα, and IL6 (16,17). IL6 stimulates acute-phase protein synthesis (CRP, fibrinogen), while IL1β/TNFα contribute to local capillary dilation and tissue injury (17). Lysozyme and protease release by neutrophils may also facilitate abscess formation. As such, CRP and fibrinogen rise rapidly and correlate with both clinical severity and systemic recovery time.

Importantly, our findings highlight that CRP's prognostic utility extends beyond diagnostic discrimination to clinical management. Its correlation with hospital stay duration suggests that this routinely available marker may guide expectations for postoperative recovery, antibiotic duration, and discharge planning—a potential benefit corroborated by Yüksel et al. (25), who found elevated CRP predicted prolonged recovery in pediatric AA .

Strengths of our study include its focus on a pediatric population with preoperative laboratory data and validated outcomes, comprehensive analysis of multiple biomarkers, and use of robust statistical methods including multivariate modeling. Nonetheless, limitations must be acknowledged: the retrospective, single-center design carries inherent bias; the number of complicated cases was small; and laboratory sampling timing was variable. Additionally, while IL1β and TNFα were not measured directly, their known role in the inflammatory cascade provides a pathophysiologic basis for our findings.

Conclusion

CRP remains the most practical and reliable indicator of both complicated appendicitis and hospital stay duration in children. Fibrinogen correlates with disease burden but lacks independent predictive strength, and emerging markers such as IG%, NLR, and MPV were not significant in our cohort. Importantly, the clinical implications of these findings suggest that CRP could be incorporated into perioperative decision-making: higher CRP levels may help identify children at greater risk of complications, guide the urgency of surgical intervention, inform the intensity and duration of antibiotic therapy, and aid in planning discharge timing. Future prospective multi-center studies should seek to determine optimal CRP thresholds and explore integrated biomarker panels that might include cytokines or IG metrics, to enhance early risk stratification and tailor pediatric appendicitis management.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Tokat Gaziosmanpasa University (03.06.2021, reference number: 83116987-506).

Contribution of the authors

Study conception and design: AİÇ, SC; data collection: SC; analysis and interpretation of results: AİÇ, SC; draft manuscript preparation: AİÇ, SC. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

The relationship between body image, self-esteem, and body mass index in primary school children

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ABSTRACT

Objective: With the increasing prevalence of childhood obesity, there is a growing interest in understanding how the ideal body image influence children's self-perception and whether this may potentially lead to various psychological problems. Therefore, this study aimed to examine the relationship between body image, self-esteem, and Body Mass Index (BMI) in primary school children, to identify individuals at risk at an early stage.

Material and Methods: The study sample consisted of 342 primary school children aged 6-12 years. The Sociodemographic Information, Children's Body Image Scale (CBIS) and Children's Rosenberg Self-Esteem Scale (CRSS) were used to gather data. Body weight and height were measured, and BMI was calculated. Data were analyzed using Chi-square, Mann–Whitney U, Kruskal–Wallis, Spearman correlation, and multiple linear regression tests.

Results: BMI was moderately associated with perceived body image ($r = 0.428$; $p < 0.001$) and body dissatisfaction ($r = 0.422$; $p < 0.001$) but showed minimal correlation with self-esteem and age (CRSS: $r = 0.011$, $p > 0.050$; NSE: $r = 0.002$, $p > 0.050$; PSE: $r = 0.014$, $p > 0.050$; Age: $r = 0.032$, $p > 0.050$), while self-esteem measures did not significantly differ by body satisfaction status (CRSS: $H = 0.599$, $p = 0.741$; NSE: $H = 0.293$, $p = 0.864$; PSE: $H = 0.950$, $p = 0.622$). Regression analysis identified BMI ($B = 0.094$; 95% CI: 0.071–0.116; $\beta = 0.411$; $p < 0.001$) as the strongest predictor of body dissatisfaction, followed by age ($B = 0.078$; 95% CI: 0.006–0.150; $\beta = 0.106$; $p = 0.035$), whereas other sociodemographic and psychological variables, including gender ($B = 0.199$; $p = 0.122$) and self-esteem (NSE: $B = –0.022$, $p = 0.368$; PSE: $B = 0.023$, $p = 0.469$), did not significantly predict dissatisfaction levels.

Conclusion: BMI has a significant influence on body image perception in primary school-aged children, whereas self-esteem appears to be less affected by body satisfaction at this developmental stage. These results highlight the need for early, gender-sensitive, and family-centered interventions to promote healthy body image.

Keywords: Body image, children, self esteem

Introduction

Self-views are conceptualized under the construct of self-perception, which emphasizes the reciprocal interaction among psychological, sociological, and physiological factors. According to Demoulin, self-perception encompasses the emotional synthesis of all positive and negative experiences and information that an individual accumulates throughout life and is composed of two subdimensions: self-efficacy and self-esteem (1). Demoulin, defines self-efficacy as one's motivation, confidence in facing challenges, and sensitivity to stress, whereas self-esteem pertains to evaluative perceptions of personally meaningful aspects of life (2). Body image, defined as the mental representation of one's physical appearance, involves an individual's perceptions, thoughts, and feelings about their own body (3). It consists of a perceptual component-the accuracy of body size and shape estimation-and an attitudinal component-emotional responses associated with that perception (4). This construct develops from infancy through interactions with caregivers and becomes a central part of self-concept formation (5). Childhood, particularly the primary school years, represents a critical stage for physical, emotional, and cognitive development (6). During this period, children become increasingly aware of their bodies, engage in social comparisons, and begin to establish stable self-perceptions. Self-esteem, reflecting one's overall sense of worth, is closely linked with body image; negative body

perceptions are associated with lower self-esteem, whereas positive body image serves as a protective factor for mental well-being (7,8). Recent research has demonstrated that body-image concerns are not exclusive to adolescence and adulthood but may emerge as early as six years of age (9). Such concerns can be shaped by factors including media influence, peer relationships, and family attitudes (10). Moreover, body dissatisfaction during childhood has been linked prospectively to lower self-esteem, disordered eating behaviors, and psychological distress in later life (11). As children reach school age, they begin to recognize the concepts of evaluation and being evaluated, and start to perceive the ideal body image based on societal standards. They become aware of the societal bias against individuals with obesity through increased interactions with peers at school and through media influence (12). Over the past 30 years, the prevalence of obesity among children and adolescents has been rising globally. One of the main contributors to this increase is the decline in physical activity and the deterioration of dietary habits and food preferences due to technological advancements. In later stages of life, obesity becomes a significant public health issue, triggering numerous chronic, metabolic, and psychological health problems, and placing a substantial burden on national healthcare systems (13). Moreover, childhood obesity not only poses physical health risks but also leads to psychological complications and adverse outcomes. It may result in social isolation and behavioral problems among children (14). In this context, Body Mass Index (BMI) plays a dual role. It is not only an indicator of physical health but also a factor influencing how children perceive themselves. In societies where thinness is idealized, overweight and obese children are more likely to experience body dissatisfaction and lower levels of self-esteem (15). Despite the growing awareness of these issues, research examining the interaction between body image, self-esteem, and BMI in early childhood remains limited. Understanding these relationships in primary school-aged children is crucial for identifying at-risk individuals at an early stage and for developing effective interventions. Therefore, the aim of this study was to investigate the relationship between body image, self-esteem levels, and BMI status in primary school children.

Materials and Methods

Sampling and Study Design: The study was conducted with 342 participants throughout the province of Kastamonu between July 2024 and June 2025. Participants were selected using simple random sampling from among students aged between 6 and 12 years from both genders enrolled in formal education in schools. Students were randomly invited, and only those who volunteered with parental consent were included. Because the study was intended to be representative of the general student population, no specific exclusion criteria were applied. This is a non-experimental, descriptive, and cross-sectional study that presents quantitative data. The data were collected by the researchers through face-to-face interviews using a structured questionnaire. The questionnaire included items on sociodemographic characteristics, body image, self-esteem, and anthropometric measurements. For anthropometric measurements, participants' body weight and height were measured, and BMI values were calculated to classify their anthropometric status. To assess body image, the Children's Body Image Scale (CBIS) was used. To evaluate self-esteem, the Children's Rosenberg Self-Esteem Scale (CRSS) was administered.

Anthropometric Measurements: Body weight and height were measured Weight was assessed to the nearest 0.1 kg using a calibrated digital scale (SECA 813, SECA GmbH & Co. KG, Hamburg, Germany), and height was measured to the nearest 0.1 cm using a portable stadiometer (SECA 213, SECA GmbH & Co. KG, Hamburg, Germany). Measurements were taken twice, and the mean value was used for analysis.

Body Image: Body image was assessed using the CBIS developed by Truby and Paxton (16). The Turkish version of the scale was validated and its reliability confirmed by Akliman et al. in (17). Body dissatisfaction score (BDS) was calculated using the formula: CBIS Score = Perceived Body Size – Ideal Body Size

In this scoring system, negative values indicate a desire to be heavier, positive values indicate a desire to be thinner, and a score of zero indicates satisfaction with body size.

Self-Esteem*:* Self-esteem was assessed using the CRSS, adapted to children by Wood et al. (18). It consists of 10 items, including 5 negatively worded items, and aims to measure levels of self-esteem in children. Each item is rated on a 4-point Likert scale. When negative items are reverse-coded, total scores range from 10 to 40, with higher scores indicating higher levels of self-esteem. The Turkish validity and reliability study was conducted by Gökdemir and Ekşi (19). This scale has two sub-dimensions: positive self-esteem (PSE) and negative self-esteem (NSE).

Statistical analysis:

All data entry, analysis, and interpretation were conducted using the IBM SPSS Statistics Version 25 software package. Descriptive statistics were presented using frequency tables. For categorical variables, data were presented as number (n) and percentage (%). For continuous variables, data were presented as median, minimum, and maximum values. The Kruskal-Wallis test was used to compare age, BMI, and CRSS (total and subdimensions) across body satisfaction groups. Post-hoc pairwise comparisons were performed using Dunn's test with Bonferroni correction to adjust for multiple comparisons following significant Kruskal–Wallis results. The general characteristics of the participants were evaluated using the Mann Whitney U test. To determine which variables influenced body satisfaction status, a Multiple Linear Regression analysis was performed. Prior to

regression analysis, assumptions of normality, linearity, and homoscedasticity were examined using histograms, Q-Q plots, and residual plots. The Shapiro–Wilk test indicated that the distribution of BDS deviated from normality ($p < 0.001$). The Spearman correlation test was used to examine the correlation between age, BMI, CRSS (total and subdimensions), and the CBIS. A p-value < 0.050 was considered statistically significant. In addition to p-values, effect sizes (η^2 for Kruskal–Wallis tests, rank-biserial r for pairwise Mann–Whitney U comparisons, Cramér's V for chi-square analyses and standardized β for regression analyses) with 95% confidence intervals were calculated to assess the magnitude and clinical relevance of the findings.

Results

The general characteristics of the participants are presented in Table I. The study included a total of 342 primary school children, with 178 (52%) females and 164 (48%) males. The median age was 9 years for boys (range: 6–12) and 8 years for girls (range: 6–12), with no significant difference between genders. The median BMI was significantly higher among boys compared to girls. The median CRSS scores did not differ significantly between genders. The gender difference in BMI was significant (p=0.025) with a small-to-moderate effect size (rank-biserial r=0.130, 95% CI [0.02–0.23]), while differences in age and CRSS were negligible (r<0.100). When parental occupations were evaluated, most mothers were unemployed. Although a higher proportion of boys had mothers who were civil servants or teachers, and more girls had mothers who were workers, Similarly, the most common occupation among fathers was worker, followed by civil servant and tradesman, with no significant gender-related differences. The majority of the children were either first or second born in their families. Birth order distribution showed no significant gender differences. Regarding body

Table I: General characteristics of participants

	Female	Male	Total	p	Effect size (95% CI)
Number of patiens	178	164	342	-	-
Age*	8 (6 - 12)	9 (6-12)	9 (6-12)	0.702†	0.03 (ns)‡
BMI*	26 (14.8-44.9)	26.7 (14.3-50.9)	26.6 (14.3-50.9)	0.025†	0.12 (0.02–0.22)‡
CRSS *	30 (20-40)	31 (19-40)	30 (19-40)	0.079†	0.09 (ns)
Mother's occupation§					
Unemployed	106 (50.5)	104 (49.5)	210 (61.4)		
Worker	40 (67.8)	19 (32.2)	59 (17.3)		
Healthcare workers	11 (55)	9 (45)	20 (5.8)	0.069‖	0.10¶
Tradesman	8 (47.1)	9 (52.9)	17 (5)		
Civil servant	5 (33.3)	10 (66.7)	15 (4.4)		
Teacher	8 (38.1)	13 (61.9)	21 (6.1)		
Father's occupation§					
Unemployed	5 (38.5)	8 (61.5)	13 (3.8)		
Worker	105 (54.7)	87 (45.3)	192 (56.1)		
Healthcare workers	3 (20)	12 (80)	15 (4.4)	0.109‖	0.09¶
Tradesman	31 (57.4)	23 (42.6)	54 (15.8)		
Civil servant	31 (49.2)	32 (50.8)	63 (18.4)		
Teacher	3 (60)	2 (40)	5 (1.5)		
Number of children§					
Only child	20 (52.6)	18 (47.4)	38 (11.1)		
2 children	80 (49.4)	82 (50.6)	162 (47.4)		
3 children	56 (57.7)	41 (42.3)	97 (28.4)	0.792‖	0.05 ¶
4 children	17 (48.6)	18 (51.4)	35 (10.2)		
5 or more children	5 (50)	5 (50)	10 (2.9)		
Birth Order§					
First child	76 (46.9)	86 (53.1)	162 (47.4)		
Second child	65 (59.6)	44 (40.4)	109 (31.9)		
Third child	33 (55.9)	26 (44.1)	59 (17.3)	0.119‖	0.08¶
Fourth child	4 (40)	6 (60)	10 (2.9)		
Fifth or later	0 (0)	2 (100)	2 (0.6)		
Body Satisfaction Status§					
Desire to be thinner	94 (55.3)	76 (44.7)	170 (49.7)		
Satisfied	39 (36.4)	68 (63.6)	107 (31.3)	<0.001‖	0.14¶
Desire to be heavier	45 (69.2)	20 (30.8)	65 (19)		

***:** median (min-max), **†:** Mann Whitney U test, **§:** n (%), **‖:** Chi-square test, **¶:** v, **BMI:** Body Mass Index, **CRSS:** Children's Rosenberg Self-Esteem Scale, p < 0.050, **ns:** not significant*

Table II: Comparison of age, BMI, and CRSS (Total and Dimensions) according to body satisfaction status

	Desire to be thinner*	Satisfied*	Desire to be heavier*	Test stat.	p†	η² (95% CI)
Age	9 (6-12)	8 (6-12)	8 (6 - 12)	4.607	0.100	< 0.01
BMI	29.3 (14.3 - 50.9)[a]	25.8 (15.6-37)[b]	25.2 (14.8-43.5)[b]	49.138	<0.001	0.14 (0.09-0.18)
CRSS	31 (19-40)	30 (21-40)	30 (22 - 39)	0.599	0.741	< 0.01
NSE	14 (6-20)	14 (7 - 20)	14 (8 - 20)	0.293	0.864	< 0.01
PSE	16 (9-20)	17 (12 - 20)	16 (12 - 20)	0.950	0.622	< 0.01

:** *median (min-max),* **†:** *Kruskal Wallis test,* ***BMI: *Body Mass Index,* ***CRSS:*** *Children's Rosenberg Self-Esteem Scale,* ***NSE:*** *Negative Self Esteem,* ***PSE:*** *Positive Self Esteem,* **[a,b]:** *For each measurement, there is no significant difference between groups that share the same letter (Dunn test). p < 0.050*

Table III: Multiple linear regression analysis

Predictor	B	95% CI for B	β	t	p	Zero order	Partial r
Number of Children	-0.06	(-0.242 - 0.136)	-0.042	-0.645	0.519	-0.105	-0.035
Birth order	-0.053	(-0.242 - 0.116)	-0.036	-0.550	0.583	-0.107	-0.030
BMI	0.094	(0.071 - 0.026)	0.411	8.279	0.000	0.439	0.413
NSE	-0.022	(-0.069 - 0.084)	-0.047	-0.901	0.368	-0.019	-0.049
PSE	0.023	(-0.039 - 0.15)	0.038	0.725	0.469	0.049	0.040
Age	0.078	(0.006 - 0.451)	0.106	2.118	0.035	0.126	0.115
Gender	0.199	(-0.053 - 0)	0.077	1.551	0.122	0.132	0.085

B: *Unstandardized Coefficient,* ***Beta:*** *Standardized Coefficient, Adj.* ***R²:*** *0.199,* ***F:*** *13.089, p:<0.001,* ***SE:*** *1.164,* ***BMI:*** *Body Mass Index,* ***NSE:*** *Negative Self Esteem,* ***PSE****: Positive Self Esteem*

satisfaction, 49.7% of the participants expressed a desire to be thinner, 31.3% reported being satisfied with their body, and 19.0% wished to be heavier. A significant gender difference was observed: girls more frequently expressed a desire to be thinner, while boys more often reported being satisfied with their body.

The comparison of age, BMI, and CRSS total and dimension scores according to body satisfaction status is presented in Table II. A statistically significant difference was found between the groups in terms of BMI scores. Post-hoc Dunn test results indicated that children who expressed a desire to be thinner (corresponding to positive BDS values) had significantly higher BMI values compared to both children who were satisfied with their bodies (BDS=0) and those who desired to be heavier (negative BDS values). No significant difference in BMI was found between the "satisfied" and "desire to be heavier" groups. The Kruskal-Wallis test for body satisfaction status showed a large effect (η^2 = 0.14, 95% CI [0.09–0.18]). No statistically significant differences were observed among the body satisfaction groups in terms of age, total CRSS scores, NSE scores, or PSE scores.

Spearman's rank-order correlation analyses were conducted to examine the bivariate associations among children's perceived body image (PBI), ideal body image (IBI), BDS, BMI, total and subscale scores of the CRSS, and age. The full correlation matrix is presented in Figure 1. BMI was moderately, positively associated with PBI and with BDS. BMI showed negligible relationships with IBI and with age, implying that weight status does not appreciably shift one's ideal body size or vary systematically across this age range. Total CRSS was essentially uncorrelated with body dissatisfaction and showed only minimal associations with PBI, BMI, and age. Age exhibited only weak, non-significant correlations with all other study variables.

A multiple linear regression are presented in Table III to examine the extent to which sociodemographic and psychological variables predict children's body dissatisfaction scores. The overall model was significant and accounted for approximately 19.9% of the variance in body dissatisfaction. Among the seven predictors, BMI emerged as the strongest predictor of body dissatisfaction, showing the highest standardized beta coefficient (β = 0.41, p < 0.001), indicating that children with higher BMI reported greater body dissatisfaction (positive BDS values reflecting a desire to be thinner). For each one-unit increase in BMI, body dissatisfaction increased by 0.094 points, holding all other variables constant. Age also had a significant but smaller effect (β = 0.11, p=0.035) such that older children reported marginally higher body dissatisfaction scores. In contrast, number of children in the family, the CRSS dimensions (NSE, PSE), birth order and gender did not significantly predict body dissatisfaction). Zero-order and partial correlations further confirmed that BMI and age were the only variables with meaningful unique contributions to the model. The model demonstrated a good overall fit (Deviance/df = 1.36).

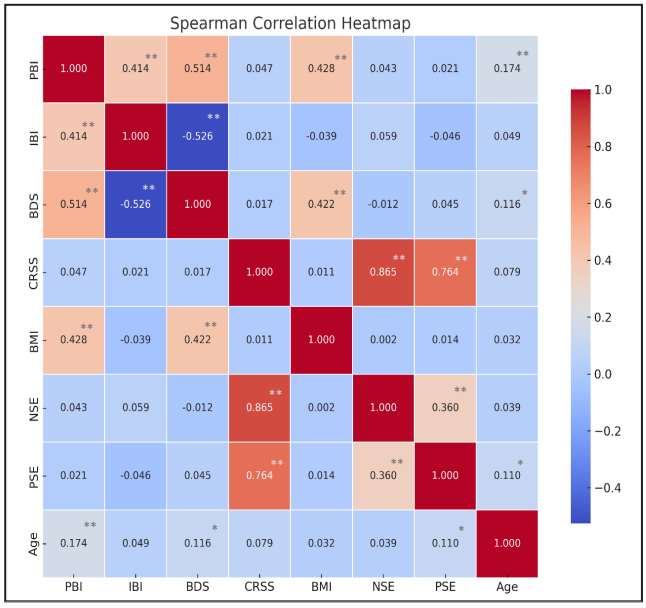

Figure 1: Age, BMI, Children's Rosenberg Self-Esteem Scale (Total and Dimensions) and Children's Body Image Scale Spearman Correlation Matrix Heatmap; Correlation coefficient range: −1 to +1; *p<0.050; **p < 0.010 (2-tailed); **BMI:** Body Mass Index, **CRSS:** Children's Rosenberg Self-Esteem Scale, ***NSE:*** Negative Self Esteem, **PSE:** Positive Self Esteem, **BDS:** Body Dissatisfaction Score, **PBI:** Perceived Body Image, **IBI:** Ideal Body Image

Discussions

BMI values differed significantly between genders, with boys exhibiting slightly higher median BMI than girls. This result is consistent with previous research suggesting that boys may have higher body weight trajectories during childhood due to differences in physical activity levels, energy expenditure, or dietary patterns (20).

No significant differences were found between girls and boys in terms of self-esteem scores (CRSS). This finding may imply that self-esteem in this age group is shaped by a broader set of factors beyond physical appearance, including familial support, academic success, and peer relationships (22). However, a clear gender pattern emerged in body satisfaction: girls more often desired to be thinner, whereas boys expressed greater satisfaction or a desire to be heavier, reflecting gender-specific social and media influences on body ideals (12,16,23).

The relationship between body satisfaction status and age, BMI, and self-esteem dimensions was examined among children and adolescents. There was no statistically significant difference in age among the three body satisfaction groups. This suggests that body satisfaction or dissatisfaction is not strongly influenced by chronological age within the 6-12 age range. In contrast, there was a statistically significant difference in BMI between groups. Positive BDS scores reflect a desire to be thinner and were indeed associated with higher BMI in our sample. Post hoc analysis revealed that children who expressed a desire to be thinner had significantly higher BMI values compared to those who were satisfied with their bodies or who desired to be heavier. The large effect of body satisfaction status indicates that the BMI differences between body satisfaction groups are not only statistically significant but also clinically meaningful. This aligns with previous findings indicating that higher BMI is a strong predictor of body dissatisfaction in children and adolescents (26,27). The observed differences suggest that body dissatisfaction in children may largely stem from perceptions of overweight, even at a young age, potentially contributing to unhealthy weight control behaviors (28). Interestingly, the total scores of the CRSS, as well as its sub-dimensions-NSE and PSE-did not significantly differ according to body satisfaction status. This finding contrasts with some literature suggesting a strong association between body image and self-esteem (29). However, other studies have noted that while body dissatisfaction can affect self-esteem, the impact may vary depending on developmental stage, cultural factors, and mediating variables such as peer and family support (6, 22). The absence of significant differences in self-esteem scores may also indicate that within this sample, body dissatisfaction has not yet generalized to broader self-worth, which may be more stable or influenced by other psychosocial factors at this developmental stage. Alternatively, the CRSS, while suitable for children, might not be sensitive enough to capture subtle emotional effects specifically related to body image in younger populations. A review of the literature reveals that the relationship between body image and self-esteem varies across age groups. This relationship appears to be strongest during adolescence, weaker in childhood, and in adulthood, it tends to be shaped by additional variables. While the current study focused on children, research specifically examining body satisfaction in this age group is limited. Therefore, interpreting findings from adolescent and adult populations to provide a broader developmental framework for interpreting the current results would be helpful in highlighting potential developmental continuities affecting body perception and satisfaction across the lifespan. Among adolescent girls in particular, failure to attain thinness ideals can lead to body dissatisfaction, which in turn may result in significant reductions in self-esteem (29, 31). In adolescent boys, a similar pressure is observed through the internalization of muscularity ideals. Body dissatisfaction during adolescence is not limited to a temporary decline in self-esteem; it can also contribute to the development of depression, eating disorders, and social anxiety (32). In young adulthood (ages 18–30), the relationship between self-esteem and body image remains significant, although it is relatively weaker compared to adolescence. This may be due to the fact that self-concept in this period is increasingly shaped by multidimensional life experiences, such as personal achievement, romantic relationships, and career development (33). Although body dissatisfaction remains a common concern within this age group, it is no longer the sole determinant of self-esteem (34).

In adulthood (age 30 and above), the relationship between body image and self-esteem becomes even more attenuated. Individuals begin to construct their self-worth beyond physical appearance, drawing from social roles, parenthood, societal contribution, and accumulated life experiences. In childhood, the relationship between body image and self-esteem is relatively weak. At this stage, self-concept is still in development, and evaluations related to body image are typically shaped by external feedback (e.g., from parents, teachers, and peers) (22). Self-esteem in this period is more strongly influenced by multiple domains such as academic success, family dynamics, and social acceptance. Therefore, dissatisfaction with body image does not necessarily lead to low self-esteem in children (9). However, especially during the transition to early adolescence (ages 11–12), with the onset of physical development and increased social comparisons, this relationship becomes more pronounced. Our findings are consistent with the existing literature on this topic.

The full correlation matrix indicates that higher adiposity co-occurs with both perceiving oneself as larger and feeling more dissatisfied with one's body.

The analysis also revealed moderate positive correlations between BMI and both PBI and BDS, reinforcing the notion that higher BMI is associated with perceiving oneself as larger and experiencing greater dissatisfaction with one's body. This relationship is well-documented across age groups highlighting the internalization of weight-related norms even among young children (11, 35).

Correlations between CRSS and body image variables were relatively weak. The association between CRSS and BDS was negligible, as was the link with PBI. Suggesting that other psychosocial factors - such as peer relationships, parental feedback, and media exposure - may play a mediating or buffering role (31).

Age was only weakly correlated with most variables, with the highest being with PBI and BDS.

The results of the multiple linear regression analysis present the predictors of body dissatisfaction, as measured by the BDS, among children. The model explains approximately 19.9% of the variance in BDS, which indicates a moderate explanatory power in psychological and behavioral research contexts (35).

Among the variables entered into the model, BMI emerged as the strongest and only highly significant predictor of body dissatisfaction. This finding reinforces the robust association between higher body mass and increased dissatisfaction with one's appearance, which is extensively supported in the literature (11,35). Children with higher BMI values likely experience greater internal and external pressures about body ideals, contributing to negative evaluations of their appearance (9). The high zero-order and partial correlations further support the strong direct effect of BMI, independent of other factors.

Age was also a statistically significant but weaker predictor. This suggests that as children grow older, they may become more aware of societal beauty norms and develop greater concern with body image (30). Although the effect size is small, it aligns with previous research indicating that body dissatisfaction tends to intensify with age, particularly as children approach adolescence (6).

In contrast, self-esteem dimensions were not significant predictors of body dissatisfaction. This result is somewhat unexpected, given that previous research has demonstrated that lower self-esteem is often linked to poorer body image (22, 31). However, the lack of significance in this sample may reflect developmental factors or the presence of other mediating variables, such as peer influence or parental attitudes (29). It is also possible that body image and self-worth operate somewhat independently during certain stages of childhood, becoming more tightly linked in later adolescence (32).

While BMI contributes to perceived body image and dissatisfaction, its effect on self-worth appears limited in this age group. These findings emphasize the need for early, developmentally appropriate interventions that target ideal body internalization and promote body acceptance without reinforcing weight-based evaluations (36).

BMI remains the most robust and consistent predictor of body dissatisfaction in childhood. The contributions of age and other psychological or demographic variables appear more nuanced and potentially mediated by external influences. These findings highlight the need for holistic, weight-neutral health education that reduces the salience of body size as a determinant of self-worth (36, 37).

This study has several limitations that should be considered when interpreting the findings. Although the regression model included key sociodemographic and psychological variables, other potential confounders that may influence body image and self-esteem were not assessed. These include socioeconomic indicators such as parental education and income level, screen time, physical activity patterns, media exposure, and experiences of peer teasing or bullying. The absence of these factors may have limited the explanatory power of the model and could partially account for the unexplained variance in body dissatisfaction scores. The cross-sectional design precludes causal inference regarding the direction of relationships among body image, BMI, and self-esteem. Longitudinal studies would be necessary to clarify whether body dissatisfaction precedes changes in self-esteem or vice versa. The data were based on self-reported measures, which may be subject to social desirability or recall bias, particularly in younger children. Finally, the study sample consisted of children from a single geographic region and relatively homogeneous socioeconomic background, which may restrict the generalizability of the results to broader or more

diverse populations. Additionally, although the CBIS was originally developed for children aged 7–12 years, a small number of 6-year-old participants were included because the official school entry age in Türkiye begins at six. These children were first-grade students who were cognitively and linguistically comparable to the lower end of the CBIS target age range. Nevertheless, this age inclusion should be considered a minor limitation when interpreting the findings.

In summary, the findings underscore the role of BMI in body image perception even among children aged 6–12, while self-esteem appears to be less directly affected by body satisfaction at this stage. These results highlight the importance of early intervention strategies focusing on healthy body image and weight perception without reinforcing weight stigma. School-based prevention programs and parent education initiatives may be effective in fostering healthier self-perceptions and body satisfaction in this age group.

Conclusion

these findings reinforce the importance of addressing body image and weight-related attitudes in primary school-aged children. The gender differences in body satisfaction and the association with BMI underline the need for gender-sensitive public health strategies and family-centered education programs. Future studies should explore the longitudinal trajectory of these variables to better understand their long-term impact on adolescent and adult health.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Çankırı Karatekin University (08.07.2024, reference number: 15).

Contribution of the authors

Study conception and design, data collection, analysis and interpretation of results,draft manuscript preparation: TT

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Evaluation of child and adolescent psychiatry outpatient clinic admissions during the COVID-19 pandemic

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ABSTRACT

Objective: This study aimed to retrospectively evaluate the changes in volume and diagnostic profile of outpatient admissions to a university hospital's Child and Adolescent Psychiatry Clinic during the COVID-19 pandemic, by comparing data from the pre-pandemic period and the first year of the pandemic.

Material and Methods: Admissions made between March 2019–February 2020 (pre-pandemic) and March 2020–February 2021 (pandemic) to the Child and Adolescent Psychiatry Department of Hacettepe University were analyzed. Number of admissions, frequency, age and gender distribution, and ICD-10 diagnostic categories were compared. In addition, referral rates from pediatric emergency, general pediatrics, and adolescent medicine units were examined. Data were retrospectively obtained from patient files and analyzed using SPSS 20.0.

Results: There was a 19% decrease in the total number of outpatient admissions during the pandemic. However, no significant difference was found in the number of new admissions. The mean age of children was significantly higher in the pandemic period ($p<0.001$). No significant difference was found in gender distribution. During the pandemic, the proportion of anxiety disorders increased significantly ($p=0.001$), whereas rates of specific learning disorders ($p<0.001$), decreased.

Conclusion: Findings indicate a qualitative shift in child and adolescent mental health service use during the pandemic, with increase in anxiety disorders and decrease in specific learning disorder.

Keywords: Adolescent psychiatry, child psychiatry, COVID-19, diagnostic distribution, pandemic, outpatient applications

Introduction

The COVID-19 pandemic has emerged a significant challenge to healthcare systems worldwide and has profoundly impacted the mental well-being of societies. Fear of disease, uncertainty of the quarantine duration, financial problems increase the risk of adverse psychological effects. The social isolation and school closures, caused increased loneliness in children and adolescents. Studies have shown that one-third of adolescents have high levels of loneliness during the COVID-19 pandemic and there is a known relationship between loneliness and mental health. Besides, disruption of daily routines caused frustration among developmentally vulnerable groups such as children with special education needs (1–4).

Studies conducted during this period have reported an upsurge in depression, anxiety, sleep disorders and post-traumatic stress symptoms among children and adolescents (5-10). In a cross-sectional study conducted among Chinese adolescents during pandemic, prevalence of depressive symptoms was 43,7%, anxiety symptoms was 37,4% and a combination of depressive and anxiety symptoms was 31.3%. Also, female gender and higher grade were higher risk factor for depressive and anxiety symptoms (7). In another study conducted in Italy and Spain, parents reported behavioral changes in their children. The most frequent symptoms were irritability, boredom, nervousness, difficulty in concentration, loneliness and restlessness (8). There are also findings indicating a decrease in externalization disorders during the pandemic. Bobo et al. (11) reported

that most children and adolescents with ADHD experience stability or improvement of their well-being which may be related to less school-related strain and flexible schedules. However, most of the available data are cross-sectional and therefore insufficient to monitor the long-term impact of the pandemic on the mental health of children and adolescents (9, 10). In addition, there are a limited number of studies comparatively evaluating the pre-pandemic and pandemic periods in Türkiye (12).

In this context, supporting the evaluation of the impact of the pandemic on mental health services with local data is of great importance for both planning health services and developing targeted intervention strategies in times of crisis.

This study retrospectively examined how outpatient psychiatric admissions to the child and adolescent psychiatry clinic of a university hospital differed in terms of diagnosis, number of admissions, age and gender between the pre-pandemic and pandemic periods.

The primary aim of this study was to evaluate the impact of the COVID-19 pandemic on outpatient referrals to a child and adolescent psychiatry clinic. In line with this objective, the following hypotheses were tested:

- The total number of outpatient visits during the pandemic period differs significantly compared to the pre-pandemic period.
- The number of patients referred by other services increased during the pandemic period.
- An increase in internalizing disorders and a decrease in externalizing disorders are expected during the pandemic period.

Materials and Methods

The period from March 2019 to February 2020 was defined as the pre-pandemic period, while the period from March 2020 to February 2021 was defined as the pandemic period. The study period encompassed the national lockdown measures in Türkiye, including school closures (initially complete between March and June 2020 with intermittent re-openings and subsequent closures during the 2020–2021 academic year), restrictions on social activities, curfews and stay-at-home orders, as well as reduced access to outpatient psychiatric services.

Data were retrospectively obtained from the hospital information management system of the Hacettepe University Department of Child and Adolescent Psychiatry, between June 2021 and February 2022. The sample size before the pandemic was 15255, while during the pandemic it was 12374. The variables examined included the date of admission, age, gender, diagnostic information based on ICD-10 codes, status as a new or follow-up visit, and referrals from the pediatric emergency, pediatrics, and adolescent health units.

Diagnoses were made by specialist clinicians based on clinical interviews and evaluations conducted during outpatient visits and were recorded in the electronic system using ICD-10 diagnostic codes. In reviewing the patient records, not only the diagnostic codes but also clinicians' written notes were taken into account.

Statistical analysis

Statistical analysis were performed using IBM Statistical Package for the Social Sciences, version 20.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). This study utilized a descriptive data analysis approach to summarize and interpret the colllected data. For numerical data, the mean and standard deviation were used for data following a normal distribution. Percentages and frequencies were used for categorical data. Chi-square tests were used for categorical variables, and independent samples t-tests were applied for continuous variables. Bonferroni corrected chi-square tests were applied as post hoc tests. A p-value of <0.050 was considered the threshold for statistical significance.

Results

Before the pandemic, a total of 15255 admissions were made to the outpatient clinic, while this number decreased to 12374 during the pandemic period; this shows that there was a 19% decline in admissions.

After excluding repeated visits, the total number of patients presenting to the outpatient clinic was 4353 in the year preceding the pandemic (March 2019–February 2020) and 5028 during the pandemic period (March 2020–February 2021), which is not significantly different ($p>0.050$). Among these, the number of new patient visits was 2093 in the pre-pandemic year, whereas 1947 of the visits during the pandemic were identified as new consultations. There was no significant difference in the number of new admissions ($p=0.068$).

The mean age of the patients was 10.4±4.2 prior to the pandemic and 10.9±4.5 during the pandemic, with the difference found to be significantly higher ($p<0.001$).

Table I: Distribution of patient admissions before and during the COVID-19 pandemic

	Pre-pandemic	During pandemic
Pediatric Emergency		
Admission frequency	45131	25331
Referral rates	0.49 %	0.85%
Pediatrics		
Admission frequency	12168	5873
Referral rates	16.6 %	19.2%
Adolescent Health		
Admission frequency	2466	1367
Referral rates	30.4 %	35.5 %

Table II: Distribution of diagnoses before and during the COVID-19 pandemic

Diagnoses	Pre-pandemic*	During pandemic*	p†
Total number of patients	4353	5028	-
ADHD	1711 (39.3)	1868 (37.2)	0.078
Anxiety disorder	339 (7.8)	494 (9.8)	0.001
ASD	361 (8.3)	432 (8.6)	0.064
Specific learning disorder	377 (8.7)	269 (5.4)	0.001
Major depressive disorder	188 (4.3)	211 (4.2)	0.798
Intellectual disability	194 (4.5)	178 (3.5)	0.089
Developmental speech and language disorder	78 (1.8)	97 (1.9)	0.577
OCD	82 (1.9)	77 (1.5)	0.385
Eating disorder	54 (1.2)	75 (1.5)	0.056
Tic disorder	42 (1.0)	54 (1.1)	0.861
Enuresis - encopresis	38 (0.9)	23 (0.5)	0.063
PTSD	11 (0.3)	23 (0.5)	0.079
Conduct disorder & ODD	8 (0.2)	21 (0.4)	0.247
Bipolar affectxve disorder	15 (0.3)	19 (0.4)	0.081
Gender dysphoria	9 (0.2)	12 (0.2)	0.097

: n(%), †: Bonferroni corrected chi-square tests, **ADHD: Attention Deficit Hyperactivity Disorder; **ASD:** Autism Spectrum Disorder; OCD: Obsessive-Compulsive Disorder; **PTSD:** Post-traumatic Stress Disorder; **ODD:** Oppositional Defiant Disorder*

No significant difference was found in terms of gender distribution, with male gender prevailing in both periods [female vs. male; 39.2 % vs. 60.8 % (pre-pandemic) ; female vs. male; 38.4 % vs. 61.6 % (pandemic); p=0.430]

Referrals from pediatric emergency, pediatrics and adolescent health units to child and adolescent psychiatry outpatient clinics have increased significantly during the pandemic period. The distribution of the admissions before and during the pandemic period according to the departments and the referral rates to the child and adolescent psychiatry outpatient clinics are shown in Table I.

In terms of diagnosis distribution, there was a significant increase in anxiety disorder diagnoses (p=0.001) and a significant reduction in attention deficit hyperactivity disorder (ADHD) (p=0.033), specific learning disorder (p<0.001) and intellectual disability (p=0.026) diagnoses during the pandemic period. After Bonferroni correction, anxiety and specific learning disorders maintained their significance (both of them, p=0.001); intellectual disability and ADHD were not found to be statistically significant (p=0.089, p=0.078). No significant difference was observed in diagnoses such as eating disorders, obsessive-compulsive disorder (OCD) and depression. This finding, consistent with some international studies, suggests that the expected increase was not observed and that the admission rates of these diagnoses may have remained stable under pandemic conditions. The distribution of the admissions before and during the pandemic according to diagnoses is presented in Table II.

A detailed analysis of the referrals diagnosed with eating disorders revealed no statistically significant difference between new and follow-up visits during the pandemic period (new vs. follow-up; n= 33 vs. n=42) compared to the pre-pandemic period (new vs. follow-up; n= 25 vs. n=29) (p = 0.056). Notably, the result obtained in the eating disorder analysis is very close to the significance threshold, indicating a possible upward trend in this diagnostic group (χ^2=1.15; p=0.056). This should be clinically considered and monitored through follow-up studies.

In contrast, for anxiety disorders, a significant difference was observed between new and follow-up visits during the pandemic (new vs. follow-up; n= 220 vs. n=274) compared to the pre-pandemic period (new vs. follow-up; n= 212 vs. n=127) (p<0.001), which was primarily attributable to an increase in follow-up visits.

Regarding attention-deficit/hyperactivity disorder (ADHD), a significant difference was found between new and follow-up visits during the pandemic (new vs. follow-up; n= 350 vs. n=1518) compared to the pre-pandemic period (new vs. follow-up; n= 641 vs. n=1070) (p< 0.001), driven by both a reduction in new visits and an increase in follow-up consultations.

For specific learning disorders, a significant difference was observed between new and follow-up visits during the pandemic (new vs. follow-up; n= 37 vs. n=232) compared to the pre-pandemic period (new vs. follow-up; n= 109 vs. n=268) (p < 0.001), which was primarily associated with a decrease in new visits.

For intellectual disability, however, no statistically significant difference was found between new and follow-up visits during the pandemic (new vs. follow-up; n= 57 vs. n=121) compared to the pre-pandemic period (new vs. follow-up; n= 65 vs. n=129) (p = 0.073).

Discussions

The COVID-19 pandemic has triggered numerous psychopathologies in children and adolescents, both due to the direct effects of infection and the difficulties created by the limitations taken against infection. In the early stages of the outbreak, one-third of parents (35.1%) reported that their children's psychological health had been significantly affected (13). Additionally, nationwide studies in the US have reported that children and adolescents' psychological well-being and behavioral health have deteriorated compared to before the pandemic (5,14). Numerous studies investigating the impact of the COVID-19 pandemic and related control measures on children and adolescents with autism spectrum disorder have reported a significant increase in parental stress, as well as high levels of anxiety, irritability, hyperactivity, stereotypical behavior, and other behavioral problems in children and

adolescents (14). The findings obtained in our study provide significant insights for the clinical evaluation of the impact of the COVID-19 pandemic on child and adolescent mental health. While a decrease was observed in the total number of admissions during the pandemic period, after excluding the repeated visits, there was no significant difference between pre-pandemic and pandemic period. The rate of new admissions remained stable, which is noteworthy. This situation indicates that despite the pandemic, individuals experiencing psychological distress continued to seek access to healthcare services.

A closer examination of the consultations conducted before and during the pandemic revealed a marked increase in referral rates to the child and adolescent psychiatry unit among the three main departments of the pediatric hospital. Based on this finding, it can be inferred that the quantitative burden of mental health symptoms and disorders observed in our clinic escalated during the pandemic period. Although there was a sharp decline in the overall number of healthcare visits during this time, a substantial proportion of the remaining consultations required referral to the child and adolescent psychiatry outpatient clinic.

The increase in anxiety disorder rates has been observed not only in this study but also in research conducted by Ravens-Sieberer et al. (15) in Germany, Patrick et al. (5) in the United States, and Racine et al. (9) in Canada. This suggests that the effects of the pandemic—such as uncertainty, loneliness, isolation, and traumatic stress—have manifested in similar mental health symptoms globally among children and adolescents. Additionally, the rise in follow-up visits among individuals with anxiety disorders supports the notion that pre-existing mental health conditions were exacerbated under pandemic conditions.

There was no statistically significant difference in total number of ADHD diagnoses between pre-pandemic and pandemic period. In France, Bobo et al. found that parents reported a decrease in ADHD symptoms of their children. This decline could be caused of reduced academic demands at home, diminished pressure from structured classroom environments and parent's less pronounced observation of their children's attention problems (11). On the other hand, a review study suggested that this decline may be related to remote learning not allowing the teacher to recognize ADHD and refer the family, rather than a true reduction in symptoms (14). Conditions like ADHD cause functional impairments in the lives of children and their families, leading to increased difficulties during the pandemic due to reduced treatment-seeking. Therefore, in similar circumstances, ensuring access to services for these children should be a priority.

A significant decrease was observed in the diagnosis of specific learning disorder. Possible reasons for this decline include the limited scope of teacher observations during online education, delays in diagnostic procedures, and the automatic extension of report durations for individuals with existing diagnoses during the pandemic period (15). Since the beginning of the pandemic, it was reported that many state school districts postponed assessments to determine for early intervention or special education services, resulting in long waiting lists (17). Teachers may be less likely to refer students for assessment during remote learning due to reduced opportunities for in-class observation (17). Delays in diagnostic procedures can lead to more pronounced learning difficulties and reduced academic achievement in subsequent years. Such children should not be overlooked, and that in similar situations, regular screenings for attention-deficit/hyperactivity disorder and specific learning disorder should be conducted, with families and educators appropriately informed.

There was no statistically significant difference in the diagnoses of ASD and intellectual disability. In a UK study of parents of children with special educational needs, most parents and children reported experiencing loss, worry and changes in mood and behaviour during the pandemic (18). In another study, worsening of any child neurodevelopmental disorder or comorbid mental health symptom was reported by 64,5% of respondents and almost one fifth of families reported an increase in the dosage of medication administered to their child (19). Children with neurodevelopmental disabilities may be particularly vulnerable to stress due to significant changes in routines and service access. Improved access to and coordination of health services as well as targeted interventions for these children and families should be conducted.

No significant increase was observed in the diagnoses of eating disorders and depression. However, several studies have reported expectations of an increase in these diagnoses, particularly among adolescent girls during the pandemic period (9,10,20-22). This finding suggests that the sample may have been limited to referrals from outside urban areas, or that presentations of eating disorder cases may have been delayed due to physical restrictions.

Similarly, no significant difference was found regarding obsessive-compulsive disorder (OCD). This finding aligns with the heterogeneous results reported in a systematic review. Among the 42 studies examined by Luginaah et al. (23), 30 reported exacerbation of OCD symptoms during the pandemic, while 12 observed no changes. This suggests that individual and familial resilience may play a determining role.

Finally, the increase in referrals from pediatric emergency, pediatrics, and adolescent health units to psychiatry indicates that the indirect effects of the pandemic should not be overlooked. The identification of children presenting with psychiatric symptoms in pediatric units and their subsequent referral to child psychiatry underscores the importance of collaborative care services.

Limitations

One of the strengths of this study is the comparative analysis of pre-pandemic and pandemic period referrals within the same institution, using a consistent medical record system and diagnostic approach. Furthermore, the inclusion of not only the number of referrals but also variables such as age, gender, and diagnostic distributions allows for a more comprehensive evaluation.

However, the study has several limitations. It is a single-center study, and the findings may not be generalizable to other institutions or geographic regions. Also, when considering 20% decrease in admissions, the effect of lockdown period of 3-4 months during the study should be taken into account as a limitation. In addition, variables such as socioeconomic status, parental education level, and regional differences were not included. The exclusion of these factors limits the ability to fully understand the underlying reasons for changes in referral patterns.

Due to its retrospective design, the accuracy of diagnoses relies solely on clinical interviews and ICD-10 coding. Standardized diagnostic tools or structured interviews were not used in the diagnostic process, which limits the ability to assess diagnostic validity.

Moreover, despite the widespread adoption of remote healthcare services—particularly telepsychiatry—during the pandemic, such consultations were not included in the present study. This may have led to an underestimation of the actual number of psychiatric referrals.

Conclusion

The COVID-19 pandemic has led to both quantitative and qualitative changes in outpatient visits to child and adolescent psychiatry clinics. A significant increase was observed in anxiety disorders, whereas a notable decrease was seen in specific learning disorder. Despite an overall decline in the number of visits, the rate of new admissions remained stable, indicating a continued pursuit of mental health support. Particular attention should be given to strengthening accessible psychosocial support services for adolescents with anxiety disorders and children with special educational needs should not be overlooked.

Future research should be supported by more comprehensive, multicenter studies that include the effects of socioeconomic factors, parental attitudes, remote education, and telepsychiatry applications. In particular, holistic models that strengthen collaboration among children, families, and schools should be developed to enhance the recognition and intervention of mental disorders.

Future research should be supported by more comprehensive, multicenter studies that include the effects of socioeconomic factors, parental attitudes, remote education, and telepsychiatry applications. In particular, holistic models that strengthen collaboration among children, families, and schools should be developed to enhance the recognition and intervention of mental disorders.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Hacettepe University (26.05.2021 , reference number: GO21/669).

Contribution of the authors

Study conception and design: CA, KN, FÇÇ; Data collection: ST; Analysis and interpretation of results: CA, ST, KN, FÇÇ; Draft manuscript preparation: CA; All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Gender effect on dextranomer hyaluronic acid injection material durability: A rat bladder model

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ABSTRACT

Objective: In failed cases treated with the endoscopic sub-ureteric injection method, no residue from the previous injection material was found during cystoscopy at the second injection. The clinical observation of an increased incidence of recurrent reflux in girls than in boys reminds us that bladder gender may influence the stability of the injection material. The aim of the study was to determine whether there is a gender-related difference in the durability of the subureteric injection material.

Material and Methods: Twenty male and female Wistar-Albino rats were evenly divided into four groups. The experimental group received a submucosal injection of 0.1cc dextranomer hyaluronic acid copolymer (Dexell®) into the bladder. In addition, the control group received 0.1cc of 0.9% NaCl. Tissue hyaluronidase activity was measured biochemically using the ELISA method. The injection sites were assessed histopathologically and immunohistochemically with CD31 and CD34 Rabbit Monoclonal Antibodies.

Results: Biochemically, tissue hyaluronidase activity in female groups was statistically significantly higher than in males. Histopathologically, there were no significant differences between the genders or between the experimental and control groups in relation to fibrosis formation. Regarding immunohistochemistry, angiogenesis was statistically significantly higher in all females, regardless of whether they were in the study or control group, compared to males. Concerning progenitor cell activity, there is no difference between the genders, whereas the difference between the study and control groups was significant.

Conclusion: Biochemically, higher hyaluronidase activity in the female rat bladder may cause a faster breakdown of the hyaluronic acid compound in the injection material. The high permeability of inflammatory cells in the female rat bladder, as detected histochemically, may accelerate the destruction process with the aid of lytic enzymes in these cells.

Keywords: Bladder, children, gender, vesicoureteral reflux

Introduction

The incidence of VUR in children is 1-2% (1,2). Approximately 30-50% of febrile urinary tract infections in children are due to VUR. Early and accurate identification of VUR may prevent urinary tract infections and related reflux nephropathy (3).

In 2017, the American Urology Association (AUA) updated primary VUR management in children and created follow-up and treatment guidelines (4). Treatment principles can be organised into three sub-headings. Conservative options include antibiotic prophylaxis and bladder and bowel training.

Since it is minimally invasive, subureteric injection should be preferred over open surgical methods (2). However, the success rate of the endoscopic subureteric injection method depends on variables in the patient profiles, such as the degree of reflux, the techniques used, and the aptitude for the process. The average success rate ranges from 46% to 92% (5). Recurrence may be due to anatomical factors, lower urinary tract dysfunction, or the time-dependent destruction of the dextranomer hyaluronic acid (Dx-HA) compound, resulting in loss of effectiveness.

The destruction of the injection material is highly dependent on time and gender. The incidence of recurrent reflux is higher in female patients than in male patients (6). Our clinical observations also indicate gender-related differences in hyaluronic acid stability, as females demonstrate a higher incidence of recurrent reflux. In this study, we aimed to compare the stability of the active substance (Dx-HA), which may show different responses depending on gender, in male and female rats.

Materials and Methods

The study was conducted between September 2021 to November 2021 at the Gülhane Animal Surgery Research Unit, within the R&D Centre Presidency. Twenty male and 20 female Wistar Albino rats weighing 310-655 (mean: 442.5) g were kept in a standard cage, each in four groups [Group A (Female Dx-HA copolymer injection group), Group B (Male Dx-HA copolymer injection group), Group C (Female control group), and Group D (Male control group)], and were fed ad libitum. The sample size was reduced from 40 to 33 owing to losses associated with anaesthesia.

Surgical technique, injection of tissue materials, and excision of tissues

The bladder was exposed by a midline abdominal incision under general anaesthesia with intramuscular Ketamine (90 mg/ kg) and Xylazine (10 mg/kg). The bladder was incised from bladder dome to the neck, and 0.1 ml of Dx-HA copolymer was injected (26-gauge Botox needle) into the trigone submucosally in groups A and B, while 0.1 ml of 0.9% NaCl was injected into groups C and D. A 6/0 silk marker stitch was placed on the bladder mucosa near the injection area (Figure 1). The bladder was then closed with a continuous 6/0 Vicryl stitch. All groups of rats were explored again 60 days after the first procedure. The entire bladder thickness (0.3x0.3 cm) containing the injection site was excised and fixed in a 10% formaldehyde solution for histopathological sampling. To measure the tissue hyaluronidase activity biochemically, the bladder tissue was immediately prepared, frozen in liquid nitrogen, and sent for biochemical analysis.

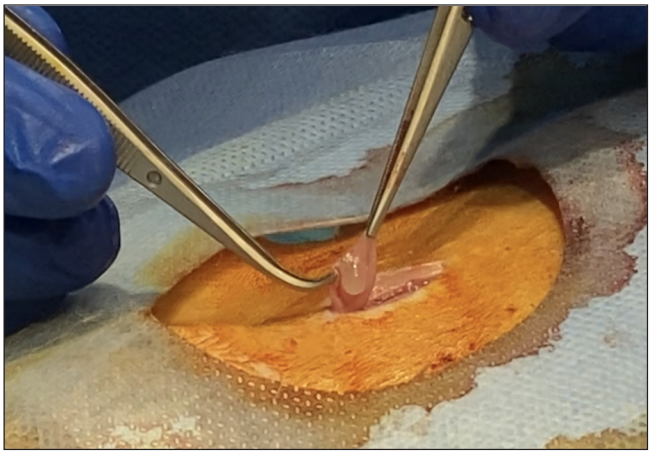

Figure 1: Injection of Dx-HA under the mucosa of the bladder wall

Histopathological evaluations

Inflammation in Hematoxylin-Eosin (H&E) stained cells and fibrosis grading was performed on Masson's trichrome-stained sections histochemically (7–9). The lymphoplasmacytic inflammatory cells, particularly the plasma cells, were counted in a large magnification field. In this context, Grade 0 indicated an absence of reaction and inflammatory cells, with no fibrosis present. In Grade 1, reactions were characterised by a maximum of 20 inflammatory cells and mild fibrosis. Grade 2 was found to correspond to moderate reactions, as indicated by the presence of 20–45 inflammatory cells and moderate fibrosis. The presence of ≥45 inflammatory cells and severe fibrosis was indicative of a Grade 3 inflammation..

Immunohistochemically, CD31 and CD34 activity were measured. Angiogenesis (number of newly formed vessels) in CD31 blocks and angioprogenitor cells in CD34 blocks were counted in the area (0.237 mm^2) where vessel proliferation is most intense under microscopic magnifications (Nikon ECLIPSE 80i microscope) (11,12). All histopathological and immunohistochemical examinations were carried out in a blinded manner by independent observers.

Rat tissue hyaluronidase measurement:

Tissue samples were stored in a deep freezer (Sanyo MDF-U6086S) at -80 C^0 until analysis. On the study day, excess blood on the tissues was removed in cold PBS (Phosphate Buffer Saline) (pH 7.4). Tissue protein measurements were performed with tissue hyaluronidase from the supernatants separated after centrifugation. Tissue hyaluronidase measurements were done with an enzyme-linked immunosorbent assay method with the original kit for Rat Hyaluronidase of BT LAB (Bioassay Technology Laboratory- Shanghai Korain) in Cobas c501 Roche Hitachi device, turbidimetrically with the Benzethonium chloride method. The tissue hyaluronidase results were calculated as ng/mg protein according to the measured proteins of the homogenates.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 28.0 (IBM Corp., Armonk, NY, USA). The study included eight variables in total, five of which were defined as dependent variables (fibrosis grade, inflammation grade, anti-CD31 expression, anti-CD34 expression, and tissue hyaluronidase level). Gender and injection-material group membership were treated as independent variables. The normality of continuous variables was assessed using visual inspection of histograms together with skewness and kurtosis values. Descriptive statistics for normally distributed continuous variables were reported as mean and standard deviation (SD). Categorical variables

were expressed as frequencies (n) and percentages (%). Group comparisons for normally distributed continuous variables were performed using the Independent samples T test. Comparation of categorical variables were assessed using the Pearson chi-square test. A two-tailed p-value of <0.050 was considered statistically significant.

Results

Tissue hyaluronidase activity in female rats is higher than in male rats, irrespective of study vs. control groups (Male vs. female; 26.85±11.06 vs. 45.84±14.95; p<0.001) (Control vs. study; 38.69±18.77 vs. 36.93±14.15; p=0.618) (Table I-II).

In the examination performed with H&E dye, microspheres filled with biomaterial and degraded (empty) microspheres were observed together in the area of the injection material in the male and female study groups. At the same time, the honeycomb appearance is kept in the microspheres of the biomaterials whose content has been degraded. Plasma cells, neutrophils, eosinophils, macrophages, and mast cells were present in the area of inflammation, with a predominance of lymphocytes around the injection material. Multinucleated giant cells and foreign body reactions were observed among the injection materials. The capsule material formed by fibroblast and collagen fibres was kept to surround the area from the outside. Significant inflammation was observed in the Dx-HA-injected male and female study groups. Foreign body reaction, microsphere formation, or inflammatory processes were not observed in the control groups (Figure 2: A/E/I/M).

In the preparations stained with hematoxylin-eosin, lymphoplasmacytic inflammatory cells, particularly plasma cells, were counted under magnification (x40) in a High Power Field (HPF). The counts of inflammatory cells were significantly higher in the study group compared to the control group (30.40±24.18 vs 5.81±7.98; p<0.001) (Table II). However, no statistically significant difference was observed in inflammatory cell counts between males and females (16.41±15.53 vs 22.21±27.17; p= 0.301).

In the histopathological examination with Masson Trichrome stain to evaluate fibrosis, microspheres filled with biomaterial and degraded microspheres were observed together, in correlation with Hematoxylin-eosin staining in the area where the injection material was present in the male and female study groups. The capsule formed by fibroblast and collagen fibres surrounded the Dx-HA copolymer from the outside (Figure 2: B/F/J/N). In line with these data, fibrosis was graded by looking at the degree of collagenisation and fibroblastic proliferation rate per HPF(x40). There was no statistically significant difference between the study and control groups, regardless of gender (p =0.123). Fibrosis

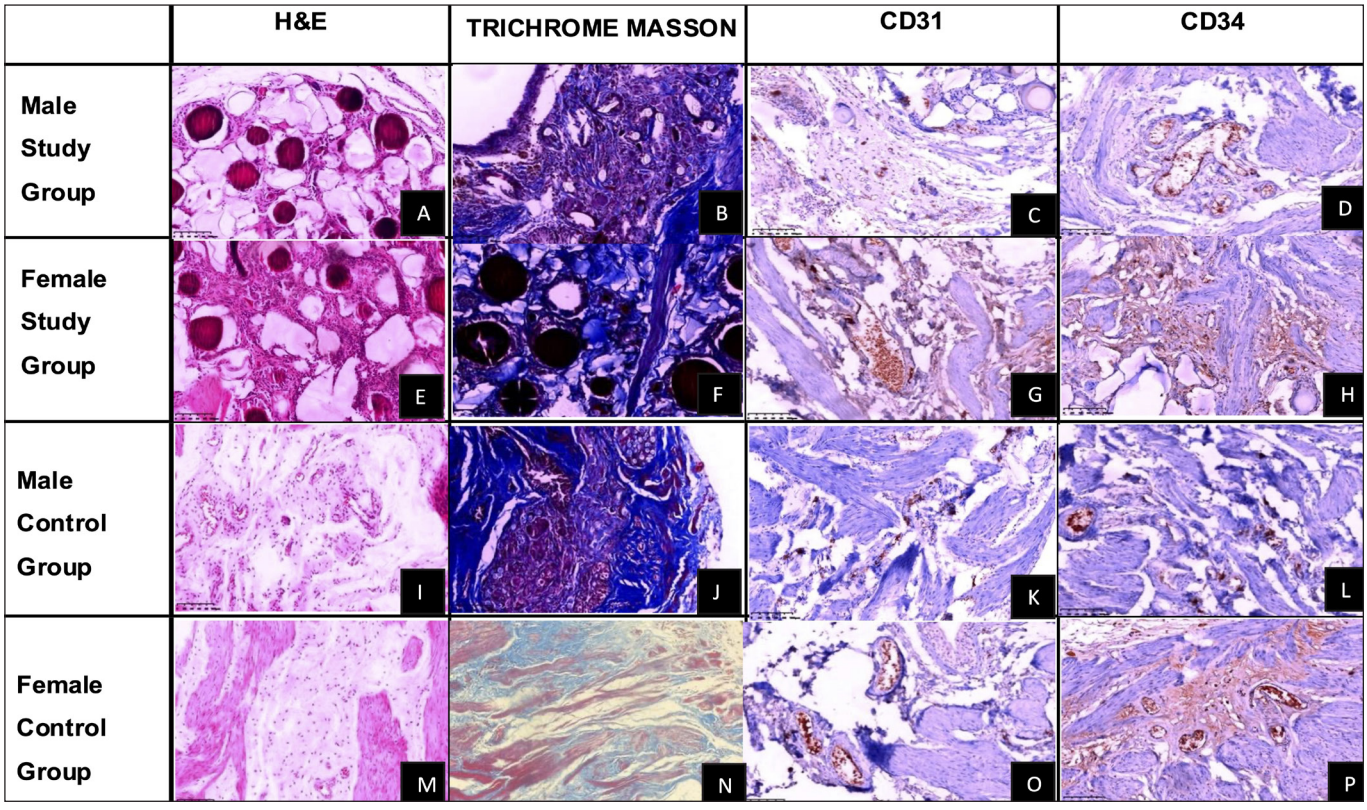

Figure 2: Evaluation of histopathological findings. Preparations stained with H&E **(A)**, and Masson Trichrome **(B)**, CD31 (C), and CD34 **(D)** in the male study group; Preparations stained with H&E **(E)**, and Masson Trichrome **(F)**, CD31 **(G)**, and CD34 **(H)** in the female study group; Preparations stained with H&E **(I)**, and Masson Trichrome **(J)**, CD31 **(K)**, and CD34 **(L)** in the male control group; Preparations stained with H&E **(M)**, and Masson Trichrome **(N)**, CD31 **(O)**, and CD34 **(P)** in the female control group.

Table I: Comparison of hyaluronidase enzyme activity between gender and test groups

Groups	Control	Study	p†	Total	p‡
Male					
n	7	7	0.328	14	<0.001
HA*	28.80±12.63	24.91±9.83		26.85±11.06	
Female					
n	9	10	0.571	19	<0.001
HA*	46.38±19.73	45.36±11.01		45.84±14.95	
Total					
n	16	17	0.328	33	-
HA*	38.69±18.77	36.93±14.15		37.78±16.31	

***:** *mean±SD,* **†:** *Control vs. Experimental (Independent Samples T-Test),* **‡:** *Male vs. Female (Independent Samples T-Test),* ***HA:** Hyaluronidase enzyme activity*

Table III: Comparison of inflammation, fibrosis, CD31 and CD34 cell counts between gender and test groups

	Group difference			Gender difference		
	Control	Study	p	Male	Female	p
Inflamatory cells*	5.81 ± 7.977	30.40 ± 24.184	<0.001	16.41 ± 15.528	22.21 ± 27.168	0.301
Fibrosis†	16 (44.44%)	20 (55.55%)	0.123	17 (47.22%)	19 (52.77%)	0.200
CD31⁺ cells*	8.12 ± 3.845	16.40 ± 8.357	<0.001	10.41 ± 8.689	14.79 ± 6.571	0.035
CD34⁺ cells*	9.81 ± 3.468	18.30 ± 7.766	0.002	13.41 ± 11.017	15.53 ± 6.013	0.282

***:** *mean±SD (Independent samples t-test),* **†:** *n(%) (Pearson's chi-squared test)*

scores were similar between male and female rats (1.24±0.75 vs. 1.53±0.70; p =0.200), and likewise comparable between the study and control groups (1.16±0.76 vs. 1.19 ± 0.66; p=0.123) (Table II).

In the CD31-stained sections, the endothelial cell counts were significantly higher in the study group compared with the control group (16.40±8.36 vs. 8.12±3.84; p<0.001). Additionally, irrespective of study or control status, females exhibited higher endothelial cell counts than males (14.79±6.57 vs. 10.41±8.69; p=0.035).

In CD34 antibody-stained preparations, angioprogenitor cells listed in the vascular trace showed a statistically significant difference in the direction of the study group (Study vs. Control; 18.30±7.77 vs. 9.81±3.47; p=0.002) (Table II). There was no statistically significant difference in gender (Male vs. Female; 13.41±11.02 vs. 15.53± 6.01; p = 0.282).

Discussion

The endoscopic treatment method is a minimally invasive procedure and is an excellent alternative to early discontinuation of antibiotic prophylaxis and open surgical approaches. While the average success rate varies between 76-92%, the failure rate after injection changes 5-25%. Furthermore, it is important to note that numerous factors can influence the efficacy of treatment. The following factors must be considered: the type and volume of injected material, the technique applied, the surgeon's experience, the degree of reflux detected, the presence of bilateral or unilateral reflux, voiding dysfunction, age, and gender(13–15). Consistent with our clinical observations, it was also found in the literature that the recurrence rate was higher in girls who underwent endoscopic injections for VUR (16). Endoscopic injection failure was higher in children younger than 54 months, children with previously failed injections, and girls (17,18).

HYAL-1 is a bladder-specific hyaluronic acid in the extracellular matrix (19,20). Pseudocapsule formation at the injection site suggests that the mechanism of action of Dx-HA involves an early inflammatory response (21). Injection materials used in treating SI cause a foreign body reaction and form a capsule consisting of fibroblast and collagen (22). What we expect from an ideal subureteric injection material is that it provides capsule formation and maintains the mass effect. Studies have shown that only 20% of the injection material persists one year after the procedure. Capsule formation was also observed around the degraded materials, and it was observed that the mass effect continued (22).

The dextranomer molecules contained in the injection material are responsible for the adhesion of the filler material to the tissue. In our study, regardless of the study and control group, statistically significantly higher tissue hyaluronidase activity was found in female rats than in male rats (p<0.001). This finding may cause faster destruction of hyaluronic acid in female rat bladders than in male rats. As a result, it may lead to a reduction in the mass effect of the dextranomer structure in the Dx-HA complex (19,20).

Our study is the first to discuss that tissue hyaluronidase activity and injection material stability may differ due to bladder gender.

In our study, when H&E stained preparations were examined, mononuclear cell migration, mainly lymphocyte, around the microspheres filled with Dx-HA in the bladder submucosa was observed in the study groups. The control groups had no significant inflammatory cell chemotaxis to the bladder submucosa. Foreign body reaction was observed with multinucleated giant cells among the injection materials. The capsule formed by fibroblast and collagen fibres was observed to surround the Dx-HA-filled microsphere from the outside, and findings similar to the study by Kajbafzadeh et al. (23) were obtained. As a result, in our study, there was a significant difference between the study group and the control group in terms of the inflammatory response ($p<0.001$). However, no significant differences were found in the contribution of the gender to the inflammatory process ($p=0.301$). The Dx-HA complex injected into the body induces a foreign body reaction, promoting the migration of all mononuclear cells to the injection site. This allows a pseudo capsule to form around the injection material over the long term. Consequently, the activity of the hyaluronidase enzyme found in the bladder degrades the binding agent hyaluronic acid in the Dx-HA complex, decreasing the effectiveness of the injection material. However, it was noted that there was no statistical difference between male and females regarding this reaction that would cause the inflammatory cell response of mononuclear cell migration to differ.

An ideal injection material in endoscopic treatment should not provoke a long-term chronic inflammatory process, as a sustained inflammatory response can lead to fibrosis. Our study found that the inflammatory process was managed by encapsulating the material created by fibroblasts and collagen fibres, as observed in preparations stained with Trichrome-Masson. To evaluate this response, we graded fibrosis by assessing the degree of collagenisation and fibroblast proliferation rate. Our study indicated no statistically significant difference regarding fibrosis between the study and control groups nor between the genders ($p=0.123$). The evaluation was conducted two months post-injection. The absence of fibrosis suggests that the Dx-HA complex is a suitable biomaterial for biocompatibility.

Inflammatory angiogenesis occurs at more excellent rates in females. In the Dx-HA group, female rats demonstrated a higher proliferation of vascular endothelial cells and inflammatory angiogenesis than male rats. The reduced angiogenesis activity in male rats may allow the injected material to remain stable for a longer duration. This suggests that HA may experience a more rapid inflammatory response in females and, consequently, may remain stable for a shorter period. This finding indicates that the stabilisation time of the Dx-HA complex may vary based on gender.

In our study to determine microvessel density using the anti-CD34 antibody against CD34, an endothelial marker, we assessed angioprogenitor cells in the most remarkable vascular proliferation region. There was no significant difference between the gender in this evaluation ($p=0.282$); however, a notable difference was observed between the study and control groups regarding microangiogenesis formation ($p=0.002$). The increase in CD34-positive cells may suggest that Dx-HA triggered inflammatory processes, substantially enhancing microangiogenesis. Nevertheless, gender was not a determining factor in this process. These findings support the notion that the biological stabilisation of Dx-HA may develop independently of gender but could depend on the severity of the inflammatory response.

The presence of progenitor cells at the injection site, even two months post-injection after their sacrifice, indicates that the inflammatory process remains ongoing. The existence of angioprogenitor cells in the injected area suggests that further activity enhances vascularity; consequently, inflammatory cells will migrate to the site, and the secreted cytokines will disrupt the structure of the filler, increase its breakdown, reduce the mass effect, and may trigger the recurrence of reflux, regardless of gender. While this finding aligns with the study by Kajbafzadeh et al. (23), a more extended follow-up period is recommended to evaluate the literature on the angioproliferation process secondary to inflammation using CD34 more effectively. Moreover, studies on inflammatory responses involving CD34 require an extended follow-up for subsequent evaluations to retain significance. Consequently, according to the literature, the assessments conducted in the sixth month are considered more reliable. In the short term, there is no significant difference in progenitor cell activity between male and female rats, suggesting that CD34 is a marker that should be assessed over a more extended period than CD31. This reliance on a relatively brief follow-up period represents a limitation of the present study, as it may have restricted the ability to fully capture late-phase inflammatory and regenerative processes.

Conclusion

Dx-HA is nearly an ideal material for the treatment of reflux. Since it does not induce chronic inflammation, it is unlikely to contribute to fibrosis's potential mid- and long-term development. However, biochemically, increased tissue hyaluronidase activity in female rat bladders may lead to a more rapid breakdown of hyaluronic acid within the Dx-HA complex. The elevated degradation rate adversely affects the stability of the injectable substance, which could diminish the volumetric augmentation efficacy of the bulking agent, thereby heightening the likelihood of suboptimal therapeutic outcomes. Consequently, this raises the possibility of suboptimal therapeutic outcomes.

Clinically, we have observed that recurrence following subureteric injection is more common in females than in males, as supported by the existing literature. Our study proposes that this may be attributed to the increased vascularity and activation of hyaluronidase in female bladders. Therefore, it should be considered that subureteric

injections administered to females will degrade more rapidly. We suggest that a larger volume be administered compared to males. Additionally, scheduling follow-up appointments for girls more frequently than for boys after the procedure may be beneficial.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Health Sciences University Gulhane institutional (02.09.2021, reference number: 2021-28).

Contribution of the authors

Concept or design: IS, SEUB, Acquisition of data: SEUB, GŞ, SD, Analysis or interpretation of data: SEUB, PS, Drafting of the article: SEUB, GBB, IS, Critical revision for important intellectual content: IS, HS, SD

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Recurrent pericarditis in children: Clinical findings and outcomes

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ABSTRACT

Objective: In this study, we aimed to evaluate the clinical findings and follow-up data of children with recurrent pericarditis (RP).

Material and Methods: This study had a retrospective design and included pediatric patients with recurrent pericarditis evaluated between January 2017 to January 2023. The initial diagnosis of pericarditis was made according to the criteria determined in the European Society of Cardiology guideline.

Results: We enrolled 16 children (14 males) with recurrent pericarditis with median age 12.8 (8 – 17) years. Eight patients (50%) presented with fever, pericardial effusion in 11 patients (68.7%). Pericardiocentesis was performed in 9 (56.2%) patients. The median erythrocyte sedimentation rate (ESR); C-reactive protein (CRP) levels at the time of diagnosis were 43 (25-70) mm/h and 107 (61-190) mg/dl, respectively. In total, 16 patients had 36 recurrences during follow-up. The main symptom during the relapses was chest pain, similar to that of the first attack. Four patients (25%) had a history of previous cardiac surgery. Three patients were treated with nonsteroidal anti-inflammatory drugs (NSAIDs) only. NSAID and colchicine were administered to 13 patients. One patient received corticosteroid and one patient received anakinra treatment.

Conclusion: Patients with recurrent pericarditis in childhood have an autoinflammatory phenotype. Furthermore, successful management of patients with recurrent pericarditis requires a teamwork approach involving cardiologists, rheumatologists and clinical immunologists.

Keywords: Autoinflammation, childhood, colchicine, pericarditis

Introduction

Recurrent pericarditis (RP) is one of the most common pericardial diseases, affecting up to 30% of adult patients suffering from acute pericarditis (1-3). Rheumatic diseases, Familial Mediterranean fever (FMF), and previous cardiac surgery are etiological factors (4). In approximately 70% of pediatric patients and more than 80% of adult patients no specific etiology can be identified and therefore pericarditis is considered idiopathic. In recent years, the underlying cause of idiopathic recurrent pericarditis (IRP) is thought to be autoinflammatory (5-9). The accepted pathogenetic scenario is that infectious agents (mostly viral) trigger the inflammation pathway through different transmissions between the immune system (10). The long-term prognosis of recurrent pericarditis is generally good. However, frequent relapses are one of the most challenging treatment problems and the quality of life in these patients can be seriously affected (11). There are insufficient published studies/data on the management, treatment and prognosis of recurrent pericarditis in children. In this study, we aimed to evaluate the clinical findings and follow-up data of 16 children and adolescents with RP.

Materials and Methods

This study had a retrospective design and included 16 pediatric patients (14 males, 2 females) with recurrent pericarditis evaluated between January 2017 to January 2023. The initial diagnosis of pericarditis was made according to the criteria determined in the European Society of Cardiology guideline. Patients whose pericarditis recurred at least once, at least 4-6 weeks after the first attack, were included in our series. The diagnosis of recurrent pericarditis was based on the following criteria: previous definitive diagnosis of acute pericarditis and presence of at least two of the four following

criteria: typical chest pain (sharp and pleuritic, improved by sitting and leaning forward), pericardial rub sound, typical electrocardiography (ECG) changes (diffuse ST elevation or PR depression), and new or worsening pericardial effusion. Patients with confirmed systemic connective tissue and autoinflamatory diseases were excluded from the study. Clinical features of pericarditis during the attacks, ECG changes, number and characteristics of relapses, laboratory findings [genetic analyses for FMF and autoinflammatory disesase, troponin, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level] and treatment records were analyzed. Previous medical history such as heart surgery and comorbidities were recorded. Patients and their parents gave informed consent.

Acute pericarditis (AP) is defined as an inflammatory condition involving the pericardium that has a sudden onset and is characterized by at least two of the following four clinical features: (A) typical chest pain that sharp, pleuritic and increases with inspiration (b) pericardial rub; (c) typical electrocardiographic changes (e.g. diffuse ST elevation or PR segment depression); (d) a new or worsening pericardial effusion (12). For the diagnosis of recurrent pericarditis, a symptom-free period of at least 4-6 weeks was required between the first attack and recurrence (13). "Refractory pericarditis" is pericarditis that recurs despite optimal medical treatment such as colchicine and corticosteroids (3).

Statistical analysis

SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. The variables were investigated using visual (histogram, probability plots) and analytical methods (Kolmogorov–Smirnov) to determine whether or not they were normally distributed. Continuous variables are presented as mean, standart deviation (SD), median and interquartile range (IQR), while categorical variables are given as numbers and percentages. A p-value of less than 0.050 was considered to show a statistically significant result.

Results

We enrolled 16 children with recurrent pericarditis with median age 12.8 years (8 – 17 years). Diagnostic criteria were pericardial chest pain in 16 cases (100%), pericardial rub in 5 cases (31.2%), ECG changes (widespread ST-segment in 5 cases (31.2%), PR segment depression in 3 cases (18.7%), low voltage QRS complex in 6 cases (37.5%). The ECG was normal in 6 patients (37.5%). Pericardial effusion was detected in 11 patients (68.7%). Eight patients (50%) presented with fever. Mild cardiac tamponade was recorded in 1 patient (6%) during the episodes (Table I).

The mean diastolic thickness of pericardial fluid was 12.5 mm. Pericardiocentesis was performed in 9 (56.2%) patients. The chest X-ray showed cardiac enlargement in 5 (31.2%) patients. The median (IQR) ESR and CRP levels at the time of diagnosis were 43 (25-70) mm/h and 107 (61-190) mg/dl, respectively. ESR and/or CRP values were elevated in all cases.

Table I: Clinical data of the patients in the present study and the other cohorts

Clinical characteristics	Present study*	Raatikka et al. (17)*	Finetti et al. (29)*	Imazio et al. (11)*	Imazio et al. (14)*
Number of patients	16	15	15	110	240
Chest pain	15 (93.8)	15 (100)	13 (87)	103 (93.6)	239 (99.6)
ECG changes	10 (63)	10(67)	13 (87)	49 (44)	60 (25)
Pericardial effusion	11 (69)	15(100)	13 (87)	86 (78)	138 (57)
Pericardial rub	6 (38)	Na	5 (33)	31 (28)	82 (34)
Elevated ESR-CRP	16 (100)	14 (93)	13 (87)	102 (93)	174 (72)
Fever	8 (50)	12 (80)	8 (53)	84 (76)	73 (30)
Tamponade	1 (6)	1 (7)	0	15 (14)	2 (1)
PPS	4 (25)	7 (47)	Na	10 (9)	21 (9)
ANA positivity	1 (7)	1 (7)	Na	18 (16)	103 (43)
NSAIDs	16 (100)	4 (27)	13 (87)	89 (81)	240 (100)
Colchicine	13 (81)	4 (27)	14 (93)	68 (62)	120 (50)
Corticosteroids	1 (6)	11 (73)	15 (100)	70 (65)	16 (7)
Anakinra	1 (6)	0	13 (87)	12 (17)	0

: n(%), **ECG: Electrocardiogram, **ESR:** Erythrocyte sedimentation rate, **CRP:** C-reactive protein, **ANA:** anti-nuclear antibodies, **NSAIDs:** nonsteroidal anti-inflammatory drugs, na not applicable, **PPS:** Post pericardiectomy syndrome*

In total, 16 patients had 36 recurrences (mean 2.25±1.05) during follow-up. The main symptom during the relapses was chest pain, similar to that of the first attack. None of the recurrences resulted in constrictive pericarditis. Four patients (25%) had a history of previous cardiac surgery. Two of these patients had atrial septal defect (ASD) surgery, one patient had fallot tetralogy surgery, and one patient had ventricular septal defect (VSD) surgery. The first attack of pericarditis in these patients occurred an average of 6.4 weeks after surgery. All patients underwent genetic testing for autoinflammatory diseases, including MEFV gene sequencing and extended autoinflammatory panels. No pathogenic or likely pathogenic variants were detected, which indicates that none of the patients had Familial Mediterranean Fever (FMF) or other monogenic autoinflammatory syndromes.

Three patients were treated with nonsteroidal anti-inflammatory drugs (NSAIDs) only. NSAID and colchicine were administered to 13 patients. One patient received corticosteroid (methylprednisolone). One patient with frequent relapses was diagnosed with refractory pericarditis and received anakinra treatment. A relapse was observed in patient under anakinra treatment, but no relapse was observed after 12 months of anakinra treatment and remission is currently ongoing. The demographic and clinical characteristics of the patients are shown in Table II.

Table II: Demographic, clinical and laboratory findings of the patients

Patient	Age at first attack (years)	Gender	Final Diagnose	Symptoms	Pericardial Rub	Typical ECG changes	Pericardial effusion (mm)	Pleural effusion	CRP (mg/dl)	ESR (mm/h)	Number of attacks	Attack number under threatment	PPS	Conseguilty
1	13	Male	PPS	CP, BP	Yes	No	No	No	297	48	4	3	Yes	Yes
2	13	Male	RIAP	CP, D, C	No	No	No	No	27.7	40	2	0	No	Yes
3	14	Male	PPS	CP, D	Yes	No	17	No	210	90	1	0	Yes	No
4	13	Male	RIAP	F, CP	No	Yes	No	No	26	32	4	3	No	No
5	12	Girl	RIAP	CP, D	Yes	No	30	Yes	303	59	2	1	No	Yes
6	10	Male	PPS	CP, D, BP	Yes	No	5	Yes	149	34	2	1	Yes	No
7	16	Male	RIAP	F, CP, D, BP	Yes	No	7,5	Yes	84	88	1	0	No	No
8	13	Male	RIAP	F, CP	Yes	No	22	No	116	21	4	5	No	No
9	8	Male	PPS	F, CP, C	Yes	No	No	No	69	43	2	1	Yes	No
10	10	Girl	RIAP	F, CP	No	No	15	Yes	139	14	1	0	No	No
11	17	Male	RIAP	F, CP, C	No	Yes	No	No	106	46	1	0	No	No
12	16	Male	PPS	F, CP	Yes	Yes	17	Yes	195	19	3	2	No	No
13	14	Male	RIAP	CP	Yes	Yes	8	No	72.9	18	2	1	No	No
14	17	Male	RIAP	CP, D	No	No	7	No	195	70	2	1	No	No
15	16	Male	RIAP	F, CP, D, BP	No	Yes	3.5	No	86	84	2	1	No	Yes
16	8	Male	PPS	CP, D	No	No	17	No	171	74	4	2	Yes	No

ECG: *electrocardiogram,* ***ESR:*** *Erythrocyte sedimentation rate,* ***CRP:*** *C-reactive protein,* ***PPS:*** *Post pericardiectomy syndrome,* ***RIAP:*** *Recurrent idiopathic acute pericarditis,* ***F:*** *fever,* ***CP:*** *chest pain,* ***D:*** *dispnea,* ***BP:*** *back pain*

Discussion

In this study, we evaluated clinical findings and treatment of children and adolescents with recurrent pericarditis. To the best of our knowledge, this is the first study on recurrent pericarditis in pediatric patients in Türkiye. There is insufficient data on recurrent pericarditis in children, and the management of the disease is based on the results of studies conducted in adults.

In the CORP 2 study of 240 cases in the adult age group with recurrent pericarditis, fever was seen in 30% and pericardial effusion in 57%, while chest pain was the main symptom in all patients (100%) (14). Additionally, antinuclear antibody positivity was more common in adults. In our study, pericardial effusion was detected in 69.7% of the patients. While fever was observed in 50% of the patients, 18.7% of the patients had serious disease. In addition, serum inflammatory markers were increased in the majority of patients, and pneumonia or pleuritis were accompanied in 31.2% of the patients. In the largest multicenter study conducted in children with recurrent pericarditis to date, 110 patients were reported by Imazo et al (11). Chest pain was the most common presenting symptom in this multicenter cohort. Pericardial effusion was reported in 80% of the patients. Additionally, similar to our study results, serum inflammatory markers were increased in the majority of patients and fever frequently accompanied the disease. Unlike the results of studies conducted in adult patients, pericardial effusion and fever are more common in childhood recurrent pericarditis, inflammatory markers are significantly higher, and pleuritis is more frequently accompanied. Male predominance (14 out of 16 patients; 87.5%) was observed in our cohort. The reason for this male bias remains unclear, but hormonal and immunogenetic mechanisms are likely to contribute. Moreover, viral triggers—particularly Coxsackie and echoviruses—are more common in boys, which may partly explain this distribution. This finding has been reported in other studies but remains an area that warrants further investigation (11,12).

In developed countries approximately 90% of recurrent pericarditis cases are defined as idiopathic or viral (11). However, recently much evidence, including clinical, genetic and therapeutic, has been presented that allows the association of cases of recurrent pericarditis with autoinflammatory disorders (8,15,16). In the present study, genetic analysis was undertaken on a group of patients. However, no instances of familial Mediterranean fever (FMF) or other monogenic autoinflammatory syndromes were identified. This finding strengthens the hypothesis that recurrent pericarditis in children is a multifactorial autoinflammatory condition with environmental and immunological influences rather than a monogenic hereditary disorder. Recurrent pericarditis in pediatric patients has a clinical course characterized by a dramatic increase in inflammatory markers, sudden fever attacks, sometimes with pleuropulmonary involvement and arthralgia. However, between attacks there are usually symptom-free periods that include complete well-being and complete normalization of inflammatory markers (8,17). This clinical course is quite similar to the clinical features of some autoinflammatory

disorders, such as FMF or tumor necrosis factor receptor related periodic syndrome (TRAPS) (18,19). For this reason, clinicians have considered recurrent pericarditis as an autoinflammatory disease and have tended to use anti-inflammatory, immune modulators and immunosuppressive drugs in its management and treatment.

Nonsteroidal anti-inflammatory drugs represent the central component of the therapy; the high dose should be used if tolerated, and given every 8 hours during the acute attack. However, most of the time, the use of NSAIDs alone is not sufficient to prevent recurrences (3, 20). Another well-established treatment is colchicine, which when combined with NSAIDs can improve the response to NSAIDs but also reduce the likelihood of RP recurrence (21,22). In the CORE study (COlchicine for REcurrent Pericarditis), colchicine treatment provided clinical and statistical benefits compared to conventional treatment (23). In this prospective, randomized study, 84 patients with at least one recurrent episode of pericarditis were received either conventional treatment with aspirin alone (group 1) or conventional treatment plus colchicine (group 2). Relapse rates at 18 months were 50.6% in group 1 and 24.0% in group 2. The CORP study (COlchicine for Recurrent Pericarditis), the first prospective, randomized, double-linkage, placebo-controlled, multicenter study in adults, included 120 patients with a first episode of recurrent pericarditis (24). Patients were randomized to receive placebo or colchicine in addition to conventional treatment. The relapse rate was 24% in the colchicine group and 55% in the placebo group. The results of these studies show that colchicine is effective in preventing recurrences when added to conventional treatment. Consistent with these findings, the majority of patients in our cohort received colchicine in combination with NSAIDs, and this approach was associated with effective disease control and a reduced number of recurrences during follow-up We recommend starting colchicine early period of disease and prolonging its use to prevent relapses.

Corticosteroids can be used as triple therapy with NSAIDs and colchicine in patients with refractory disease. Many patients with RP receiving corticosteroid therapy may experience an exacerbation of RP after dose reduction and become completely dependent on corticosteroids to remain asymptomatic. This situation causes significant side effects due to corticosteroid use (17, 25). Imazio et al. (26) demonstrated that corticosteroid use in the treatment of acute pericarditis is an independent risk factor for recurrence. In their study, they compared patients who were received corticosteroids and those who were not. They revealed that pericarditis recurred more frequently compared to other treatments, and that the number of hospitalization increased due to drug-related side effects. Consistent with these observations, corticosteroids were required in only a limited number of patients in our cohort, reflecting their reserved use in refractory cases and supporting a treatment strategy favoring NSAIDs and colchicine as first-line therapy. Therefore, we believe that the use of corticosteroids should not be used except in patients with underlying autoimmune disease and in patients resistant to conventional treatments where new treatment regimens are contraindicated.

Interleukin-1 beta (IL-1β) receptor antagonist (anakinra) appears to be an effective alternative for IRP patients who frequently relapse or develop significant steroid side effects or corticosteroid dependence despite colchicine and anti-inflammatory therapy (27-29). Picco et al. (27) describe a dramatic therapeutic response to anakinra in 3 pediatric patients with steroid-dependent RP. Administration of anakinra in his patients led to resolution of all clinical symptoms and normalization of acute phase reactants. After complete remission, anakinra treatment was stopped and a flare-up of the disease was observed within a few weeks. All symptoms disappeared again by restarting anakinra. No new relapse was observed in any patient during an average follow-up of 6 months. They reported that the use of anakinra could prevent recurrence of the disease (27). Subsequently, Finetti et al. (29) showed that anakinra was effective in preventing recurrences as monotherapy in 15 patients with recurrent pericarditis, 12 of whom were pediatric patients, who were corticosteroid dependent and using colchicine. In accordance with these reports, anakinra was used in a patient with refractory disease in our cohort and was associated with sustained clinical remission during follow-up. If the combination of high-dose NSAIDs and colchicine is insufficient in the treatment, anakinra treatment can be considered instead of corticosteroids as a third-line treatment.

The most reliable biomarker for monitoring pericarditis is CRP. In our cohort, CRP levels were elevated during acute attacks and decreased in parallel with clinical improvement, supporting its reliability for disease monitoring. Normalization of CRP with the disappearance of symptoms is used to monitor patients. Especially, reduction or discontinuation of colchicine or corticosteroids treatment should be based on CRP levels (7).

Limitations

This study has some limitations inherent to its retrospective, single-center design and the small sample size (n=16), which may limit the statistical power and generalizability of the findings. Additionally, the lack of long-term follow-up data prevents a comprehensive evaluation of late complications, such as constrictive pericarditis or chronic pericardial effusion. Despite these limitations, our results contribute valuable insight into the clinical characteristics and therapeutic responses of pediatric recurrent pericarditis in a tertiary care setting.

Conclusion

Although recurrent pericarditis generally has a good prognosis, the pathogenesis is still unclear. Patients with recurrent pericarditis in childhood have an autoinflammatory phenotype due to fever, elevated acute phase markers, symptom-free periods between attacks, and the presence of pleuritis/arthritis. The fact that IL-1 antagonists are very useful in resistant cases may be encouraging for researchers to conduct new research to understand the pathogenesis of the disease. Furthermore, successful management of patients with recurrent pericarditis requires a teamwork approach involving cardiologists, rheumatologists and clinical immunologists.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Dr. Sami Ulus Hospital Maternity and Child Health and Diseases Training and Research Hospital (16.03.2022, reference number: E-22/03-308).

Contribution of the authors

Manuscript İB, SO, EAA; literature search EAA, SO, EB; study desing EAA, UAÖ,SO, EB; writing İB, EAA, SO, VD, EB. All authors read and approved the final manuscrip

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Original Article

Feeding problems in preterm infants: Associations with perinatal risks and development

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ABSTRACT

Objective: This study aimed to examine behavioral feeding difficulties in preterm infants compared with term infants and to explore how perinatal risk factors, birth weight, and developmental outcomes are associated with feeding problems in preterm infants.

Material and Methods: A total of 107 infants aged 18–24 months were included, comprising 60 preterm and 47 term infants. Feeding behavior was assessed using the Behavioral Pediatrics Feeding Assessment Scale (BPFAS), and developmental status was evaluated with the Bayley Scales of Infant and Toddler Development–Third Edition (Bayley-III). Preterm infants were further classified as small (SGA), appropriate (AGA), or large (LGA) for gestational age and perinatal risk levels were based on National Neonatology Association guidelines.

Results: Sociodemographic characteristics were comparable between groups. No significant differences were observed between preterm and term infants across any BPFAS domains, although preterm infants tended to show slightly higher scores. Within the preterm group, Bayley-III composite and subscale scores were not correlated with BPFAS outcomes. However, SGA infants demonstrated significantly higher total frequency, total problem, and poor strategies scores than their AGA and LGA peers ($p = 0.021$, $p=0.023$, $p=0.032$, respectively). BPFAS scores did not differ significantly by perinatal risk classification, though higher values were consistently observed in the high-risk group.

Conclusion: Feeding difficulties in preterm infants likely result from the interplay of biological, developmental, and environmental factors. Within this context, SGA infants may be particularly susceptible, with potential implications for later growth and metabolic health. Early identification and holistic, multidisciplinary follow-up that integrates nutritional, developmental, and family-centered care are essential to support healthy feeding patterns and prevent long-term complications.

Keywords: Feeding behaviors, preterm infant, perinatal period, risk factor

Introduction

Feeding difficulties in early childhood are recognized as complex conditions that arise from interactions between the child and the environment. Feeding is not only a biological function but also a key developmental task, requiring coordinated oral-motor skills, sensory processing, and regulation within the family context (1). Pediatric feeding disorders are viewed as multifactorial, involving medical, nutritional, skill-related, and psychosocial dimensions. According to the World Health Organization's International Classification of Functioning, Disability, and Health (ICF), they are defined as age-inappropriate oral intake associated with functional impairment (2). Globally, there is growing consensus that adequate nutrition in infancy and early childhood is essential for healthy growth, supports cognitive and psychomotor development, and lays the foundation for long-term health and well-being (3).

Preterm infants are particularly vulnerable to feeding difficulties due to cerebral immaturity, neurobehavioral dysfunction, and the invasive interventions frequently required in neonatal intensive care. These factors may interfere with the acquisition of essential oral feeding skills, reduce opportunities for positive feeding experiences, and negatively affect parent–infant interactions (1,4-6). Although several studies suggest that preterm infants experience feeding problems more often than term peers, findings

are not consistent, with some reporting this difference mainly among very preterm infants and others showing no significant disparities (5,7,8). In Türkiye, research on this subject remains limited, yet some evidence indicates that moderate and late preterm infants may also be more likely to encounter feeding difficulties compared to term infants (9).

Feeding difficulties in preterm infants are thought to be influenced by a range of perinatal risk factors such as low birth weight, prolonged respiratory support, congenital malformations, and nasogastric feeding. However, the evidence regarding these associations is somewhat variable, which may be related to methodological heterogeneity (10,11). Additionally, preterm infants are inherently more vulnerable to developmental difficulties; such vulnerabilities may contribute to or exacerbate feeding problems during early childhood (1). The primary aim of this study was to compare behavioral feeding difficulties between preterm and term infants. The secondary aim was to investigate how perinatal risk factors, birth weight, and developmental outcomes are associated with feeding problems in preterm infants.

Materials and Methods

This is a prospective study with a cross-sectional design, conducted at the Division of Developmental Pediatrics, Hacettepe Univercity Faculty of Medicine, and approved by the Institutional Ethics Committee. Patients were recruited between January and June 2023. The study included 60 preterm infants who were followed at the Developmental Pediatrics outpatient clinic. Preterm infants were recruited using a convenience sampling method during routine follow-up visits within the study period, based on the following inclusion criteria: a gestational age of less than 37 weeks, age between 18 and 24 months at the time of assessment (corrected for prematurity), and absence of any major medical conditions, including congenital anomalies, neurological impairments, or genetic disorders. The control group comprised 47 term infants recruited using a convenience sampling method from the general pediatrics outpatient clinic of Hacettepe Univercity Faculty of Medicine. All were born at ≥37 weeks of gestation, assessed between 18 and 24 months of age, and had no history of developmental disorders or chronic medical conditions. These infants were selected from children who presented for minor acute illnesses or routine well-child visits. Exclusion criteria for both groups included any major medical condition, as previously defined, or lack of parental consent. Only children whose parents provided written informed consent were included in the study.

Sociodemographic characteristics of the children and their families were obtained using a structured form developed by the investigators and were either filled out by the parents. Feeding problems of preterm and term infants were evaluated using the Behavioral Pediatrics Feeding Assessment Scale (BPFAS), which was completed by mothers.

As part of the study procedures, all preterm infants underwent developmental evaluation with the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III), administered by the same experienced child development specialist. The small for gestational age (SGA), appropriate for gestational age (AGA), and large for gestational age (LGA) categories were determined based on the Fenton growth charts for preterm infants (12). Bayley-III assessment was not performed in term infants, and all term infants were AGA.

Clinical data of preterm infants were obtained from hospital files and electronic medical records. Information collected included gestational age, birth weight, multiple birth, Apgar scores, duration of Neonatal Intensive Care Unit (NICU) stay, severe hyperbilirubinemia, and classification as SGA or LGA. Additional neonatal morbidities—such as congenital heart disease, metabolic, neurological, or genetic disorders, bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), need for mechanical ventilation and its duration, and severe neonatal sepsis—were also reviewed. Based on these parameters, infants' overall health status was categorized as low, moderate, or high risk, according to the criteria of the National Neonatology Association (13).

The Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III)

The Bayley-III is among the most frequently applied and well-established developmental assessment instruments worldwide. It measures cognitive, language, and motor abilities in children between 1 and 42 months of age. The tool demonstrates adequate psychometric properties, with test–retest reliability coefficients greater than 0.67 and internal consistency values exceeding 0.86. It also shows good concurrent validity when compared with various standardized developmental diagnostic tests used in American populations (14). It is age-normed and has a standard deviation (SD). Each case's distribution for the sum of scaled scores is converted to composite scores (mean=100, SD=15). Because culturally validated normative data for this test are unavailable, only composite scores were analyzed. All assessments were administered by an experienced, certified developmental pediatrician and a child development specialist who were members of the research team.

Behavioral Pediatrics Feeding Assessment Scale (BPFAS)

The BPFAS is a caregiver-report instrument consisting of 35 items rated on a 5-point Likert scale (from never to always) to capture both problematic and adaptive feeding behaviors. The first 25 items address the frequency of child feeding behaviors (e.g., "Whines or cries at mealtimes" and "Gets up from the table during meals"), whereas the remaining 10 items reflect parental perceptions and strategies in response to feeding (e.g., "I feel frustrated or anxious when feeding my child" and "I use threats to encourage my child to eat"). For each item, parents also indicate whether the behavior constitutes a problem by responding "yes" or "no" to the question, "Is this a problem for you?" (15). From parental responses, eight subscales are derived: total frequency, total problem, child frequency, child problem, parent frequency,

parent problem, restriction, and poor strategies. Frequency scores indicate how often behaviors occur, while the problem scores represent the particular items that parents believe to be problematic. No cutoff score was used, as there is no validated threshold for the BPFAS in our country. Total scores were compared between groups and analyzed for associations with clinical factors. Previous research has demonstrated that the BPFAS yields reliable estimates of feeding difficulties (Cronbach's alpha ≥ 0.80) and shows good validity across different pediatric populations (16). The Turkish version of the BPFAS has been shown to have sufficient internal consistency and criterion-related validity (17).

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics, Version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean and standard deviation (SD) or as median with range (min–max), according to data distribution, while categorical variables were expressed as frequencies and percentages. The distribution of continuous variables was evaluated for normality using both visual inspection (histograms and probability plots) and formal statistical tests (Kolmogorov–Smirnov and Shapiro–Wilk). For comparisons between two groups, either the independent samples t-test or the Mann–Whitney U test was applied. Comparisons across SGA, AGA, and LGA groups were performed using the Kruskal–Wallis test due to non-normal distributions, whereas perinatal risk categories were analyzed using one-way ANOVA. Post-hoc pairwise comparisons with Bonferroni correction were carried out when global tests were significant. The Pearson chi-square test was used for categorical comparisons. Correlations between continuous variables were evaluated using Pearson or Spearman correlation coefficients, depending on distributional assumptions. A two-tailed p-value<0.050 was considered statistically significant.

Results

Sociodemographic characteristics are presented in Table I. The mean ages of preterm and term infants were comparable, and no significant difference was observed between the groups in terms of gender distribution, parental age, education, employment status, or family-related variables (birth order, number of siblings, family size). As expected, preterm infants had significantly lower birth weights and gestational ages than term infants (both $p < 0.001$). Among the preterm infants (n=60), 71.7% were classified as AGA (n=43), 20.0% as SGA (n=12), and 8.3% as LGA (n=5). Regarding perinatal risk status, 43.3% of infants (n = 26) were categorized as high risk, 35.0% (n=21) as moderate risk, and 21.7% (n=13) as low risk.

Feeding problems, as assessed by the BPFAS, are summarized in Table II. Across all BPFAS domains—including total frequency, total problem, child frequency, child problem, parent frequency, parent problem, restriction, and poor strategies—no statistically significant differences were found between preterm and term infants. Although preterm infants tended to have higher mean scores in several subscales, these differences did not reach statistical significance.

Table I: Sociodemographic characteristics of preterm and term infants

Variable	Preterm infants	Term infants	p
Total number of patients	60	47	-
Age (months)*	19.69±1.37	20.05±1.79	0.250
Gender (male)†	33 (55)	31 (65.96)	0.251
Birth weight (grams)‡	1970 (600-3890)	3340 (2600-4250)	0.001
Gestational age (week)‡	34 (24-34)	39 (38-42)	0.001
Maternal age (year)*	32.01±6.17	31.40±4.98	0.581
Maternal education level (above high school)†	29 (48.3)	26 (55.32)	0.857
Employed mothers†	11 (18.3)	12 (25.53)	0.571
Paternal age (year)*	35.11±5.46	34.10±5.45	0.360
Paternal education level (above high school)†	29 (48.3)	26 (55.32)	0.952
Employed fathers†	53 (88.3)	46 (97.9)	0.470
Birth order‡	2 (1-3)	2 (1-4)	0.491
Number of siblings‡	2 (1-4)	2 (1-4)	0.478
Number of members in the family‡	4 (1-6)	4 (3-6)	0.350

**: mean±SD (Independent samples t-test), †: n(%) (Pearson chi-square test), ‡: median (min-max) (Mann–Whitney U test)*

Table II: Comparison of BPFAS scores between preterm and term infants

Variable	Preterm infants*	Term infants*	p†
Total frequency score	62.01±18.10	56.93±9.37	0.376
Total problem score	3.50±6.12	1.48±2.89	0.358
Child frequency score	43.78±12.30	40.38±6.93	0.219
Child problem score	2.38±4.11	1.10±2.09	0.217
Parent frequency score	18.23±6.82	16.55±3.10	0.879
Parent problem score	1.11±2.15	0.38±0.94	0.241
Restriction score	11.40±4.02	11.61±2.80	0.414
Poor strategies	6.48±3.07	6.12±1.75	0.232

: mean±SD, **BPFAS: Behavioral Pediatric Feeding Assessment Scale, †: Independent samples t-test*

In the preterm group, no significant correlations were found between Bayley-III composite or subscale scores (cognitive, language, and motor domains) and any of the BPFAS total or subscale scores (Table III). Among preterm infants, comparison of BPFAS scores across growth status categories (SGA, AGA, LGA) revealed several significant differences. Infants born SGA had higher median total frequency and poor strategies scores compared with both AGA and LGA peers, indicating more frequent and problematic feeding behaviors. In addition, SGA infants showed significantly higher total problem scores than AGA infants and higher child frequency scores than LGA infants. Conversely, AGA

Table III: Correlations between Bayley-III composite scores and BPFAS outcomes in the preterm group (n = 60)

Bayley III scores		Total		Child		Parent		Restricted	Poor strategies
		Frequency	Problem	Frequency	Problem	Frequency	Problem		
Cognitive	rho	0.021	0.047	-0.018	0.041	0.059	0.065	-0.130	-0.022
	p*	0.872	0.720	0.893	0.755	0.652	0.620	0.321	0.866
Language	rho	0.105	0.159	0.090	0.161	0.112	0.169	0.023	0.123
	p*	0.424	0.225	0.492	0.220	0.393	0.198	0.863	0.350
Motor	rho	-0.093	0.016	-0.091	0.087	-0.112	-0.071	-0.084	0.047
	p*	0.478	0.906	0.488	0.510	0.396	0.590	0.522	0.719

:** *Spearman's correlation,* ***BPFAS: *Behavioral Pediatrics Feeding Assessment Scale,* ***Bayley-III:*** *Bayley Scales of Infant and Toddler Development, Third Edition.*

Table IV: Comparison of BPFAS Scores by growth status at birth in preterm infants

BPFAS Scores	SGA*	AGA*	LGA*	p†
Total frequency	64.5 (55.5–88.8)[a]	57.0 (50.0–64.0)[ab]	53.0 (46.0–55.5)[b]	0.021
Total problems	3.5 (1.3–13.3)[a]	1.0 (0.0–2.0)[b]	0.0 (0.0–2.0)[ab]	0.023
Child frequency	44.5 (39.3–59.3)[a]	41.0 (35.0–47.0)[ab]	36.0 (30.0–39.5)[b]	0.024
Child problem	2.0 (0.3–9.8)[ab]	1.0 (0.0–2.0)[a]	0.0 (0.0–1.0)[b]	0.044
Parent frequency	22.0 (15.3–29.5)	15.0 (10.0–20.0)	15.0 (15.0–18.0)	0.069
Parent problem	2.0 (0.3–3.8)	1.0 (0.0–2.0)	0.0 (0.0–1.0)	0.058
Restricted	12.5 (10.3–16.5)	10.0 (10.0–14.0)	9.0 (7.5–14.0)	0.075
Poor strategies	6.5 (5.3–12.0)[a]	5.0 (5.0–8.0)[b]	5.0 (5.0–5.5)[ab]	0.032

:** *median (min-max),* **†:** *Kruskal–Wallis test,* ***SGA: *Small for Gestational Age,* ***AGA:*** *Appropriate for Gestational Age,* ***LGA:*** *Large for Gestational Age,* ***BPFAS:*** *Behavioral Pediatrics Feeding Assessment Scale,* **[ab]:** *Post-hoc pairwise comparisons were performed using Dunn's test with Bonferroni correction. Values sharing the same superscript letter do not differ significantly*

Table V: Comparison of BPFAS Scores by perinatal risk status in preterm infants

BPFAS Scores	Mild risk	Moderate risk	High risk	p†
Total number of patients	13	21	26	-
Total frequency*	57.6±8.8	57.95±15.6	67.5±22.1	0.121
Total problems*	2.46±4.1	1.95±5.1	5.27±7.3	0.144
Child frequency*	41.3±5.8	41.2±10.3	47.1±15.3	0.188
Child problem*	1.85±2.6	1.24±3.2	3.58±5.1	0.133
Parent frequency*	16.4±5.0	16.7±5.9	19.7±7.9	0.100
Parent problem*	0.62±1.7	0.71±1.9	1.69±2.5	0.195
Restricted*	12.5±3.6	9.9±3.5	12.1±4.4	0.089
Poor strategies*	6.2±2.7	5.9±2.6	7.15±3.5	0.364

:** *(mean, SD),* **†:** *One-way ANOVA,* ***BPFAS: *Behavioral Pediatrics Feeding Assessment Scale*

infants demonstrated higher child problem scores compared with LGA infants. No other significant group differences were observed (Table IV). In preterm infants, BPFAS scores did not differ significantly according to perinatal risk classification; nevertheless, higher values were consistently observed in the high-risk group (Table V).

Discussion

Behavioral feeding problems, as measured by the BPFAS, did not differ significantly between preterm and term infants, although preterm infants tended to show slightly higher scores. Within the preterm group, developmental status assessed by Bayley-III was not associated with feeding outcomes. In contrast, birth growth status emerged as a key factor: infants born SGA demonstrated more frequent and problematic feeding behaviors compared with AGA and LGA peers. Although perinatal risk classification did not yield statistically significant differences, higher feeding difficulty scores were consistently observed among infants in the high-risk group.

Several studies, including both term and preterm infants, have reported that preterm infants experience more feeding difficulties than their term counterparts, regardless of gestational age (7, 18). In a recent meta-analysis, Walton et al. (5) reported that preterm children showed greater oromotor feeding difficulties and more challenging mealtime behaviors during late infancy and early childhood compared

with term peers, and they emphasized that the overall quality of evidence was low. In contrast, a study using the BPFAS, similar in design to the present research, found no significant differences in feeding problems between preterm and term children aged 3 to 4 years. The authors suggested that this finding may reflect the benefits of high-quality neonatal care, structured follow-up, and consistent parental guidance regarding feeding (8). Consistent with this interpretation, the results of our study may also be related to the comprehensive developmental follow-up, high-quality neonatal care, early physiotherapy interventions, and routine feeding counseling provided to preterm infants and their parents during visits to developmental pediatrics clinics.

In the present study, no significant associations were found between feeding difficulties and cognitive, language, or motor scores in preterm infants. Crapnell et al. (1) found that feeding difficulties were significantly associated with lower cognitive, language, and motor scores at two years of age in infants born before 30 weeks of gestation. In Türkiye, to our knowledge, the only study addressing this issue found that higher levels of feeding problems at ages six to seven were associated with poorer cognitive functioning in preterm children (19). On the other hand, several studies have highlighted the complexity of the relationship between development and feeding, suggesting that these associations may be bidirectional (20-22). The absence of significant associations in our study may partly be explained by the limited sample size, as well as by the structured developmental and feeding follow-up provided to preterm infants in developmental pediatrics clinics.

Perinatal risk factors associated with feeding difficulties in preterm infants have been examined in several studies (4,7). Crapnell et al. (4) found no significant associations between any perinatal risk factors except hypotonia and feeding problems at two years of age in infants born before 30 weeks of gestation. In contrast, a review by Sandra et al.(23) which included all infants born before 37 weeks, identified gestational age and birth weight as significant risk factors, and sex, duration of mechanical ventilation, and length of tube feeding as potential risk factors. Studies investigating children diagnosed with feeding disorders have similarly highlighted prematurity, small for gestational age status, and congenital malformations as major perinatal risks, although findings have been inconsistent (10,11). In our study, preterm infants with higher perinatal risk scores tended to have worse feeding outcomes, but these differences did not reach statistical significance. These findings may reflect recent advances in neonatal care, including improved clinical practices and a trend toward shorter durations of respiratory support.

One of the most noteworthy findings of the present study was the association between being SGA and feeding difficulties among preterm infants. Although SGA has been repeatedly linked to feeding problems in childhood, studies focusing specifically on preterm populations are relatively scarce, and the mechanisms underlying this association remain unclear (4,10,11,18,23). Proposed explanations include neurological vulnerability, intrauterine programming, slower postnatal weight gain, and disruptions in early mother–infant interaction, which may affect appetite regulation and feeding behavior. It has also been suggested that feeding problems observed in SGA infants, such as poor appetite, might represent self-protective responses aimed at preventing future metabolic abnormalities or, alternatively, result from neurological or endocrine dysfunction. Taken together, these findings underscore that feeding problems in SGA preterm infants likely arise from an interplay of biological, developmental, and environmental factors rather than a single causal pathway (18).

Limitations

Several aspects of this study strengthen its contribution to the existing literature. It addresses a relatively underexplored topic by simultaneously examining behavioral feeding difficulties and developmental outcomes in preterm infants, with additional consideration of perinatal and growth-related risk factors. To our knowledge, this is the first study from Türkiye to approach this issue comprehensively, integrating developmental and perinatal risk perspectives within the same framework. The use of standardized and validated instruments such as the BPFAS and Bayley-III enhances the reliability and comparability of findings. Furthermore, preterm infants were followed in a tertiary developmental pediatrics clinic, ensuring high-quality data collection, whereas the term group was recruited from a comparable hospital setting.

However, several limitations should also be acknowledged. The sample size was modest, particularly within subgroups of preterm infants, which may have limited the statistical power to detect small effect sizes. The cross-sectional design precludes causal inferences regarding the relationship between developmental status and feeding outcomes. In addition, the study relied on parent-report measures for feeding behaviors, which may be subject to reporting bias. Furthermore, as all term infants were AGA, we were unable to examine associations between birth weight and feeding outcomes in this group. Future longitudinal and larger-scale studies incorporating objective observational methods are warranted to clarify causal pathways and developmental trajectories.

Conclusion

Advances in neonatal care have improved the survival of preterm infants, leading to a growing focus on their long-term growth and development. Even so, feeding difficulties remain common and multifactorial, reflecting both biological vulnerability and early environmental influences. Our findings suggest that preterm infants born small for gestational age are more susceptible to feeding problems, highlighting the importance of regular developmental and nutritional follow-up during early childhood. Early, family-centered, and multidisciplinary support that targets modifiable risk factors may foster healthy growth and reduce the likelihood of later obesity and chronic disease.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Hacettepe University (date: 01.11.2022, number: 2022/18-18).

Contribution of the authors

Study conception and design: EÖ, ENÖ, ENMK, GÖ, YÜ; Data collection: ENMK, GÖ, YÜ; Analysis and interpretation of results: EÖ, ENÖ; Draft manuscript preparation: EÖ; All authors reviewed the results, contributed to the final version of the manuscript, and approved it for publication.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

A comprehensive clinical and microbiological profile of culture-positive urinary episodes in children with acute lymphoblastic leukemia

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ABSTRACT

Objective: This study aimed to assess the frequency, causative microorganisms, antimicrobial resistance patterns, and unusual clinical and laboratory findings of culture-positive urinary episodes throughout the entire chemotherapy course in pediatric patients with Acute Lymphoblastic Leukemia (ALL).

Material and Methods: We reviewed the medical records of 93 pediatric ALL patients who completed BFM-based chemotherapy protocols between 2019 and 2025. A total of 1265 urine cultures were analyzed. Culture positivity was defined as ≥105 colony-forming units per milliliter (CFU/mL) of a single or two different pathogens. For retrospective analysis, contamination was defined by a negative control culture within 48–72 hours or clinical resolution without antibiotic treatment. Data on urinalysis, neutropenia status, and antibiotic resistance were collected.

Results: Forty-eight patients (51.6%) experienced a median of two culture-positive episodes. Incidence was highest during intensive treatment phases (induction, reinduction). Escherichia coli was the most common agent (39.8%), followed closely by Klebsiella pneumoniae (36.7%). Overall ESBL positivity was 26.6%. A concerning 30.6% of *K. pneumoniae* isolates showed carbapenem resistance. Standard urinalysis was found to be unreliable, with 71.4% of positive cultures lacking typical findings; leukocyturia was only present when the absolute neutrophil count was relatively preserved. Three cases of urosepsis (3%) were identified, all involving highly resistant organisms.

Conclusion: Pediatric ALL patients, particularly during intense chemotherapy, face a high burden of culture-positive urinary episodes and a notable shift towards multidrug-resistant non-*E. coli* pathogens like *K. pneumoniae*. The unreliability of standard urinalysis in this immunocompromised population necessitates the routine collection of urine cultures during febrile neutropenia workups, irrespective of symptoms, to ensure timely, targeted therapy guided by local resistance data. The observed extreme resistance profile appears to be a transient reflection of the intensive chemotherapy environment.

Keywords: Acute Lymphoblastic Leukemia, carbapenem resistance, febrile neutropenia, *Klebsiella pneumoniae*, urinalysis, urinary tract infection

Introduction

Urinary tract infection (UTI) is the most common bacterial infection in children, affecting 3% to 7.5% of febrile children each year (1). It remains a frequent and concerning cause of morbidity, even in healthy children, due to early complications like urosepsis and the risk of recurrent episodes that can lead to kidney scarring and suggest underlying urological abnormalities. Diagnosis and classification of UTIs involve differentiating between asymptomatic bacteriuria and symptomatic bacteriuria (positive culture with symptoms such as pain, fever, or dysuria). They are also categorized by site (upper vs. lower UTI), anatomical or functional status (uncomplicated vs. complicated), and source (community vs. nosocomial). These require careful clinical and bacteriological evaluation to guide treatment (2).

The diagnostic reliability of symptom-based and anatomical definitions of UTI is challenged in immunocompromised children. Children with acute lymphoblastic leukemia (ALL)

are severely immunosuppressed, mainly due to both leukemia and treatment-induced neutropenia. In this highly vulnerable group, febrile neutropenia (FN) can obscure symptoms of pyelonephritis, and standard urinalysis results, such as leukocyturia and nitrites, are less dependable. Furthermore, broad-spectrum empirical antimicrobial therapy should not be delayed during FN while waiting for urine culture results or even the complete urinalysis findings.

The risk of UTIs is not well-defined in pediatric oncology, and much of the current literature has concentrated on studying and managing infections within the context of FN (3,4). This focused approach often limits understanding of non-febrile or asymptomatic bacteriuria, as well as UTIs occurring outside periods of severe neutropenia, which may still significantly contribute to morbidity. Additionally, while some studies have expanded their scope to include asymptomatic bacteriuria through surveillance cultures, there remains limited data thoroughly describing the full range of culture-positive urinary episodes across different phases of ALL treatment (5).

This study retrospectively investigated the frequency, causative microorganisms, antibiotic resistance patterns, and atypical clinical and laboratory findings of culture-positive urinary episodes across the entire chemotherapy course in pediatric patients with ALL. By detailing the unique microbiological and clinical characteristics of UTIs in this cohort, we aim to provide essential data to enhance diagnostic precision and optimize management strategies.

Materials and Methods

This study employed a retrospective, observational design. We reviewed the medical records of 181 patients diagnosed with ALL and completed their two-year BFM-based chemotherapy protocols at Ankara Bilkent City Hospital, Pediatric Hematology Oncology Department, between August 1, 2019, and July 31, 2025. Patients were included if they were younger than 18 years at the time of ALL diagnosis. We excluded patients who experienced relapse, required a hematopoietic stem cell transplant, or died during chemotherapy. We recorded patient demographics, ALL subtype and risk classification, any history of UTI before diagnosis, the total number of urine cultures per patient during and after treatment, follow-up durations, and urinary ultrasonography (US) findings. For this study, one culture-positive urinary episode was considered distinct from another if the interval between urine culture samples was more than two weeks. A urine culture was considered positive if it showed growth of a single pathogen at a concentration of ≥105 colony-forming units per milliliter (CFU/mL), or if it showed growth of two different pathogens, with each organism isolated at a concentration of ≥105 CFU/mL. For culture-positive episodes suspected to be contaminants, a retrospective criterion was established: they were defined as episodes in clinically stable patients who did not require treatment, where a follow-up urine culture obtained within 48–72 hours of the initial positive culture returned negative, or where clinical follow-up showed resolution without antibiotic therapy. For all identified culture-positive urinary episodes, we collected specific information, including the phase of chemotherapy during which the culture was obtained, the clinical reason for obtaining the culture, urinalysis findings, concurrent white blood cell (WBC) count, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC), C-Reactive Protein (CRP) level, and, if available, blood culture results and treatments administered. Laboratory results (WBC, ANC, ALC, and CRP) were recorded if they were obtained within three days before or after the date of the positive urine culture. Leukocyturia was defined as ≥5 WBCs per high-power field in the urine sediment, and hematuria was defined as ≥5 red blood cells per high-power field. In accordance with our unit's established clinical practice, urine samples for analysis and culture were collected using either clean-catch mid-stream urine or bag urine culture.

Statistical analysis

Descriptive statistics were presented as median (minimum–maximum) for continuous variables and as frequencies (percentages) for categorical variables. The normality of the data distribution was assessed using the Kolmogorov-Smirnov test. Since the continuous variables were not normally distributed, the Mann-Whitney U test was employed for comparisons between independent groups. Categorical independent variables were compared using the chi-square test. All tests adopted a p-value of ≤0.050 for statistical significance. Analyses were conducted using IBM Statistical Package, version 26.0 (SPSS Inc., Armonk, NY, IBM Corp., USA)

Results

Patient demographics and rate of positive urine cultures

A total of 93 patients were included in the study, comprising 54 (58.1%) males and 39 (41.9%) females. The median age at leukemia diagnosis was 6.6 years (range; 1-18). Eighty patients (86%) had precursor B-cell ALL, and 13 (14%) had T-cell ALL. Sixty-eight patients (73.1%) had intermediate-risk disease, while 25 (26.9%) had high-risk disease. Four patients (4.1%) had a history of UTI before their ALL diagnosis. Over the two-year chemotherapy period for ALL, a total of 1265 urine cultures were collected, with a median of 12 per patient (range: 2-57). Of these, 98 cultures (7.7%) showed growth, detected in 48 patients (51.6%).

Details of culture-positive episodes

Forty-eight patients with positive cultures had a median of 2 positive cultures (range; 1-8). Twenty-nine (29.6%) of 98 episodes occurred in boys, while 69 (70.4%) occurred in girls. The most common clinical reasons for obtaining positive cultures were FN (n: 36; 36.7%) and, in conjunction with urinalysis (n: 30; 30.6%). Other reasons included dysuria and abdominal pain (n: 13; 13.3%), elevated CRP (n: 4; 4.1%), and fever (n:2; 2%). These positive cultures were identified during different treatment phases: 28 episodes (28.6%) occurred during induction, 24 (24.5%) during consolidation, 32 (32.7%) during reinduction, and 14 (14.3%) during maintenance. The link between culture positivity and patient characteristics, such as age, gender, and ALL classifications, is detailed in Table I.

Table I: The characteristics of patients according to urine culture positivity.

	Negative	Positive	p‡
Number of patients	45	48	-
Age, years*	6.9 (1.8-17.5)	4.7 (1-18)	0.053
Gender†			
Male	34 (63)	20 (37)	0.001
Female	11 (28.2)	28 (71.8)	
ALL subtype†			
pre-B cell ALL	38 (47.5)	42 (52.5)	0.671
T cell ALL	7 (53.8)	6 846.2)	
Risk group†			
Intermediate risk	37 (54.4)	31 (45.6)	0.055
High risk	8 (32)	17 (68)	

: median(range), †: n (%), ‡:** *Mann-Whitney U-test and chi-square test,* ***ALL: *Acute lymphoblastic leukemia*

Table II: Identified agents in urine cultures and resistance profiles

	Total	ESBL positivity	Carbapenem resistance
Number of episodes	98	29	12
*Escherichia coli**	39 (39.8)	13 (33.3)	1 (2.6)
*Klebsiella pneumoniae**	36 (36.7)	12 (33.3)	11 (30.6)
*Enterococcus spp.**	8 (88.2)	-	-
*Proteus mirabilis**	7 (7.1)	-	-
*Pseudomonas aeruginosa**	6 (6.1)	-	-
*Enterobacter cloacae**	4 (4.1)	3 (75)	-
*Klebsiella oxytoca**	3 (3.1)	-	-
*Acinetobacter spp.**	3 (3.1)	-	-
*Morganella morganii**	1 (1)	1 (100)	-
*Citrobacter braakii**	1 (1)	-	-
*Candida albicans**	1 (1)	-	-

:** *n(%),* ***ESBL: *Extended-spectrum beta-lactamase*

Of the 98 positive cultures, 11 (11.2%) contained two different agents, while the remaining 87 (88.8%) revealed a single agent, totaling 109 agents. A diverse range of bacteria was identified as the cause of the infections. The most common agents were *Escherichia coli (E. coli*), found in 39 episodes (39.8%), and *Klebsiella pneumoniae* (*K. pneumoniae*), found in 36 episodes (36.7%). In girls, 46.4% of episodes were caused by *E. coli* (32/69), whereas in boys, *E. coli* infections accounted for 24.1% (7/29) (p = 0.040). Overall, extended-spectrum beta-lactamase (ESBL) positivity was detected in 26.6% (29/109) of the agents, with 33.3% (12/36) of *K. pneumoniae* and 33.3% (13/39) of *E. coli* being ESBL positive. Carbapenem resistance was found in 11% (12/109) of all isolates, primarily driven by *K. pneumoniae*, which showed a high resistance rate of 30.6% within its species (11/36 isolates). The details of all identified agents and their resistance profiles are provided in Table II. Seventeen of the 98 cultures (71.4%) showed no positive urinalysis results. Of the 28 cultures (28.6%) that yielded findings, 22 (22.4%) were positive for leukocytes, 18 (18.4%) for leukocyte esterase, and 8 (8.2%) for nitrites, respectively. Additionally, hematuria was detected in 3 (3.1%) of the cultures.

Laboratory evaluations during episodes of positive culture showed a median WBC count of 1380/mm^3 (range; 60-14120/mm3), a median absolute neutrophil count of 605/mm^3 (range; 20-12990/mm^3), a median lymphocyte count of 405/mm^3 (range; 0-4530/mm^3), and a median CRP of 6.5 mg/L (range; 0-160 mg/L). A comparison between patients with and without leukocyturia showed significant differences in blood cell counts. The median WBC count was 2490/mm^3 (range; 110-14120/mm^3) in patients with leukocyturia, significantly higher than the 1200/mm^3 (range; 60-6090/mm^3) observed in those without (p=0.004). Similarly, the median ANC was 1255/mm^3 (range: 50-12990/mm^3) in the leukocyturia group, compared to 400/mm^3 (range; 20-5630/mm^3) in the group without leukocyturia (p=0.002). Bacterial growth was also found in 10 (18.2%) of the 55 blood cultures collected during periods of positive urine cultures. A match was seen in 3 of these 10 cases (30%), where the same bacterial species was identified in both blood and urine samples. These patients were thus considered to have urosepsis. The details of the urosepsis episodes are outlined in Table III.

Treatment and follow-up

Of the 98 positive culture episodes, 20 (20.4%) were considered contaminants and were not treated. Twenty-four (24.5%) episodes were treated based on urine culture results, with 13 receiving oral antibiotics and 11 receiving systemic therapy. The remaining 54 (55.1%) episodes were treated with systemic antibiotics due to FN or accompanying infections.

All patients, regardless of their urine culture results, underwent a urinary ultrasonographic examination. These were performed either after the cessation of chemotherapy in 54 patients (58.1%) or during ongoing chemotherapy in 39 patients (41.9%). Overall, 86 (92.5%) examinations revealed normal findings. Other findings included nephrolithiasis in 3 (3.2%) patients, an atrophic kidney in 2 (2.2%) patients, and renal cysts in 2 (2.2%) patients.

During a median follow-up of 17.3 months (range: 0-42) after completing ALL treatment, 7 additional positive cultures were detected in 4 (12.9%) of the 31 patients who underwent follow-up cultures. These episodes were usually associated with dysuria and/or fever. Cultures from these episodes revealed a single pathogen without ESBL production or carbapenem resistance, and all were managed in an outpatient setting.

Discussion

Children with ALL are highly vulnerable to infections because of the severe immunosuppression caused by the primary disease and intensive chemotherapy. This vulnerability is worsened by impaired mucosal barrier integrity. Since most UTIs tend to originate from the periurethral area, this risk significantly increases in children with ALL. Although rare in healthy children, this group can also experience hematogenous spread to the urinary tract from bloodstream

Table III: Characteristics of patients with urosepsis and details of the episodes

	Case 1	Case 2	Case 3
Age (year)	2.5	6	6
Gender	Female	Female	Female
ALL subtype	Precursor B cell	Precursor B cell	Precursor B cell
ALL risk group	High risk	Intermediate risk	Intermediate risk
UTI history before ALL	No	No	No
Phase of chemotherapy	Induction	Reinduction	Reinduction
Clinical status	Febrile neutropenia	Febrile neutropenia	Febrile neutropenia
WBC count (/mm^3)	60	300	360
ANC (/mm^3)	40	80	50
CRP (mg/L)	0	10	0
Urinalysis findings	None	None	Positive leukocytes, leukocyte esterase, nitrites
Bacteria in urine culture	Carbapenem-resistant *Klebsiella pneumoniae*	ESBL-positive *Escherichia coli*	Acinetobacter baumannii and *Escherichia coli*
Bacteria in blood culture	Carbapenem-resistant *Klebsiella pneumoniae*	ESBL-positive *Escherichia coli*	Acinetobacter baumannii
US findings	Normal	Normal	Normal
UTI after ALL	No	No	No

***ALL:** Acute lymphoblastic leukemia, **CRP:** C-reactive protein, **ESBL:** Extended-spectrum beta-lactamase, **US:** Ultrasonography, **UTI:** Urinary tract infection, **WBC:** White blood cell*

infections (6). Due to severe neutropenia, relying on typical symptoms or standard urinalysis results for diagnosis is highly limited. Additionally, immunocompromised children often experience multiple hospital admissions, prolonged hospital stays, and extended courses of antibiotics, making them more susceptible to unusual bacteria or antibiotic resistance (7). Considering these factors, a different approach is needed for interpreting culture-positive urinary episodes in this population.

Our study confirmed an elevated susceptibility to bacteriuria, with 51.6% of ALL patients experiencing a median of two positive urine cultures during their two-year treatment for ALL. This figure is exceptionally high compared to the cumulative incidence reported in the general pediatric population (6.6% in girls and 1.8% in boys in the first six years of life) (8). The high rate of microbial detection confirms that the urinary tract is a frequently colonized site in ALL patients. Studies on children with cancer and UTIs are limited. Shim et al. (9) observed that 74.6% of children with cancer experience UTI at least once (mean 2.8) during chemotherapy. Consistent with general pediatric epidemiology, we observed a significant gender disparity, with girls exhibiting a significantly higher culture positivity rate (71.8% vs. 37.0%). Although not statistically significant, the tendency toward higher culture positivity in younger children (median age; 4.7 years vs. 6.9 years) aligns with the known risk pattern in early childhood (10-12). Additionally, the higher rates seen during intensive treatment phases (induction, consolidation, reinduction) and among patients on high-risk protocols suggest that increased chemotherapy intensity and the resulting profound immunosuppression and hospitalization lead to increased urinary tract vulnerability.

While *E. coli* is the leading cause of pediatric UTIs, accounting for up to 85% of community-acquired cases, our group showed a notable shift in etiology from *E. coli* to non-*E. coli* bacteria, which are common in immunocompromised patients (13). This change was especially prominent in boys (24.1% in boys versus 46.6% in girls), supporting the idea that their infections are more likely to be nosocomial or related to immune suppression from chemotherapy. Although *E. coli* remained the most common isolate at 39.8%, we also saw a nearly equal proportion of *K. pneumoniae* at 36.7%. The microbial causes of UTIs in pediatric oncology patients are highly varied. Comparing our results with existing literature reveals significant differences. Hirmas et al. (14) reported *E. coli* at 51% of isolates, with *K. pneumoniae* at just 9%. Similarly, Shim et al. (9), who focused strictly on children undergoing chemotherapy, found *E. coli* at a rate of 25.6% and *K. pneumoniae* at a rate of 10.5%. Predavec et al. (5) noted *E. coli* at 32.2%, followed by *Klebsiella spp*, at 22.4%. In contrast to these studies, our research revealed an unusually high rate of *K. pneumoniae* at 36.7%. This significant shift toward *K. pneumoniae* suggests regional variations in the microbial environment. It may reflect a higher burden of hospital-acquired infections or a different colonization pattern in our center, considering that *K. pneumoniae* is frequently involved in healthcare-associated infections.

Beyond variations in etiology, a comparative analysis of antimicrobial resistance profiles highlights the growing threat posed by multidrug-resistant (MDR) organisms in this vulnerable population. Hirmas et al. (14) reported that 37% of Gram-negative bacteria produced ESBL, although overall multi-drug resistance was lower at 3%. Predavec et al. (5) found that ESBL production in *K. pneumoniae*

episodes accounted for 20.6%. Our finding of an overall 26.6% ESBL positivity aligns with the broad range observed in these cohorts, confirming that empirical therapy failure due to ESBL production remains a common concern. This trend is consistent worldwide. For example, the Israeli cross-sectional study by Shkalim Zemer et al. (15) reported a significant increase in ESBL-positive *E. coli* rates from 6.1% in 2007 to 25.4% in 2021 within the general pediatric population, emphasizing the widespread evolution of resistance that affects even immunocompromised groups. However, the most concerning finding in our study is the high rate of extreme resistance. The detection of 30.6% carbapenem resistance in our *K. pneumoniae* isolates (making up 11% of all agents) contrasts with the 3% multidrug resistance rates reported by Hirmas et al. (14). This highlights a considerably more severe resistance issue at our center and suggests that first-line empirical antibiotic regimens commonly used for FN may be insufficient against a sizable proportion of community and/or nosocomially acquired uropathogens. Madney et al. (16) reported that surveillance for carbapenem-resistant Enterobacteriaceae in children with cancer led to the appropriate use of targeted antibiotics, resulting in a decrease in the need for intensive care unit admission and a significant reduction in the 30-day mortality rate. A comprehensive review by Mahony et al. (17) highlights that the main risk factors for MDR organisms-UTI in children are prior antibiotic use and hospitalization. Given that our ALL patients have continuous exposure to these high-risk factors due to intensive chemotherapy and prolonged hospital stays, this explains why the MDR organisms' burden is significantly high.

The role of UTIs in FN among pediatric cancer patients remains uncertain, posing a significant diagnostic challenge. In our study, the most common reason for urine cultures was FN (36.7%). While some literature suggests that UTIs are a rare cause of infection in these patients, showing a low incidence of 1.2% of FN episodes, others argue that the frequency of UTIs (up to 8.6%) can be as common as bacteremia in this population (3,4,18). The nature of FN itself worsens this diagnostic uncertainty. Unlike infections of the respiratory or gastrointestinal tracts, UTIs may present with nonspecific symptoms or no apparent signs, except for fever. As a result, UTIs may go undiagnosed unless urine cultures are routinely performed. Missing this diagnosis carries significant risk, especially given the high prevalence of MDR bacteria in the urinary tract. This is clinically important due to the low but notable urosepsis rate (3% in our group, compared to 1.3-2.1% in the literature) (9,14). All three cases of urosepsis in our study occurred during FN with severe neutropenia and involved highly resistant organisms, specifically carbapenem-resistant *K. pneumoniae* and ESBL-positive *E. coli*. This highlights the urinary tract as a critical reservoir for life-threatening MDR sepsis. Therefore, we strongly recommend that urine cultures be routinely obtained as part of the initial diagnostic assessment for all patients with FN, regardless of urinary symptoms or urinalysis results. We found out that a significant portion of positive cultures (71.4%) lacked positive urinalysis findings. Neutropenia explains this weak correlation, as inflammatory responses are suppressed. Leukocyturia only appeared when neutrophil and WBC counts were considerably higher, indicating it is only reliable when ANC is preserved. This emphasizes that clinical suspicion and culture results, rather than urinalysis, should guide diagnosis in ALL patients.

Microbiological surveillance in pediatric oncology primarily focuses on detecting gastrointestinal colonization, as MDR bacteria in stool are associated with increased blood culture positivity and mortality in children with ALL (19). While stool samples are primarily used, some studies suggest stool surveillance may not predict MDR sepsis or mortality (20). The behavior of the urinary tract during immunosuppression is less well understood. Routine urine surveillance is not a standard practice, and data to support it are lacking. However, approximately 30.6% of positive cultures in our cohort were collected during routine workups, supporting the use of proactive culture collection. Given the high prevalence of resistant isolates, routine urine cultures during intensive chemotherapy may help identify MDR organisms early, enabling targeted therapy during FN. Yet, routine urinary surveillance requires careful evaluation due to risks such as increased costs, difficulty distinguishing between infections and colonization, and the potential to promote antibiotic resistance.

The clinical management of culture-positive episodes in this cohort was notably complex. The high rate of episodes deemed contaminants (20.4%) highlights the inherent challenges in sterile sample collection. This issue is likely exacerbated by the need to use non-invasive methods, thereby increasing the risk of false-positive cultures. Despite this, the majority of positive episodes necessitated treatment, frequently systemic therapy, primarily due to concurrent FN. This reflects the essential aggressive approach required in this high-risk population, where clinical status often mandates immediate intervention based on culture results.

Importantly, our follow-up data provide critical reassurance regarding long-term pathology and etiology. The majority of patients (92.5%) exhibited normal findings on urinary US, strongly suggesting that the observed high infection and extreme resistance rates are driven by transient factors—profound immunosuppression and exposure to the hospital environment—rather than by underlying anatomical abnormalities. Furthermore, the low recurrence rate (12.9%) and the general susceptibility of pathogens found after the cessation of ALL treatment suggest that the extreme drug resistance profile is a transient reflection of the intensive chemotherapy environment and substantially resolves upon immune recovery.

This study has several limitations inherent to its retrospective, single-center design. Firstly, as an observational retrospective study, it relies on the integrity and completeness of electronic medical records and laboratory information system data, which may introduce selection or information bias. Secondly, the single-center setting, while providing a uniform patient cohort, limits the generalizability of our findings, particularly the exceptionally high rate of carbapenem resistance in *K. pneumoniae* isolates, which appears to reflect a specific institutional microbial environment. Thirdly, the use of non-invasive urine collection methods increases the risk of

contamination. Although we established a clear retrospective criterion for defining contamination, this remains an interpretive challenge.

Conclusion

This study provides a comprehensive profile of urinary episodes in pediatric ALL, confirming a high incidence, especially during intensive chemotherapy phases. Our most important findings relate to microbial challenges: we identified a significant etiologic shift, with *K. pneumoniae* nearly equal to *E. coli*. We also detected a concerning carbapenem resistance rate in *K. pneumonia* isolates. This extreme resistance profile is critical, as urosepsis cases were exclusively linked to these highly resistant organisms. Clinically, our data show that standard urinalysis is unreliable because of the immunosuppressed state; the vast majority of positive cultures lacked typical findings, and leukocyturia was only present when ANC was relatively preserved. Therefore, we strongly recommend routine urine culture collection during FN workup, regardless of symptoms or urinalysis results, to facilitate timely, targeted therapy. Although driven by transient immunosuppression, the urgent need for local resistance data to guide empirical antimicrobial protocols remains essential.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (30.07.2025, reference number: TABED 1–25-1510).

Contribution of the authors

Study conception and design: DK, ÖAB, SGÖ, NYÖ; data collection: DK, MPA, BD, GHET, MI; analysis and interpretation of results: DK, SGÖ; draft manuscript preparation: DK, MI, SGÖ, NYÖ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Orjinal Article

Radiological evaluation of Chiari 1 malformation: Diagnostic findings and postsurgical imaging

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ABSTRACT

Objective: Chiari 1 malformation is a congenital anomaly characterized by downward displacement of the cerebellar tonsils through the foramen magnum. Surgical decision-making in Chiari 1 largely depends on clinical symptoms and imaging findings, particularly the presence of headache and syringohydromyelia. This study aimed to evaluate the radiological characteristics and postoperative imaging changes in pediatric patients with Chiari 1 and Chiari 1.5 malformations.

Material and Methods: This retrospective study included 101 pediatric patients (age range; 1–18 years) diagnosed with Chiari 1 or Chiari 1.5 based on brain and cervical spine MRI findings between November 2022 and April 2025. Clinical and radiological data, including tonsillar descent, syringomyelia, craniovertebral junction anomalies, and basal angle measurements were analyzed. Twenty-one patients underwent posterior fossa decompression and postoperative MRIs were evaluated at 3 and 6 months. Statistical analyses were performed using chi-square, Mann–Whitney U, Wilcoxon signed-rank, and McNemar tests, with $p < 0.050$ considered significant.

Results: Among the 101 patients, 52 (51%) were female, and 49 (49%) were male (mean age; 11.1±4.9 years). Headache was significantly more frequent in operated patients (66.7% vs. 32.5%, p=0.014). Syringomyelia was also more common in the surgical group (33.3% vs. 3.8%, $p < 0.001$), and tonsillar descent was greater (14.3±5.3 mm vs. 9.5±3.6 mm, $p<0.001$). No significant differences were found between the groups regarding age, sex, basal angle, or foramen magnum diameter. Postoperative follow-up revealed regression of syrinx dimensions and clinical improvement in all operated patients.

Conclusion: Headache, syrinx formation, and greater tonsillar descent are key radiological and clinical predictors of surgical intervention in pediatric Chiari 1. While craniovertebral junction anomalies and hydrocephalus may coexist, they appear less predictive of surgical necessity. Posterior fossa decompression remains a safe and effective treatment in symptomatic pediatric patients, leading to both clinical and radiological improvement.

Keywords: Chiari 1 malformation, craniovertebral junction, pediatric MRI, posterior fossa decompression, syringomyelia

Introduction

Chiari malformation was first described in 1890 by the Austrian pathologist Hans Chiari (1). It represents a spectrum of developmental abnormalities primarily involving the posterior fossa and the craniocervical junction. To date, nine subtypes have been described in the literature (2,3). Advances in neuroimaging techniques have contributed significantly to the recognition and expansion of this classification.

For accurate diagnosis and appropriate management, it is essential to evaluate Chiari 1 not as an isolated malformation but within the context of associated deformities and related Chiari subtypes. As the primary treatment modality is surgical, the identification of subtypes, associated anomalies, and the exclusion of other potential causes of tonsillar descent are of critical importance (4).

Diagnosis is established when the cerebellar tonsils extend ≥5 mm below the foramen magnum, defined by a line between the basion and opisthion on the midsagittal plane.

Confirmation of tonsillar descent on coronal images is important for diagnostic accuracy (5).

Among the related and overlapping entities, Chiari 0 represents the presence of a syrinx without cerebellar tonsillar herniation (<5 mm below the foramen magnum). Chiari 0.5 is characterized by no tonsillar herniation (<5 mm below the foramen magnum) but with the cerebellar tonsils located ventral to the line bisecting the medulla on the midsagittal plane. Chiari 1 is defined as a caudal herniation of the cerebellar tonsils >5 mm below the foramen magnum, while Chiari 1,5 describes tonsillar herniation associated with caudal displacement of the obex below the foramen magnum (2).

In daily radiological practice, Chiari 0, 0.5, and 1.5 are less frequently used terms; the most commonly recognized entity within this spectrum is Chiari 1. The current study includes patients diagnosed with Chiari 1 and Chiari 1.5 malformations. Differentiating Chiari 1.5 from Chiari 1 is important, as herniation of the obex below the foramen magnum at the cervicomedullary junction has been associated with less favorable surgical outcomes in some reports (6).

Associated abnormalities include posterior angulation of the atlas and odontoid process, basilar invagination, platybasia, and various craniocervical junction anomalies such as vertebral fusion or segmentation defects. In Chiari İ 1, clival hypoplasia and disruption of the normal parallel alignment between Chamberlain's and McRae's lines are also frequently observed radiologic findings (7).

Syringohydromyelia is considered a complication of the disease and is thought to result from impaired CSF dynamics at the craniocervical junction (8). Approximately 30% of patients are asymptomatic (9). When symptomatic, the most common presentation is suboccipital headache induced by coughing or Valsalva maneuvers. Other manifestations include dizziness, cranial nerve dysfunction, paresthesia, and cerebellar signs (10).

The decision for surgery in Chiari 1 patients is guided by clinical presentation and imaging findings, particularly the presence of headache and syringohydromyelia (11). Neurosurgeons generally recommend surgery under these conditions (12). The most widely accepted surgical approach is posterior fossa decompression with duraplasty which typically involves suboccipital craniectomy and C1 laminectomy to achieve decompression. Postoperative radiological evaluation is essential for assessing potential complications such as cerebellar parenchymal changes and posterior fossa alterations (13-15).

This study aimed to retrospectively characterize the radiological features of Chiari 1 and evaluate postoperative imaging changes in a cohort of symptomatic and incidentally detected patients.

Materials and Methods

Brain and cervical MRI examinations performed between November 2022 and April 2025 in pediatric patients aged 0–18 years were retrospectively reviewed.

Preoperative and postoperative clinical data related to Chiari 1 were reviewed, including the presence of headache (particularly Valsalva-induced), vertigo, sensory disturbances, seizures, and syncope.

Imaging Technique

All MRI examinations were performed using a 1.5-Tesla scanner (SIGNA™ Explorer, GE Healthcare Technologies, Chicago, Illinois, USA) equipped with standard head and spine coils. The cervical spine protocol included sagittal and axial T1- and T2-weighted sequences, while the brain MRI protocol comprised axial T1-, T2-, and FLAIR-weighted, coronal T2-weighted, and 3D T1-weighted sequences. The 3D T1-weighted sequence, routinely included in the brain MRI protocol, was primarily used for detailed evaluation of the craniocervical junction. Imaging parameters included a slice thickness of 3–4 mm, an interslice gap of 0.5–1 mm, and a field of view adjusted according to patient size.

Phase-contrast cine MRI was used to assess cerebrospinal fluid (CSF) dynamics at the craniocervical junction. Imaging was performed in the mid-sagittal plane using a velocity-encoded (VENC) phase-contrast sequence gated to the cardiac cycle. Typical acquisition parameters included: repetition time (TR), echo time (TE), section thickness of 3–5 mm, and a VENC value of 5–12 cm/s to visualize bidirectional CSF pulsations. Flow-sensitive images were reconstructed to generate magnitude and phase maps for the evaluation of CSF flow voids and patency at the foramen magnum.

Imaging analysis

All imaging studies were independently reviewed by two pediatric radiologists with 15 and 8 years of experience, respectively, and discrepancies were resolved by consensus.

On brain MRI, the degree of tonsillar descent below the foramen magnum was assessed on mid-sagittal T1- or T2-weighted images; in cases of asymmetric herniation, the greater degree of descent was recorded.

Patients with tonsillar herniation <5 mm, incomplete clinical data, or herniation secondary to intracranial space-occupying lesions causing increased intracranial pressure were excluded from the study. In patients with tonsillar herniation >5 mm, the anteroposterior diameter of the foramen magnum was measured. Both Chiari 1 and Chiari 1.5 were identified, and surgical reports along with postoperative imaging studies were retrospectively examined. Follow-up MRI examinations were performed at 3 and 6 months postoperatively.

Hydrocephalus was assessed in all patients, and postoperative MRI scans were reviewed to document

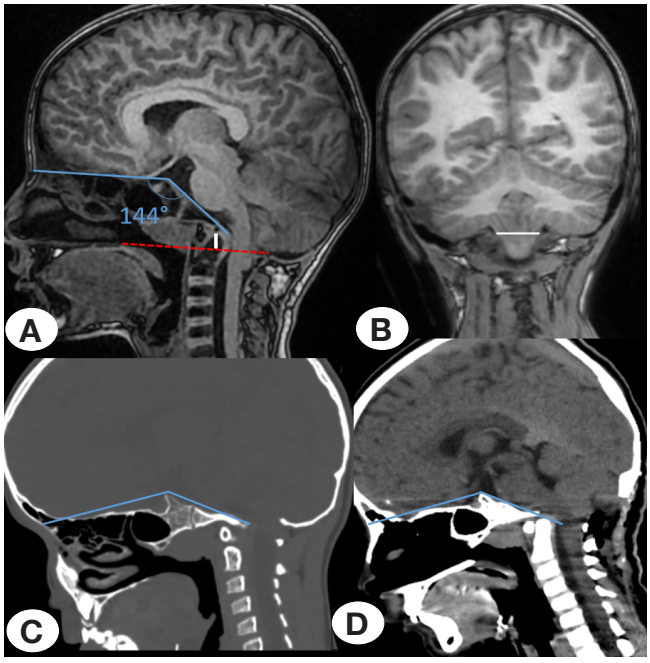

Figure 1: Associated abnormalities in Chiari 1. In a patient with Chiari 1, **A)** sagittal and **B)** coronal T1-weighted MRI, along with **C,D)** Sagittal CT demonstrates a widened basal angle measuring 144° (blue angle), consistent with platybasia. The dens projects above the Chamberlain line (dashed red line), indicating basilar invagination (white line in A). Cerebellar tonsillary herniation also shows descent of the cerebellar tonsils below the foramen magnum (white line). **D)** Following posterior fossa decompression, the basal angle remains unchanged; however, the cerebellar tonsils are restored to their normal position.

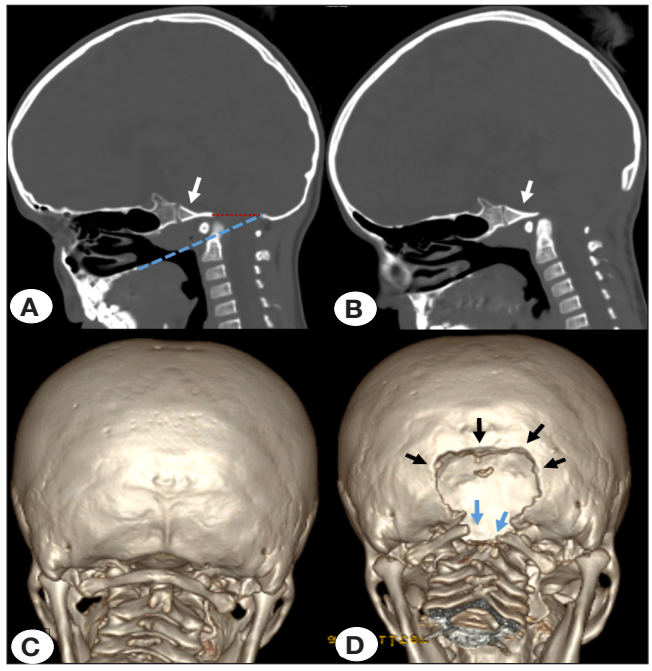

Figure 2: In a patient with Chiari I malformation, **A,B)** sagittal CT images demonstrate an abnormal angulation between the Chamberlain line (dashed blue line) and the McRae line (dashed red line). These lines are normally parallel; however, in Chiari I malformation, clival hypoplasia (white arrows) leads to loss of parallel alignment. **C,D)** preoperative and following decompression operation, 3D reformatted CT images show a post-suboccipital craniectomy defect (black arrows) and an osteotomy defect in the posterior arch of the atlas (blue arrows).

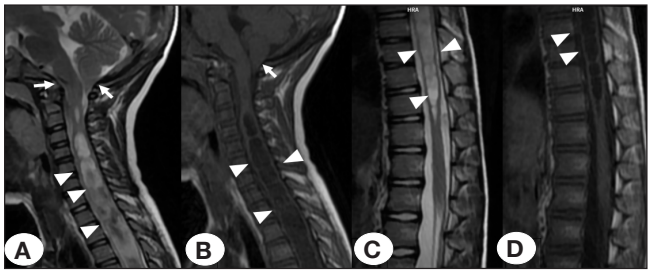

Figure 3: Syringohydromyelia. **A,B)** Sagittal T2-weighted, **C,D)** T1-weighted spinal MRI images demonstrate cerebellar tonsillar herniation with secondary foramen magnum stenosis (white arrows) and an extensive syringohydromyelia involving nearly the entire spinal cord (white arrowheads).

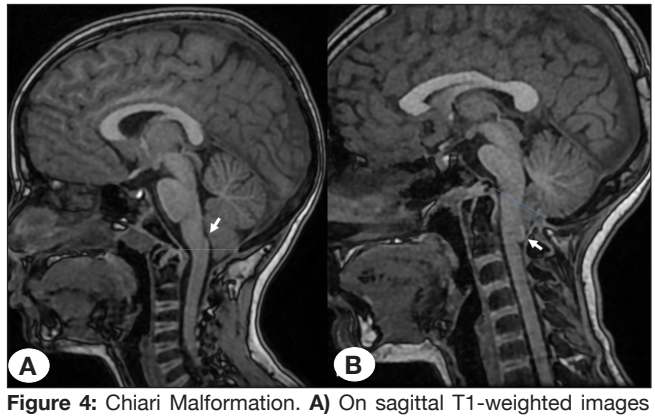

Figure 4: Chiari Malformation. **A)** On sagittal T1-weighted images cerebellar tonsillar herniation indicates a Chiari 1 when the obex (white arrow) remains above the foramen magnum (blue dashed line), **B)** a Chiari 1.5 when the obex (white arrow) is displaced caudally below the foramen magnum (blue dashed line).

ventricular changes, interval improvement or resolution, and any CSF diversion procedures performed.

Cervical spine MRI and CT—when available—were evaluated for vertebral fusion and segmentation defects and craniocervical junction abnormalities. Basal angle measurements were obtained in all patients, with pre- and postoperative comparisons performed in those who underwent surgery (Figure 1-2). Additionally, cervical MRI was reviewed for the presence, location, and dimensions of syringomyelia, and in surgically treated patients, postoperative syrinx. measurements were also recorded (Figure 3).

CSF-flow MRI was performed in patients with Chiari 1 or Chiari 1.5 malformation, as well as in those demonstrating clinical or radiologic findings suggestive of hydrocephalus, craniocervical junction anomalies, foramen magnum stenosis, or cord compression on cranial or cervical MRI (Figure 4). CSF-flow MRI was not performed in Chiari 1 patients who lacked these additional clinical or imaging indications. In patients who underwent CSF-flow MRI, the absence of the

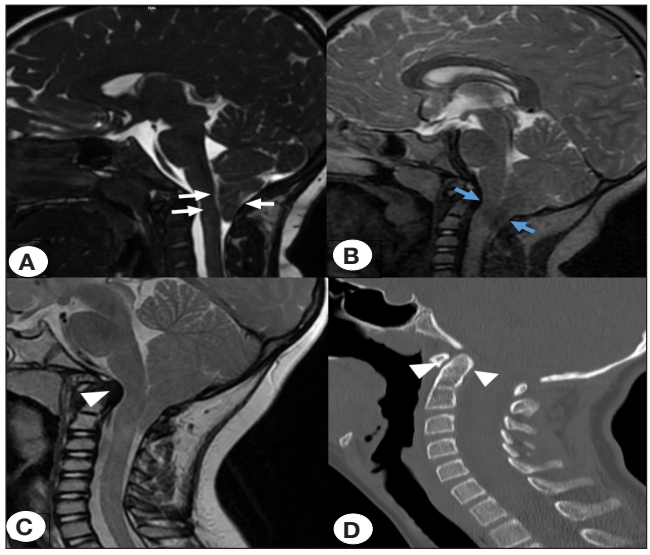

Figure 5: In a patient with Chiari 1, Sagittal FIESTA **A)** and T2-weighted **C)** MRI sequences of the craniocervical junction demonstrate marked narrowing of the foramen magnum secondary to significant cerebellar tonsillar herniation (white arrows). On the DRIVE sequence **B)**, loss of the normal cerebrospinal fluid (CSF) flow void is noted (blue arrows), with additional contribution from posterior angulation of the C2 odontoid process (arrowhead) to the foramen magnum narrowing. Similar posterior angulation of the odontoid process is also evident on the sagittal CT image **D)**.

normal CSF flow void at the level of the foramen magnum was documented (Figure 5).

Statistical analysis

Statistical analysis were performed using SPSS version 26.0 (IBM Corp.). The Kolmogorov-Smirnov test was employed to assess the normality of data distribution. Frequencies and percentages are presented for qualitative data, while for quantitative data, the mean and standard deviation are reported for variables. In the comparison between the operated and non-operated groups, categorical data were compared using the chi-square test, and quantitative variables were compared using the Mann–Whitney U test. Preoperative and postoperative syrinx dimensions and angle measurements were compared using the Wilcoxon signed-rank test, and the presence of syrinx was compared using the McNemar test. A p-value <0.050 was considered statistically significant.

Results

A total of 101 patients were included, with 21 (21%) undergoing surgical treatment for Chiari malformation and 80 (79%) managed conservatively. The majority had Chiari 1, while only 3 (3%) patients were diagnosed with Chiari 1.5; these were included in the operated group. Given the small number of Chiari 1.5 cases, subgroup statistical comparisons were not performed.

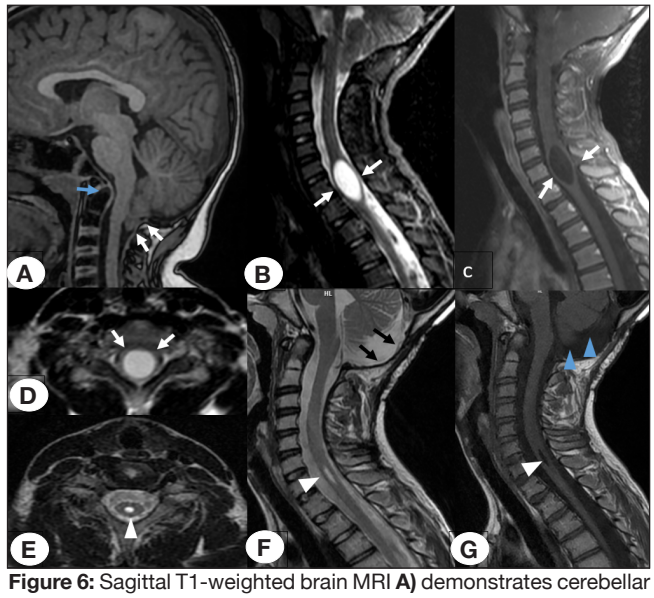

Figure 6: Sagittal T1-weighted brain MRI **A)** demonstrates cerebellar tonsillar herniation (white arrows) and posterior angulation of the C2 odontoid process (blue arrow). On preoperative cervical MRI, sagittal T2- **B)**, sagittal T1- **C)**, and axial T2-weighted **D)** images reveal a syrinx within the central spinal canal at the C7 level. In the postoperative evaluation **(E-G)**, marked regression of the syrinx is observed (arrowheads). Post-suboccipital craniectomy bone defect (black arrows), expansion of the posterior fossa, and upward repositioning and decompression of the cerebellar tonsils (blue arrowheads in f and **G)** are also noted.

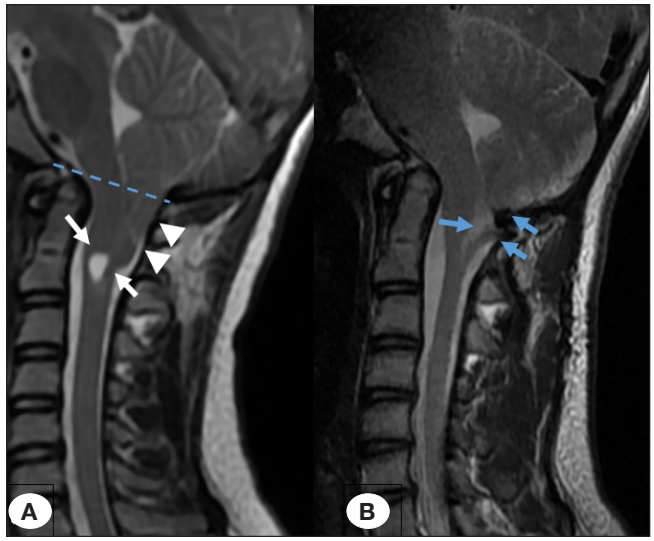

Figure 7: Sagittal T2-weighted cervical spinal MRI obtained **A)** Preoperatively and b. postoperatively demonstrates marked regression of cerebellar tonsillar herniation (arrowheads) and a residual small syrinx cavity within the spinal cord (white arrows), consistent with postoperative improvement in Chiari 1. The postoperative images also show decompression of the foramen magnum region (blue arrows) *The blue dashed line indicates the foramen magnum level.

The mean age of the cohort was 11.1±4.9 years (range; 1–18 years). There were 52 females (51%) and 49 males (49%), with no significant sex predominance observed.

Clinical symptoms attributable to Chiari 1 were absent in 44 patients (43.6%), and the diagnosis was made incidentally

Table I: Craniovertebral and spinal anomalies in patients with Chiari 1 according to surgical status

Anomaly	Operated*	Non-operated*
Posterior angulation of odontoid process	11 (52)	17 (21)
Basilar invagination	1 (5)	5 (6.2)
Platybasia	1 (5)	4 (5)
Vertebral fusion anomaly	0	2 (2.5)
Scoliosis	2 (10)	5 (6.2)
Total	21	80

***:** *n(%)*

Table II: Comparison of morphometric measurements between operated and non-operated patients

	Operated (n = 21)	Non-operated (n = 80)	p
Basal angle*	124.3±7.1	124.3±7.7	0.876
Foramen magnum diameter*	35.3±3.6	36.1±4.6	0.336
Tonsillar herniation*	14.3±5.3	9.5±3.6	<0.001

***:** *mean ±SD*

Table III: Comparison of preoperative and postoperative measurements

	Preoperative	Postoperative	p
Syrinx AP diameter (mm)*	7.25 (2-12)	3.9 (2–7)	0.043
Syrinx CC length (mm)*	55.5 (6-200)	55.1 (6-200)	0.893
Basal angle†	124.3±7.1	126.7±6.2	0.215
Presence of syrinx‡	8	7	1.000

***:** *mean (range),* **†:** *mean±SD,* **‡:** *n(%),* ***AP:** Anteriorposterior,* ***CC:** Craniocaudal*

during imaging performed for other reasons. Headache exacerbated by the Valsalva maneuver, a symptom considered characteristic of Chiari malformation, was reported in 40 patients (39.6%). Vertigo was present in 12 patients (11.9%), seizures or syncope in 1 patient each (1%), and extremity numbness in 4 patients (3.9%). Craniovertebral and spinal anomalies were observed in both operated and non-operated patients (Table I). Posterior angulation of the odontoid process was the most frequent anomaly in both group, whereas basilar invagination, platybasia, vertebral fusion anomalies, and scoliosis were less common. Two patients with scoliosis accompanied by syrinx underwent surgery. Patients without syrinx were followed up (n=5). No vertebral fusion anomalies were identified in any of the operated patients.

Comparisons between operated and non-operated Chiari 1 patients revealed several significant differences. Headache was significantly more frequent in the operated group (66.7% vs. 32.5%, p=0.014), and syrinx formation was markedly more common (33.3% vs. 3.8%, p<0.001). In addition, the mean tonsillar herniation distance was significantly greater in operated patients (14.3±5.3 mm) compared with non-operated patients (9.5±3.6 mm, p<0.001) (Table II).

Here were no statistically significant differences between the operated and non-operated groups regarding age, gender distribution, vertigo, syrinx dimensions (anteroposterior or craniocaudal), foramen magnum diameter, basal angle (p> 0.050 for all). Overall, these results suggest that headache, syrinx formation, and greater tonsillar descent are strongly associated with surgical intervention, whereas the presence of other craniovertebral anomalies appears less predictive (Table III).

Overall, clinical symptoms improved in all operated patients, and, when present, syrinx anteroposterior diameters demonstrated regression (Figure 6,7).

Hydrocephalus was identified in seven patients, six of whom underwent surgical intervention. One patient was managed with a ventriculoperitoneal (VP) shunt. The presence of hydrocephalus was significantly associated with the decision to perform posterior fossa decompression (p <0.001). All patients with hydrocephalus demonstrated a decrease in ventricular size postoperatively, and none required an additional CSF diversion procedure.

All operated patients underwent a posteroinferior occipital craniectomy combined with a laminectomy of the posterior arch of the atlas, and seven patients additionally underwent duraplasty. Clinical improvement was observed in all cases.

In one patient who underwent duraplasty with tonsillar resection, early postoperative diffusion restriction consistent with cytotoxic edema was observed in the cerebellar tonsils; this finding resolved on both the 3- and 6-month follow-up scans.

Discussion

The evaluation of the cerebellar tonsils in relation to the foramen magnum is essential in routine cranial and cervical MRI or CT assessment. Tonsillar descent <5 mm is defined as tonsillar ectopia, whereas descent >5 mm is considered tonsillar herniation, consistent with Chiari malformation. In pediatric patients with Chiari 1, cervical or whole-spine MRI is recommended to assess for associated anomalies such as syringomyelia, tethered cord, and craniocervical junction abnormalities (16). Management typically involves follow-up for ectopia or herniation <1 cm, while herniation >1 cm accompanied by symptoms, syrinx, or hydrocephalus may warrant surgical intervention (17).

In this retrospective study of 101 pediatric patients with Chiari 1 and Chiari 1.5, we observed that headache, syrinx formation, and greater tonsillar descent were significantly associated with the decision to perform surgical intervention. The majority of patients presented with Chiari 1, and only a

small subset had Chiari 1.5, consistent with previous reports highlighting the rarity of the latter in the pediatric population (18). Although Chiari 1.5 are less frequently observed, the obex in these patients is positioned below the foramen magnum, contributing to increased foramen magnum stenosis and neural compression, which may accentuate clinical manifestations. Several studies have also proposed that Chiari 1.5 represents a progressive variant of Chiari 1 (19). A hypothesis that may account for its relative rarity in the pediatric population.

Headache exacerbated by the Valsalva maneuver was the most common clinical symptom in operated patients, supporting its utility as a predictive symptom for surgical intervention. This aligns with prior studies that have identified Valsalva-induced headache as a hallmark feature of symptomatic Chiari malformation (20,21). Dizziness, parestehesias, seizures, and syncope were observed less frequently in the cohort; however, notable improvement in these symptoms was also documented following surgical decompression. Symptoms such as headache and paresthesia may provide important guidance in the differential diagnosis of other neurological disorders. Although numbness and paresthesias are often interpreted as suggestive of demyelinating disease, it is crucial to assess these manifestations within the context of Chiari 1, as they can also occur as a direct consequence of the malformation itself (2).

Syringomyelia was significantly more prevalent in the operated group, consistent with the well-established association between syrinx presence and symptomatic Chiari malformation (22,23). In our cohort, surgical decompression resulted in regression of syrinx dimensions in all patients, supporting the efficacy of posterior fossa decompression in restoring normal CSF dynamics and reducing syrinx size. In our study, postoperative follow-up imaging was conducted at 3 and 6 months. During this interval, a significant reduction in the anteroposterior diameter of the syrinx was observed; however, no appreciable decrease in the craniocaudal dimension was detected. This discrepancy may reflect the relatively short follow-up period, underscoring the need for longer-term imaging to fully assess syrinx resolution. Notably, the mean tonsillar herniation distance was greater in operated patients, corroborating previous studies that have suggested the degree of herniation as a factor influencing surgical decision-making (24,25).

Following the assessment of cerebellar tonsillar herniation, it is essential to evaluate the craniocervical junction for anomalies and potential instability. Growing evidence suggests that craniocervical instability may contribute to tonsillar herniation in at least a subset of patients with Chiari 1 (5,26,27). In our cohort, craniovertebral junction anomalies—including posterior angulation of the odontoid process, basilar invagination, and platybasia—were frequently observed. Although these anomalies did not appear to influence the decision for surgical intervention in our study, their presence remains clinically significant, as they may impact patient morbidity and long-term outcomes.

In our cohort, hydrocephalus emerged as a strong predictor for surgical intervention, aligning with previous reports identifying ventricular enlargement as a marker of disease severity in Chiari 1 (28,29). Nearly all patients with hydrocephalus underwent posterior fossa decompression, and the statistical association between hydrocephalus and the decision for surgery was highly significant ($p<0.001$). This finding supports the notion that concurrent hydrocephalus not only reflects increased intracranial pressure dynamics but also influences neurosurgical management strategies. Early recognition of hydrocephalus may therefore facilitate timely surgical planning and potentially improve postoperative outcomes.

All surgeries consisted of a posteroinferior occipital craniectomy with C1 laminectomy, and seven patients underwent duraplasty. Clinical improvement was observed in all patients, and postoperative imaging demonstrated resolution of syrinx and, in one case, transient diffusion restriction in the cerebellar tonsils that resolved by 3 months. These findings indicate that posterior fossa decompression is generally safe and effective in children, with low rates of transient complications and favorable radiological and clinical outcomes (30).

Limitations

Limitations of this study include its retrospective design and the single-center setting, which may limit generalizability. Additionally, thoracic and lumbar vertebral anomalies were not evaluated, and the small number of Chiari 1.5 patients precluded subgroup analysis. Prospective, multicenter studies with larger cohorts are needed to further delineate predictors of surgical intervention and long-term outcomes in pediatric Chiari malformations.

Conclusion

In conclusion, our findings emphasize that headache, syrinx formation, and increased tonsillar descent are key factors associated with the decision to operate in pediatric Chiari 1. While craniovertebral junction anomalies may coexist, they appear less predictive of surgical necessity. Posterior fossa decompression is effective in achieving clinical improvement and syrinx regression, supporting its continued role as the primary surgical intervention in symptomatic pediatric patients.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Etlik City Hospital (13.03.2025, reference number: 2025-124).

Contribution of the authors

Study conception and design: ŞY, BU; data collection: ŞY, ZZDÖ; analysis and interpretation of results: ŞY, HB, MEE; draft manuscript

preparation: ŞY, BU. All authors reviewed the results and approved the final version of the article.

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Conflict of interest
The authors declare that there is no conflict of interest.

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Original Article

Social pediatrics internship students' perspectives on the Covid-19 pandemic's effects on children

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ABSTRACT

Objective: Social pediatrics evaluates children's health within the context of society, environment, education, and family, employing a global, holistic, and multidisciplinary approach to child health. Our study aimed to explore the viewpoints and attitudes of fifth-year medical students who completed the Social Pediatrics Internship Education Program regarding the effects of the COVID-19 pandemic on children.

Material and Methods: We asked medical students to write about the most common effects of the COVID-19 pandemic on children from their perspective using a Google Form. Subsequently, we employed both quantitative and qualitative methodologies to analyze the responses provided by the medical students.

Results: Overall, 246 students voluntarily participated in the study and wrote a total of 1722 items. The medical students predominantly addressed the impact of the COVID-19 pandemic on various facets of children's well-being, including development, physical activity, community/social dynamics, physical health, mental health, safety, healthcare access and provision, and infectious diseases.

Conclusion: This study highlights the ability of medical students who undertook the Social Pediatrics programme to demonstrate empathy and adopt a social pediatrics perspective when examining the impact of COVID-19 on children.

Keywords: Children, COVID-19 pandemic, education, medical students, pediatrics

Introduction

The coronavirus disease 2019 (COVID-19), declared by the World Health Organization in March 2020, has affected more than 216 countries worldwide (1). Although children were not considered the main actors in the pandemic because severe disease was not usually observed in them, the pandemic has profoundly affected children's health worldwide, with vulnerable populations disproportionately bearing the burden (2,3). Besides the catastrophic socioeconomic impacts, the fear of infection, strict social quarantine measures, and closure of schools and other public places have had negative effects on children's health (2,3).

In Türkiye, as in many parts of the World, countermeasures including stay-at-home orders, social distancing, school closures, and mask requirements were implemented to combat the pandemic (4).

Research indicates that regulations such as school closures may reduce the spread of infections during pandemics (5). However, in the long term, prolonged disruptions to physical activity, socialization, and stress may exacerbate cardiovascular and metabolic risk factors in children and adolescents (6,7). A systematic review reported that anxiety, depression, irritability, boredom, inattention, and fear of COVID-19 were predominant new-onset psychological problems in children during the COVID-19 pandemic. It has also been reported that existing behavioral problems, such as autism and attention-deficit hyperactivity disorder, may also exacerbate. This highlights the need for targeted interventions that consider social determinants of health, including economic stability, education, neighborhood conditions, psychosocial context, and healthcare access (2, 8,9). There are many studies on the impact of COVID-19 that have focused primarily on the well-being and experiences

of children, parents, and healthcare providers (2, 3, 10-12). To our knowledge, no published study has investigated future physicians' perspectives on the challenges children will face due to global crises.

This study aimed to explore the perceptions of medical students who completed the Social Pediatrics Internship Program regarding the effects of the COVID-19 pandemic on children. The findings will contribute to the literature by highlighting the awareness medical students gain about child health problems during social pediatrics training. Additionally, they will help institutions evaluate and enhance programs to better prepare future physicians for disaster periods, ensuring they can effectively address the unique needs of the most vulnerable populations.

Materials and Methods

The study was conducted between February 1 and June 30, 2024, and included fifth-year medical students who had completed the two-week Social Pediatrics Internship Education Program within the 2022-2023 academic year.

Structure of the social pediatrics internship program

Social pediatrics adopts a holistic, multidisciplinary approach to child health, focusing on the interplay of physical, mental, and social well-being within societal, environmental, and familial contexts. It addresses child health problems linked to social determinants, emphasizing prevention, early diagnosis, and quality-of-life enhancement. Countries such as Türkiye and the Netherlands recognize social pediatrics as a subspecialty of Pediatrics (13). Social Pediatrics lectures are taught during the fifth year of the six-year education at Hacettepe University, Faculty of Medicine. Medical students undertake a two-week internship program in social pediatrics during the fifth academic year. They also rotate through pediatric clinics to gain experience in pediatrics, in addition to theoretical courses.

The content of the lectures given by Social Pediatricians are not specifically related to COVID-19 infection or the pandemic, but due to its relevance at the time of the study, topics such as transmission routes, prevention, clinical features, and treatment methods are discussed, particularly in the courses "Control and management of communicable diseases" and "Integrated management of childhood illnesses."

Study design

Before conducting the main study, a pilot investigation with 20 medical students revealed key perceived effects of the COVID-19 pandemic on children's health. Based on these preliminary findings, a Google Form survey was developed and shared through WhatsApp groups coordinated by student representatives. After providing online informed consent, participants were asked to respond to the open-ended exploratory question: "What are the effects of the COVID-19 pandemic on children's health? Please list and elucidate the most significant topics for you."

All participants were fifth-year medical students completing their mandatory two-week Social Pediatrics Internship at Hacettepe University Faculty of Medicine. This internship integrates theoretical courses and clinical practice in Adolescent Health, Developmental Pediatrics, and Pediatric Genetics. As confirmed by the university registry, all students in this cohort were aged 23-25 years, making additional demographic collection unnecessary and preventing potential identification.

Statistical analysis

Data were analyzed using a qualitative and quantitative method. Responses were transcribed, coded, and analyzed using MAXQDA 2024 software. One researcher wrote down all the text. Then, two researchers independently analyzed, coded, and generated preliminary themes. A qualitative research expert supervised the process and resolved any discrepancies between coders. The researchers established different codes during the analysis, grouping them into thematic sections under a specific category. The topics discussed by the students were grouped under seven headings based on their similarities, and the emphasis on these items was also calculated as a percentage.

Triangulation and Analytical Rigor

To enhance the credibility and validity of the findings, a triangulation strategy was adopted, consistent with Denzin's theory of triangulation, which emphasizes the integration of multiple perspectives to strengthen research trustworthiness(14, 15). In this study, researcher triangulation was ensured by having two researchers independently code and interpret the data, while a third researcher with expertise in qualitative methods served as a supervisor to resolve disagreements and provide analytical oversight. In addition, method triangulation was applied by complementing qualitative thematic analysis with descriptive quantitative calculations of theme frequency. This combined approach enabled a more comprehensive interpretation of students' perceptions, enhancing the transparency, rigor, and interpretive depth of the findings (14, 15).

Results

Among the 246 subjects who participated in the study, 135 (54.9) were male. The medical students wrote an average of 7 items (range: 6-9), totaling 1.722 items.

We classified the students' perspectives on the most common impacts of the COVID-19 pandemic on children into seven categories according to the issues, with the most commonly reported effects presented as follows: 1. Effects on development, 2. Effects on health supervision and provision, 3. Effects on physical health, 4. Effects on infectious diseases. 5. Effects on mental health, 6. Effects on safety, and 7. Effects on community/ social structure.

The percentage distribution of the effects reported by medical students is shown in Table I. Within the analyzed data framework, statements of medical students are given in Tables II-VI.

Table I: Distribution of COVID-19 pandemic effects on children reported by medical students (n=246)	
Effects on development	
Socialization problems	169 (68.7)
Retardation in social development	101 (41.1)
Retardation in motor development	49 (19.9)
Retardation in cognitive development	40 (16.3)
Retardation in neurological development	37 (15.0)
Reduction in playing games	37 (15.0)
Separation from healthcare worker parents	20 (8.1)
Retardation in language development	10 (4.1)
Loss of communication skills due to mask	4 (1.6)
Effects on health supervision and provision	
Disruptions in vaccination	70 (28.5)
Decrease in hospital admissions	61 (24.8)
Interruption in medical check-ups	54 (22.0)
Delay in hospital admission	54 (22.0)
Disruption in child health follow-up	50 (20.3)
Disruption in antenatal care and follow-up, an increase in birth complications	18 (7.3)
Increased infant mortality	13 (5.3)
Effects on physical health	
Decrease in physical activity /playing outside	167 (67.8)
Increased risk of metabolic diseases	131 (53.2)
Undernutrition and growth retardation	80 (32.5)
Vitamin D deficiency	25 (10.2)
Decreased exposure to sunlight	27 (11.0)
Increased disorders of muscle, joint, spine, and posture	18 (7.4)
Increase in allergic diseases	9 (3.6)
Staying away from unhealthy foods outside*	2 (0.8)
Effects on infectious diseases	
Risk of contracting the COVID-19	77 (31.3)
Risk of acute complications of COVID-19	53 (21.5)
Risk of long-term effects of COVID-19	30 (12.2)
Increase in HIV infection in children	12 (4.9)
An increase in hygiene awareness*	7 (2.8)
Decrease in other infectious diseases *	6 (2.4)
Insufficient development of microbiota	3 (1.2)
Effects on mental health	
Increase in mental/psychological disorders	125 (50.8)
Increased anxiety	70 (28.5)
Increased depression	64 (25.5)
Trauma due to illness or loss of a family member	64 (25.5)
Internet addiction	35 (14.2)
Sleep disorders	27 (11.0)
Increased stress and HPA axis overactivation	25 (10.2)
Increase in eating disorders	22 (8.9)
Increase in ADHD	13 (5.3)
Increased suicide rates among adolescents	9 (3.7)
Relief from school/exam stress*	1 (0.4)
Effects on safety	
Exposure to abuse-neglect	92 (37.4)
Exposure to domestic violence	82 (33.3)
Increase in child marriage	14 (5.7)
Increase in child labor	7 (2.8)
Increase in home accidents	9 (3.7)
Disruption of child protection programs	2 (0.8)
Effects on The Community /Social Structure	
Disruption in education	163 (66.3)
Economic problems (unemployment)	97 (39.4)
Spending more time with parents and family *	19 (7.7)
Increase in hygiene awareness *	7 (2.8)
Decrease in the resources allocated for pediatric diseases	3 (1.2)
Acquiring new interests and hobbies *	2 (0.8)
Increase in plastic pollution	2 (0.8)
Decrease in air pollution*	1 (0.4)

***:** *Protective effects*

Effects on development

Medical students' comments regarding the pandemic's effects on the socialization and social development of infants, children, and adolescents were more prominent than other issues (Table I). The most frequently noted issues included socialization difficulties and limitations in the surrounding environment (68.7%), and retardation in social development (41.1%). Additional concerns regarding social development included reduced participation in games (15.0%), and separation from healthcare worker parents (8.0%). Developmental concerns were retardations in motor (19.9%), cognitive (16.3%), neurological (15.1%), and language development (4.1%) (Table I).

The students discussed the COVID-19 pandemic's effects on children's development; the harms of increased screen time; the difficulties faced by children with special needs; sustainable developmental goals; and the importance of play and peer communication (Table II).

"We must consider the child's health as a whole. When we look at it from this perspective, a pandemic affects children's health and development both physically, psychologically, and socially" (Medical student).

"The normal development of children confined to home for long periods has been greatly affected. Children were negatively affected, especially considering the importance of interacting with their friends at these ages" (Medical student).

Effects on health supervision and provision

This issue raised concerns, including disruptions in childhood vaccination schedules (28.5%), reduced hospital admissions and limited access to healthcare services (24.8%), interruptions in the routine check-ups of chronically ill children (22.0%), delays in hospital admissions (22.0%), and disruption in child health follow-up (20.3%) (Table I).

The students noted their concerns about disruptions to follow-ups and vaccinations, delays in prevention and management, avoidance of hospitals, and increases in child mortality during the pandemic (Table III).

"There has been a significant decrease in routine health services that children and pregnant women receive, such as immunization and antenatal care. This can increase mortality rates in the long run" (Medical student).

Table II: Statements about the children's development

Developmental areas
"We must consider the child's health as a whole. When we look at it from this perspective, a pandemic affects children's health and development both physically, psychologically, and socially."
"Since children do not spend time with their friends and cannot socialize, there may be difficulties in social integration and a predisposition to asociality."
"The normal development of children confined to home for long periods has been greatly affected. Children were negatively affected, especially considering the importance of interacting with their friends at these ages."
Harms of increased screen exposure
"Sedentary lifestyle and screen exposure increased. Increased screen exposure is a risk factor for a child's cognitive, social, and other developmental areas."
"Confining children to the home may cause communication difficulties due to the restriction of children's motor skills in the development process and their social communication with their peers."
Difficulties of children with special needs
"Since children who need special education cannot go to special education, their development has been adversely affected."
Sustainable developmental goals
"Delay in implementing sustainable development goals will negatively affect children's education, development, and mental health in the long run"
Importance of playing and communicating with peers
"Play is an important factor in the development of children's imagination. I think that kindergarten children who cannot go to school are socially affected worse".
"Children learn better in communication with their peers while playing. I think language development is affected especially in children between 3 and 5."

Table III: Statements about the children's health supervision and provision

Disruption of follow-ups, and vaccinations
"Perinatal screening and vaccination services have been disrupted due to the overload on the health system."
"There has been a significant decrease in routine health services that children and pregnant women receive, such as immunization and antenatal care. This can increase mortality rates in the long run."
"The children whose vaccination schedules were delayed because their parents were afraid to go to the hospital are at risk of infectious diseases. The infections can affect the brain, cause developmental delay, and serious complications."
"Children have been deprived of the health care they need. The disruption in the follow-up of children with chronic diseases caused delays in vaccination schedules and growth-development follow-ups."
Delay in prevention and management
"There were problems related to being unable to determine treatment arrangements."
"During the pandemic, depending on the decrease in the frequency of visits to the hospital, there may be delays in the follow-up of children starting from the neonatal period. This may have led to the failure to prevent health problems."
Avoidance from hospitals
"With the pandemic, hospitals have become risky areas. Children with chronic diseases may have health problems due to the avoidance of hospitals with a fear of COVID-19."
Increase in child mortality
"Child mortality rates will likely rise in the long run, especially with the avoidance in access to immunization and antenatal health care."

Effects on physical health

During the pandemic, most medical students (67.8%) reported a significant reduction in children's physical activities and outdoor play. Over half (53.2%) highlighted an increased risk of obesity, diabetes, and secondary atherosclerosis. Other concerns included undernutrition and growth retardation (32.5%); reduced sunlight exposure (11.0%); vitamin D deficiency (10.2%); and increased musculoskeletal disorders (7.4%). A positive impact was staying away from unhealthy foods outside (0.8%) (Table I).

The students' main concerns were increased obesity, malnutrition, and disruption of breastfeeding (Table IV).

"Deterioration of nutrition and inability to play active games increased body mass index and obesity in children" (Medical student.)

"Malnutrition may develop due to the poor diet of children whose families were dismissed due to the economic problems caused by the pandemic"(Medical student).

Effects on infectious diseases

The risks of children contracting COVID-19 (31.3%), acute complications (21.5%), and the long-term effects of the disease (12.2%) were reported as significant negative effects. However, a decrease in other infectious diseases due to mask use (2.4%) and increased hygiene awareness (2.8%) were reported as positive effects (Table I).

The students mainly reported concerns regarding COVID-19 morbidity, mortality, and complications, as well as the positive effects of increased hand hygiene and mask use (Table IV).

"Children have a longer life expectancy, and even if they survive the COVID-19 infection, there is a risk of morbidity in all affected organs, especially the lungs" (Medical student).

Effects on mental health

About half (50.8%) of medical students reported an increase in mental health disorders among children and adolescents. Most frequently cited issues were increases in anxiety, depression,

Table IV: Statements about the children's physical health and infectious diseases

Physical Health
Increase in obesity
"Deterioration of nutrition and inability to play active games increased body mass index and obesity in children."
Malnutrition
"Malnutrition may develop due to the poor diet of children whose families were dismissed due to the economic problems caused by the pandemic."
Disruption of breastfeeding
"Due to fears of contagion and separation from their children, COVID-19-positive mothers were unable to breastfeed regularly. We do not know how the lack of mother's milk affects children in the long term."
"During the pandemic, without regular access to breast milk, infants may be more susceptible to illnesses and other health issues. Additionally, the emotional bond between mother and child formed through breastfeeding can benefit the child's psychological development."
Increase in allergic and autoimmune diseases
"Excessive use of hand sanitizers may cause allergic dermatitis on children's hands, excessive use of surface disinfectants in public areas may increase the risk of allergic diseases and asthma in children."
Infectious diseases
Morbidity, mortality, and complications of COVID-19
"Children have a longer life expectancy, and even if they survive the COVID-19 infection, there is a risk of morbidity in all affected organs, especially the lungs."
"COVID-19 usually does not cause severe illness in children. However, children with COVID may develop multisystem inflammatory syndrome and atypical Kawasaki disease."
Prevention of infections by increased hand hygiene practices and mask use
"Many infections in children, including respiratory and gastrointestinal infections, will be prevented via the settled handwashing habits and the widespread use of masks."

and trauma due to illness or loss of a family member (25.5%), internet addiction (14.2%), sleep disorders (11.0%), and stress linked to HPA axis overactivation (10.2%). Higher rates of eating disorders, particularly overeating (8.9%), ADHD (5.3%), and suicide among adolescents were also noted. A small positive effect (0.4%) regarding relief from school and exam stress was reported (Table I).

The students mentioned increased stress because of financial problems, school closures, and socialization-psychological problems; increased screen time and internet addiction; adolescents' mental health; cleaning obsession; decreased self-esteem; and burnout syndrome in parents. In addition, they noted increased family bonds and decreased exposure to bullying as positive effects (Table V).

"Considering the effects of the COVID-19 pandemic on children's health, first of all, psychiatric problems come to mind. As the adults around the child have anxiety and struggle with financial difficulties, the child becomes nervous as the parents are nervous."(Medical student).

Effects on safety

Medical students reported exposure to abuse/neglect (37.4%) and domestic violence (33.3%) as the most typical effects (Table I). Others included increased child marriage (5.7%), child labor (2.8%), home accidents (3.7%), and disruption of child protection programs (0.8%) (Table I, Table VI).

"Stress caused by other individuals in the house can cause violence, neglect, and abuse to increase. Unemployment and economic problems may cause the child's needs not to be met" (Medical student).

Effects on the community/social structure

The medical students highlighted primarily the disruption to education resulting in inequality of opportunity due to school closures (66.3%), and economic problems stemming from rising unemployment (39.4%) (Table I). Positive effects were spending more time with family (7.7%), increased hygiene awareness (2.8%), and the development of new hobbies (0.8%) (Table I).

The students reported that inequality in educational opportunities, working parents, health and education disparities among disadvantaged children, and school closures were their primary concerns (Table VI).

"The pandemic has exacerbated the disadvantage faced by poor children. Families in poverty are more likely to have insecure income sources, less access to health services, and concomitant diseases" (Medical student).

"Children in vulnerable groups, such as those living in refugee camps or orphanages and children with disabilities, require face-to-face education and home health services more than others "(Medical student).

Discussion

This study examined how medical students who completed a Social Pediatrics Internship interpreted the effects of the COVID-19 pandemic on children's health using a social determinants perspective. The students' evaluations reflected the pandemic's multidimensional effects on children, consistent with global findings, and highlighted the importance of integrating social pediatrics into undergraduate medical education to improve crisis preparedness for child health.

Developmental consequences

Medical students emphasized that the COVID-19 pandemic disrupted children's play, peer interaction, and exploration, leading to developmental delays in motor, cognitive, and social domains. They also noted that these effects were

Table V: Statements about the children's mental health

Increased stress because of financial problems	*"Considering the effects of the COVID-19 pandemic on children's health, first of all, psychiatric problems come to mind. As the adults around the child have anxiety and struggle with financial difficulties, the child becomes nervous as the parents are nervous."* *"With parents losing their jobs, many families are unable to provide the same level of support as before, leading to an increased risk of poverty and deprivation. This can put an immense psychological burden on children, as well as leaving them without access to the basic resources they need for their development."* *"A significant increase in unemployment and financial uncertainty has resulted in children experiencing anxiety and stress. In addition, their fundamental rightstonutrition, shelter, and living conditions are adversely affected."* *"Due to acute stress of the pandemic, the hypothalamic-pituitary axis is activated and causes glucocorticoid release. This disrupts proinflammatory and anti-inflammatory regulation. Eating disorders and excess weight gain due to a sedentary life can cause anxiety in children."*
School closures and socialization-psychological problems	*"Schools are places where children socialize. With the closure of schools, children experienced psychological problems such as loneliness and depression, and their suicidal tendencies increased."*
Increased screen time and internet addiction	*"Children's attendance on computers and tablets for education, as well as long-term quarantines, have increased children's screen exposure and internet addiction risk."*
Adolescents' mental health	*"Personality development in adolescents may be disrupted. There may be an increase in mental health problems such as depression and suicide attempts."* *"During the adolescent years, problems such as arguments with parents, identity crises, a decrease in motivation for lessons, and anxiety due to the need for social interaction increased due to theexpansionin time spent at home during pandemic restrictions, but its poor quality"* *"With parents working at home, their presence and attention to their children have been limited. This has led adolescents to feel a sense of disconnection from their parents. As a result, they have felt more isolated, anxious, and have struggled with their lives."*
Obsession with cleaning	*"The frequent use of disinfectants may give children unrealistic expectations of hygiene, leading them to believe that their environment must always be pristine. This can lead to an obsession with cleaning and a fear of germs, which can lead to anxiety and other psychological issues."*
Decreased self-esteem	*"Children are becoming more dependent on their families due to the lack of peer interaction. This will decrease the development of self-esteem, which will help in getting future responsibilities and making decisions."*
Burnout syndrome in parents	*"Since children are spending more time with their families, Burnout syndrome has become more prevalent among caregivers."*
Increased family bonds	*"By working fewer hours and spending more time together, families can bond and create a stronger sense of connection and harmony that can reduce stress levels.*
Decreased exposure to bullying	*"Educating children at home provides them with a safe and secure learning environment that can help to protect them from stressors such as bullying."*

more severe for children with special needs who lost access to early intervention and education. Their observations align with studies reporting decreased physical activity, increased sedentary behaviors, and impaired motor and socio-emotional development associated with prolonged screen time, limited environmental exposure, and disrupted daily routines (2,3,16,17). Research also highlights that stress, reduced educational opportunities, and exposure to economic hardship pose risks to long-term developmental trajectories (11,16,18,19). The students' recognition of these broader consequences reflects an understanding of how societal disruptions can hinder children's sustainable development, signaling an awareness beyond individual clinical symptoms.

Importantly, the students framed these developmental effects as multidimensional—physiological, psychosocial, and environmental—demonstrating a holistic interpretation consistent with the core principles of social pediatrics. Their focus on vulnerable groups and early childhood needs suggests that social pediatrics training enables future physicians to identify inequities early, advocate for preventive action, and integrate developmental surveillance with social determinant-based care. Thus, this study contributes to medical education by showing that structured social pediatrics instruction helps students conceptualize child development not only as a clinical issue but as a socially mediated outcome that requires interdisciplinary and policy-driven solutions.

Medical students' awareness of these issues may stem from attending the lecture "Following up and supporting early childhood development".

Health supervision and provision

Medical students emphasized that the COVID-19 pandemic disrupted routine child health services, including vaccinations, developmental screening, and follow-ups. They linked these disruptions to reduced healthcare utilization, delayed diagnoses, and increased vulnerability to vaccine-preventable infections. Similar declines in child vaccinations and preventive care have been documented worldwide, including Türkiye, where service cancellations and socioeconomic hardships have contributed to delayed access, particularly among underserved populations (20, 21). These reflect that child health outcomes depend not only

Table VI: Statements about children's safety, community or social structure

Safety

Child abuse, neglect, and domestic violence

"Stress caused by other individuals in the house can cause *violence, neglect, and abuse to increase. Unemployment and economic problems may cause the child's needs not to be met."*

"Children are most frequently subjected to violence by their caregivers. Quarantine measures make it difficult to detect violence and abuse."

"Since children are spending more time with their families, Burnout syndrome has become more prevalent among caregivers, and this can cause increased abuse risk."

Early marriage and child labor

"Without the safe space of schools for a prolonged time, children became more vulnerable to exploitation. This was especially true for children from poorer backgrounds, who faced higher risks of being forced into early marriage or labor. Furthermore, parental lack of education made it harder to detect signs of abuse, worsening the problem."

"Schools' closing has resulted in the early marriage of girls, the presence of adolescent pregnancies, and the poor level of education of mothers."

Home accidents

"Children's obligation to stay at home has come with the curfew, and especially younger children whose families are at work, and reach sharp objects, etc., and may face home accidents more."

Community/ Social Structure

Inequality in opportunity for education

"The schools are closed. Children are more likely to rely on their families, rather than peer interaction, for guidance and advice. This can lead to them not having the experience of making their own decisions or solving problems, which can cause issues as they become independent adults."

"Children's right to education has been violated. Not all children have the same rights in Türkiye. There is great socioeconomic inequality. When the schools closed, some children could not access online education."

"As far as social mobilization and social development are concerned, disruption of education is also a leading factor when considering pandemics' long-term effects."

Working parents

"Due to the closure of kindergartens and schools, working parents had to take care of their school-going children at home or leave them with caregivers."

Disparity in health and education of disadvantaged children

"*The pandemic has exacerbated the disadvantage faced by poor children. Families in poverty are more likely to have insecure income sources, less access to health services, and concomitant diseases."*

"Children in vulnerable groups, such as those living in refugee camps or orphanages and children with disabilities, require face-to-face education and home health services more than others."

"With the decrease in job opportunities, many immigrants and refugees faced a higher unemployment risk. This has made it more difficult for them to access healthcare, food, and housing."

"Increased poverty, the lack of access to resources, such as qualified education, health services, and even necessities, has caused health and educational disparity."

Results of the school closures

"Due to the closure of schools, children in poor economic circumstances are forced to drop out of school and work as child laborers. This puts these vulnerable populations at greater risk, decreasing access to health services."

"Children have been unable to attend school because of the restrictions. I believe that a lost generation has been created."

Positive effects of the pandemic

"It can be said that children have the opportunity to spend more time with their families, and stay away from unhealthy food outside. Use of masks and hand hygiene may reduce infection rates, and air pollution may decrease."

"Due to the pandemic, home accidents have occurred because children stay home and remain alone in the house."

on clinical care but also on equitable access to healthcare systems.

The students' ability to interpret health supervision failures as structural rather than isolated events suggests that social pediatrics training helps future physicians recognize systemic barriers in child health. By identifying how economic instability, healthcare interruptions, and geographic disparities shape preventive care, students demonstrated competencies aligned with social pediatrics principles: protecting vulnerable groups through equitable service delivery and advocacy. Thus, this study shows that integrating social pediatrics into medical education supports the development of physicians who can critically evaluate child healthcare systems, particularly during crises.

Medical students probably gained awareness of this issue through lectures on "The State and Determinants of Childhood Health in the World and Türkiye" and "Child Health Supervision."

Physical health

Medical students identified that the pandemic heightened both obesity and undernutrition risks, reflecting how opposing nutritional problems can coexist during crises due to lifestyle changes and socioeconomic disparities. They linked increased screen time, reduced outdoor activity, sedentary behaviors, and food insecurity to metabolic disorders, vitamin D deficiency, and unhealthy dietary patterns. These concerns are consistent with global reports showing a rise in childhood obesity, reduced physical activity, poor dietary quality, and increased mortality related to undernutrition, particularly in resource-limited families (10, 22-26). Students also noted that disruptions in breastfeeding and excessive hygiene practices may negatively influence immune development, highlighting awareness of early-life determinants of health.

The students' interpretation of physical health impacts demonstrates their ability to connect biological outcomes with structural drivers such as poverty, food insecurity, and unequal access to health. This perspective is central to social pediatrics, as it recognizes that physical growth and metabolic outcomes are shaped by social conditions rather than solely individual behaviors. The findings suggest that social pediatrics training enables students to evaluate child health through preventive and equity-oriented frameworks, strengthening their capacity to advocate for nutrition-sensitive policies and early-life interventions during public health crises.

Medical students' comments on the issue were related to the lectures "Prevention of adult diseases during childhood period", "Complementary Feeding", and "The Psychosocial Assessment of Adolescents (IHEADSS=Home, Education/employment, peer group Activities, Drugs, Sexuality, and. Suicide/depression)." within the scope of the education program.

Infectious diseases

Medical students highlighted the significant impact of the COVID-19 pandemic on children, including risks of infection and complications such as multisystem inflammatory syndrome and atypical Kawasaki disease. Students suggested that preventive measures, such as mask-wearing, hand hygiene, and social distancing, reduced the spread of infectious diseases, including COVID-19, among children. Kanda et al. (27) from Japan, found that while the incidence of upper respiratory tract infections, bacterial pneumonia, gastrointestinal and urinary tract infections decreased, sexually transmitted infections increased significantly. Another study reported a decrease in the frequency of nearly all infections, except for COVID-19, particularly for airborne diseases, which may be due to reduced disease notifications during the pandemic (28).

Still, concerns arose about increased HIV infections due to reduced hospital visits and maternal-infant HIV screenings in high-risk regions. These issues were addressed in the internship program's "Control and Management of Communicable Diseases" course.

Mental health

Medical students emphasized that the pandemic substantially affected children's mental health, linking increased anxiety, depression, suicidal tendencies, sleep and eating disturbances, and digital addiction to prolonged isolation, parental stress, financial hardship, and bereavement. These interpretations are consistent with international findings showing that quarantine, school closures, and socioeconomic instability contribute to heightened emotional distress and behavioral disorders among children and adolescents (11, 18, 29-34). The students also recognized positive aspects, such as strengthened family bonds, indicating a balanced understanding of psychosocial dynamics. Their ability to attribute mental health outcomes to relational and economic stressors—rather than to individual symptoms alone—reflects a social determinants perspective central to social pediatrics. Instead of viewing mental distress as a purely clinical diagnosis, students demonstrated awareness of contextual risk factors such as unemployment, household strain, and reduced support systems. This suggests that social pediatrics training fosters competency in recognizing how structural environments shape children's mental health. Strengthening such training in medical education may help future physicians engage in preventive interventions, family-centered counseling, and advocacy for mental health resources during crises.

The similar concerns noted by the students were mainly addressed in the lecture "Adolescent Psychosocial Assessment (IHEADSS)" of Social Pediatrics.

Safety

Medical students identified safety concerns as a significant issue during the COVID-19 pandemic, emphasizing the heightened risk of violence, abuse, exploitation, and neglect faced by children during global crises. They attributed the rise in abuse and domestic violence to prolonged home confinement during lockdowns, being away from school and community safeguards. They highlighted that reduced access to adults capable of identifying and responding to abuse, coupled with amplified gender inequities and school closures, increased risks such as early marriage, teen pregnancy, hazardous child labor, and human trafficking. Additionally, the rise in home accidents was linked to children being left alone while parents worked during the pandemic.

Children in resource-limited settings were particularly vulnerable due to already-constrained child protection services, which became even less accessible during the pandemic (35). These challenges underline the critical need for strengthened child protection mechanisms during such crises.

A lecture on this issue, "Child Abuse and Neglect: Prevention and Management," was also given during the internship program.

The Community/Social Structure

Medical students emphasized that the pandemic disrupted children's social environments by closing schools and kindergartens, reducing peer interaction, and shifting families toward insular, home-based support systems. They associated these changes with widening socioeconomic inequalities, as unequal access to digital learning, unstable household income, and limited community services disproportionately affected vulnerable groups such as refugees, low-income families, children with disabilities, and institutionalized children. These concerns align with global data indicating that the pandemic exacerbated poverty, educational disparities, child marriage and child labor, and barriers to essential services, particularly in marginalized populations (12,30,36-38). Students' reflections demonstrate an ability to connect child well-being with broader community systems rather than viewing health outcomes as isolated individual events. By recognizing that social protection, educational access, and economic stability directly influence children's health trajectories, they displayed competencies aligned with social pediatrics principles. This suggests that structured training helps medical students adopt a

population-level perspective, preparing them not only as clinicians but also as advocates for equity-driven policies, community support mechanisms, and child protection systems during public health crises.

Medical students' comments on this issue were covered mainly in parallel with the lectures on "Social pediatrics" and "The state and determinants of childhood health in the world and Türkiye".

This study utilized an online qualitative survey design, which facilitated a higher response rate among medical students compared with traditional face-to-face approaches and supported open expression without time pressure or social desirability concerns. The use of a single open-ended exploratory question enabled focused yet rich and holistic insights into how students conceptualized the impact of the COVID-19 pandemic on children's health. Allowing students to freely articulate their opinions encouraged critical reflection on the curriculum and generated valuable suggestions regarding training needs. The findings highlight the essential role of integrating a social pediatrics perspective into medical education to better prepare future physicians for protecting child health in epidemics, disasters, and other public health crises.

What does this study add ?

Existing research on the pandemic's impact has primarily focused on the well-being and experiences of children, parents, and practicing healthcare professionals, while largely overlooking the perspectives of future physicians. Our study addresses a significant gap in the current literature by examining medical students' perceptions within the field of social pediatrics during the COVID-19 pandemic and provides unique evidence on how medical education—especially when delivered during a global health emergency—shapes students' understanding of childhood vulnerability and the social determinants of health.

Limitations

The present study is subject to several limitations. First, students' perceptions were assessed only after completing the Social Pediatrics Internship, which restricts the ability to identify changes attributable specifically to the training. A pre- and post-internship assessment could provide clearer evidence regarding the internship's impact on students' knowledge and perspectives. Second, the survey did not collect individual information regarding personal COVID-19 experiences (e.g., family illness, psychosocial impact), which may have influenced students' interpretations and introduced potential subjective bias. Third, although participants were recruited from four separate internship groups, data were collected from a single institution. This reflects a methodological decision rather than a sampling limitation, as this university provides the only structured Social Pediatrics Internship program of its kind in Türkiye; nonetheless, the single-site design may limit generalizability to other medical curricula. Finally, the cross-sectional nature of the study restricts time triangulation, preventing longitudinal comparisons.

Conclusions

This study demonstrates that social pediatrics training enables medical students to critically evaluate child vulnerabilities during global crises through a social determinants lens. By revealing how students connect pandemic-related consequences with preventive care, inequities, and systems-based challenges, this research highlights the value of integrating structured social pediatrics curricula in undergraduate education. These findings suggest that social pediatrics education equips future physicians with competencies needed to protect vulnerable child populations and to inform policy and disaster planning.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Hacettepe University (06.02.2024, reference number: SBA 23/323).

Contribution of the authors

Study conception and design: SSY; data collection: MC, BEK; analysis and interpretation of results: SSY; draft manuscript preparation: MC, BEK. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Hypertension in children with congenital adrenal hyperplasia: Prevalence and associated factors

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ABSTRACT

Objective: Congenital adrenal hyperplasia (CAH) is a group of inherited disorders of adrenal steroidogenesis that may predispose affected patients to hypertension through both disease- and treatment-related mechanisms. Although hypertension represents an important comorbidity in CAH, its prevalence and contributing factors in the pediatric population, particularly across different CAH subtypes, remain incompletely defined. The aim of this study was to evaluate the prevalence and determinants of hypertension in patients with CAH.

Material and Methods: This retrospective, single-center study included 143 children and adolescents aged 1–21 years with a confirmed diagnosis of CAH who were followed at a tertiary pediatric center. Blood pressure measurements obtained during routine outpatient visits were evaluated according to age-, gender-, and height-specific pediatric reference values. Patients were classified by CAH subtype, and demographic, clinical, and treatment-related characteristics were compared between patients with and without hypertension. Correlations between blood pressure levels and clinical parameters were analyzed.

Results: A total of 143 patients with CAH (female-to-male ratio, 1.38) were included, with a median follow-up duration of 111.33 months (IQR; 144.70). Hypertension was diagnosed in 15 patients (10.5%). The prevalence of hypertension differed significantly according to CAH subtype ($p<0.001$), with the highest rate observed in patients with 11β-hydroxylase deficiency (88.8%), followed by those with 21-hydroxylase deficiency (8.4%). No cases of hypertension were observed in other CAH subtypes. Patients with hypertension received significantly higher hydrocortisone doses compared with normotensive patients ($p=0.012$), while fludrocortisone dose did not differ between groups. Blood pressure levels showed strong correlations with age at last visit and moderate correlations with follow-up duration and body mass index. Hypertensive cardiomyopathy was detected in 40% of hypertensive patients and was more frequent in those with 11β-hydroxylase deficiency.

Conclusion: Hypertension is a relevant clinical finding in children with CAH and is closely associated with disease subtype, particularly 11β-hydroxylase deficiency. Long-term follow-up, regular blood pressure monitoring and careful evaluation of glucocorticoid exposure may be important for cardiovascular risk assessment in this population.

Keywords: Congenital adrenal hyperplasia, hypertension, 11-beta-hydroxylase deficiency, 21-hydroxylase deficiency, glucocorticoids

Introduction

Congenital adrenal hyperplasia (CAH) comprises a group of autosomal recessive disorders characterized by complex hormonal imbalances resulting from deficiencies of enzymes involved in adrenal steroidogenesis, leading to impaired cortisol synthesis with variable disturbances in mineralocorticoid and androgen production (1). The clinical spectrum of CAH is heterogeneous and depends on the underlying enzymatic defect, with 21-hydroxylase deficiency being the most common subtype, followed by rarer forms such as 11β-hydroxylase, 3β-hydroxysteroid dehydrogenase, and 17α-hydroxylase deficiencies (2-4). The 21-Hydroxylase is a key enzyme in adrenal steroidogenesis,

and the severity of CAH due to its deficiency is determined by the level of residual enzyme activity (2). CAH due to 11beta-hydroxylase deficiency is characterized by androgen excess and hypertension and is autosomal recessively inherited (5). One of the most common clinical features of 11 beta-hydroxylase deficiency is hyporeninemic hypokalemic hypertension (4). Advances in hormone replacement therapy and neonatal screening have markedly improved survival in patients with CAH; however, long-term disease and treatment-related complications, particularly those affecting cardiovascular health, remain a major clinical concern (1,6).

Hypertension is one of the major contributors to the increased cardiovascular disease risk in patients with CAH (6,7). Previous studies have reported that 20–66% of children with CAH exhibit elevated systolic or diastolic blood pressure (8, 9). Moreover, 24-hour ambulatory blood pressure monitoring studies have demonstrated an absence of normal nocturnal dipping in blood pressure in many patients with CAH (10,11). Its pathophysiology is multifactorial and may include excess mineralocorticoid activity, accumulation of steroid precursors with mineralocorticoid properties, chronic glucocorticoid overtreatment, and altered regulation of the renin–angiotensin–aldosterone system (12). Certain CAH subtypes, particularly 11β-hydroxylase deficiency, are classically associated with a higher risk of hypertension due to the accumulation of deoxycorticosterone, whereas hypertension in patients with 21-hydroxylase deficiency is more often related to treatment-related factors (4,9).

Data on the prevalence and determinants of hypertension in pediatric CAH remain limited, and the relative contributions of disease duration, CAH subtype, and cumulative steroid exposure to blood pressure regulation are not fully understood. Therefore, the aim of this study was to evaluate the prevalence of hypertension in patients with CAH, to examine its distribution across CAH subtypes, and to investigate clinical and treatment-related factors associated with hypertension.

Materials and Methods

This retrospective, single-center study was conducted in the Pediatric Nephrology and Endocrinology Department of Ankara Child Health Hematology-Oncology Training and Research Hospital, and Ankara Bilkent City Hospital and the data were collected from the five-year period preceding June 2020. Patients with a confirmed diagnosis of CAH who were under regular follow-up during this period were eligible for inclusion. A total of 143 children and adolescents aged 1 to 21 years with diagnosis of CAH were included in the study. Clinical and laboratory data were obtained retrospectively from the hospital electronic medical records. Patients with incomplete medical records were excluded. Demographic and clinical data recorded included sex, date of birth, age at diagnosis of CAH, age at last visit, follow-up duration with CAH, height, and weight measurements, and BMI (kg/m^2) values were recorded. Systolic and diastolic blood pressure measurements were obtained using an oscillometric device by trained healthcare personnel, with an appropriately sized cuff and the child in a seated position after at least 5 minutes of rest. At each routine outpatient visit, blood pressure was measured at least two to three times, and the average of the last two readings was used for analysis. Hypertension was defined as systolic and/or diastolic blood pressure values ≥95th percentile for age, sex, and height, based on normative pediatric blood pressure reference values, documented on at least three separate clinic visits (13). For patients diagnosed with hypertension, age at hypertension diagnosis, interval between CAH diagnosis and hypertension diagnosis, follow-up duration with hypertension and medication data of anti-hypertensives were documented. In these patients, echocardiographic findings were also recorded to assess hypertensive cardiomyopathy. Hypertensive cardiomyopathy was assessed by transthoracic echocardiography during routine clinical follow-up. Left ventricular hypertrophy was identified based on left ventricular mass index, calculated using standard methods and interpreted according to age- and sex-adjusted reference values applied in clinical practice. Additionally, in patients with hypertension, daily hydrocortisone (mg/m^2/day) and fludrocortisone (mg/day) doses at the time of hypertension diagnosis were recorded, whereas in normotensive patients, doses of these medications at the last follow-up visit were documented.

Patients were classified according to CAH etiology based on clinical, biochemical, and genetic data when available. CAH subtypes included 21-hydroxylase deficiency, 11β-hydroxylase deficiency, 3β-hydroxysteroid dehydrogenase deficiency, 17α-hydroxylase deficiency, and unknown etiology.

Statistical analysis

All statistical analyses were performed using BM Statistical Package for the Social Sciences, version 22.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Normally distributed variables were expressed as mean and standard deviation (SD), while non-normally distributed variables were presented as median and interquartile range (IQR). Qualitative variables were presented as numbers and percentages (%).

Comparisons between patients with and without hypertension were performed using the Student's t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Categorical variables were compared using the chi-square test with exact methods (Fisher's exact test, Monte Carlo simulation) applied when appropriate.

Correlations between systolic and diastolic blood pressure levels and clinical parameters were evaluated using Spearman's correlation analysis. Correlation strength was interpreted as negligible (r=0.00–0.10), weak (r=0.10–0.39), moderate (r=0.40–0.69), strong (r=0.70–0.89), or very strong (r=0.90–1.00) (14). Statistical significance was set at $p<0.050$.

Results

A total of 143 patients with CAH (female-to-male ratio, 1.38) were included in the study, with a median follow-up duration of 111.33 months (IQR;144.70). During follow-up, 15 patients (10.5%) were diagnosed with hypertension. Baseline demographic and clinical characteristics of patients with and without hypertension are summarized in Table I. Age at diagnosis of CAH and age at last visit did not differ significantly between patients with hypertension and without hypertension. Follow-up duration with CAH tended to be longer in patients with hypertension; however, this difference did not reach statistical significance. Gender distribution and BMI were similar between groups. Patients with hypertension received significantly higher hydrocortisone doses than patients without hypertension (p=0.012), whereas fludrocortisone dose did not differ between the two groups (Table I).

Among patients with hypertension, the mean age at hypertension diagnosis was 11.15±6.45 years, with a median of 12.54 years (IQR; 9.18). The interval between CAH diagnosis and hypertension diagnosis was 10.50±6.40 years (median [IQR]; 11.92 years [9.53]). The median follow-up duration after hypertension diagnosis was 12.56 months (IQR; 43.80) (Table I). All hypertensive patients were receiving hydrocortisone therapy, whereas only six of the 15 (40%) patients were treated with fludrocortisone.

The prevalence of hypertension according to CAH subtype is shown in Table II. Hypertension was most frequently observed in patients with 11β-hydroxylase deficiency, followed by those with 21-hydroxylase deficiency. No cases of hypertension were observed in patients with 3β-hydroxysteroid dehydrogenase deficiency, 17α-hydroxylase deficiency, or unknown etiology. A significant association was observed

Table I: Demographic and clinical results of CAH with and without HT groups

Variable	Total patients*	Patients with HT*	Patients without HT*	p
Total number of patients	143	15	128	-
Age at diagnosis of CAH (years)*	2.54±4.44/0.08 (4.06)	0.65±1.39/0.06 (0.22)	2.76±4.62/0.08 (5.26)	0.523†
Age at last visit (years)*	11.84±6.16/13.49 (11.31)	13.04±6.28/15.90 (6.61)	11.70±6.15/13.20 (11.6)	0.414†
Follow-up duration with CAH (month)*	111.33±77.71/105.13 (144.70)	148.67±75.90/173.33 (101.87)	106.95±77.03/89.53 (137.68)	0.060†
Age at diagnosis of HT (years)*	-	11.15±6.45/12.54 (9.18)	-	-
Interval between CAH and hypertension diagnosis (years)*	-	10.50±6.40/11.92 (9.53)	-	-
Follow-up duration with HT (month)*	-	22.65±23.85/12.56 (43.80)	-	-
Gender (n) (female/male)	83/60	7/8	76/52	0.345‡
BMI (kg/m^2)*	21.82±5.82/20.95 (7.44)	22.98±6.03/23.04 (10.15)	21.69±5.80/20.88 (7.35)	0.418‖
Systolic blood pressure (mmHg)*	108.54±15.87/106.0 (25.0)	136.80±16.26/140.0 (15.0)	105.23±12.13/105.0 (20.75)	>0.001†
Diastolic blood pressure (mmHg)*	65.0±12.29/64.0 (13.0)	88.13±14.39/90.0 (15.0)	62.29±8.69/63.0 (12.0)	>0.001†
Dose of hydrocortisone (mg/m^2/day)*	14.62±4.80/14.20 (5.90)	17.90±4.67/17.30 (6.60)	14.33±4.74/14.0 (5.90)	0.012‖
Dose of fludrocortisone (mg/day)*	0.10±0.07/0.10 (0.05)	0.15±0.15/0.07 (0.28)	0.10±0.06/0.10 (0.05)	0.984†

:** *mean±SD/median (IQR),* **†:** *Mann-Whitney U test,* **‡:** *Chi-Square test,* **‖:** *Student's t-test,* ***CAH: *congenital adrenal hyperplasia,* ***HT:*** *hypertension,* ***BMI:*** *body mass index*

Table II: Rate of HT according to type of CAH

CAH type	Total patients	Patients with HT	Patients without HT	p†
Total number of patients	143	15	128	-
21-hydroxylase deficiency*	83 (58.0)	7 (8.4)	76 (91.6)	<0.001
11β-hydroxylase deficiency*	9 (5.6)	8 (88.8)	1 (1.1)	
3β-hydroxysteroid dehydrogenase deficiency*	2 (1.4)	0	2	-
17α-hydroxylase deficiency*	1 (0.7)	0	1	-
Unknown*	48 (34.3)	0	48	-

:** *n(%),* **†:** *Fisher's exact test,* ***CAH: *congenital adrenal hyperplasia,* ***HT:*** *hypertension*

Table III: Correlations between systolic and diastolic blood pressure levels and the clinical parameters

Clinical parameters	Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)	
	r*	p	r*	p
Age at diagnosis of CAH (years)	0.19	0.017	0.22	0.006
Age at last visit (years)	0.83	<0.001	0.82	<0.001
Follow-up duration with CAH (month)	0.65	<0.001	0.64	<0.001
BMI (kg/m^2)	0.56	<0.001	0.56	<0.001
Dose of hydrocortisone (mg/m^2/day)	0.39	<0.001	0.34	<0.001
Dose of fludrocortisone (mg/day)	-0.20	0.085	-0.18	0.104

:** *Spearman correlation,* ***CAH: *congenital adrenal hyperplasia,* ***BMI:*** *body mass index*

between CAH subtype, particularly 21- and 11-hydroxylase deficiencies, and the presence of hypertension (p<0.001). There was no significant difference in the age at diagnosis of hypertension between patients with 21-hydroxylase and 11β-hydroxylase deficiencies (p= 0.298).

Systolic and diastolic blood pressure levels were weakly correlated with age at CAH diagnosis but showed strong positive correlation with age at last visit. Moderate correlations were observed with follow-up duration and BMI, while hydrocortisone dose showed weak positive correlations with blood pressure levels. No significant association was found between fludrocortisone dose and blood pressure (Table III).

In hypertensive patients, seven patients (46.7%) were treated with amlodipine alone, three patients (20.0%) received combination therapy with amlodipine and spironolactone, one patient (6.7%) was treated with amlodipine and enalapril, and four patients (26.6%) were not on antihypertensive treatment. Among patients with hypertension, hypertensive cardiomyopathy was observed in six patients (40%); however, no cases of proteinuria or hypertensive retinopathy were detected. Hypertensive cardiomyopathy was significantly more frequent in patients with 11β-hydroxylase deficiency compared with those with 21-hydroxylase deficiency (50% vs. 28.5%; p<0.001).

Discussion

In this retrospective cohort study, we evaluated the prevalence of hypertension in children with CAH and found that 10.4% of the cohort had hypertension. By comparison, hypertension affects approximately 2–5% of the general pediatric population, a rate lower than that observed in our cohort of children with CAH (8,15). Previous studies have reported elevated systolic and/or diastolic blood pressure in 20–66% of patients with CAH (8). In a study by Bonfig et al. (16), the prevalence of hypertension among patients with classic CAH was 12.5%, which is comparable to the prevalence observed in our cohort.

In recent study, hypertension showed a strong association with CAH subtype, with the highest prevalence observed in patients with 11β-hydroxylase deficiency, followed by those with 21-hydroxylase deficiency, while no cases were identified in the remaining subtypes. Comparative studies evaluating hypertension prevalence among different CAH subtypes remain limited. In the literature, the prevalence of hypertension has been reported to be approximately 9.1-12.5% in patients with 21-hydroxylase deficiency, whereas it reaches 50–59% in those with 11β-hydroxylase deficiency (18-20). In our study, the higher prevalence observed in 11β-hydroxylase deficiency is not unexpected when considering the underlying pathophysiology (16,17). Excess accumulation of mineralocorticoid-active steroid precursors in this subtype provides a plausible mechanistic explanation (18).

Additionally, the significantly higher frequency of hypertensive cardiomyopathy observed in patients with 11β-hydroxylase deficiency in our cohort further underscores the potential impact of prolonged mineralocorticoid excess and cumulative blood pressure burden. However, the absolute number of patients with 11β-hydroxylase deficiency in our cohort was small, and therefore subtype-specific prevalence estimates and cardiovascular outcomes, including hypertensive cardiomyopathy, should be interpreted with caution. In light of these findings, the significant association between CAH subtype and hypertension status and related complications highlights the importance of etiological classification when assessing cardiovascular risk in patients with CAH. Maccabee-Ryaboy et al. (8) performed a comparative analysis across CAH subtypes and reported early-onset hypertension, often before five years of age, among boys with salt-wasting CAH. In contrast, in our cohort, no significant differences were observed between patients with and without hypertension in terms of age or gender.

Beyond CAH subtype, treatment-related factors appear to play a critical role in blood pressure regulation. In this study, patients with hypertension received significantly higher hydrocortisone doses compared with normotensive patients, and hydrocortisone dose showed weak but significant correlations with blood pressure levels. Although patients with hypertension in our cohort received significantly higher hydrocortisone doses, this finding should be interpreted cautiously. Given the retrospective design of the study, a causal relationship between hydrocortisone dose and hypertension cannot be established. Higher glucocorticoid doses may reflect greater disease severity,

difficulties in achieving adequate hormonal control, or clinician-driven dose escalation in response to androgen excess rather than glucocorticoid overtreatment alone. Therefore, hydrocortisone dose in this context is more likely to represent a marker of cumulative disease and treatment burden than a direct determinant of hypertension. In contrast, fludrocortisone dose was not associated with hypertension or blood pressure levels in our cohort. Patients with classic 21-hydroxylase deficiency require lifelong glucocorticoid replacement therapy, with hydrocortisone being the most commonly used agent during childhood. Because impaired conversion of progesterone to deoxycorticosterone leads to aldosterone deficiency and salt wasting in many patients, mineralocorticoid replacement with fludrocortisone is frequently required, and salt supplementation is often recommended in early life (21).

Our finding supports the concept that chronic or supraphysiological glucocorticoid exposure may contribute to blood pressure elevation through multiple mechanisms, including increased vascular tone, enhanced sodium retention, adverse effects on body composition, and alterations in metabolic profile. Over time, these effects may lead to cumulative cardiovascular burden, particularly in patients requiring higher glucocorticoid doses for disease control. Despite appropriate consideration of age, sex, height, and weight, substantial interindividual variability in hydrocortisone dose requirements persists among patients with CAH, making it challenging to anticipate hydrocortisone-related side effects (21).

In contrast, fludrocortisone dose was not associated with blood pressure levels in our cohort. Supporting this finding, a study including 24 infants with CAH treated with fludrocortisone reported no elevation in blood pressure during the first year of life (22). Although mineralocorticoid therapy has been proposed to contribute to the development of hypertension in CAH, the lack of an observed association in our study may be related to the narrow dosing range maintained in clinical practice. Additionally, the limited number of patients receiving fludrocortisone and the heterogeneity of CAH subtypes within our cohort may have reduced our ability to detect a dose–response relationship.

In infants with CAH, higher fludrocortisone dose requirements and variable mineralocorticoid sensitivity have been suggested as potential risk factors for fludrocortisone-related hypertension (23). Bonfig et al. (17) reported the highest prevalence of hypertension among CAH patients receiving both glucocorticoid and fludrocortisone therapy in those aged 12–24 months. Considering the findings this study, the absence of a relationship between fludrocortisone dose and blood pressure in our cohort may be partly attributable to the relatively older age at hypertension diagnosis. Similarly, Lawrence et al. (21) reported a low regression coefficient in blood pressure prediction models, suggesting that a 100 µg increase in fludrocortisone dose was associated with only a modest (~1 mmHg) increase in systolic and diastolic blood pressure. This modest effect size is consistent with our findings and may further explain the lack of a significant association between fludrocortisone dose and blood pressure in our cohort.

In our study, the median age at hypertension diagnosis was 12.5 years, and the strong correlation between blood pressure levels and age at last visit is consistent with expected age-related increases in blood pressure during childhood and adolescence. This finding suggests that associations between blood pressure and other variables, such as hydrocortisone dose and follow-up duration, may be partially influenced by age and pubertal maturation. Because hydrocortisone exposure and disease duration inherently increase over time, these relationships are likely to reflect cumulative treatment and disease burden rather than age-independent effects. Given the relatively small number of hypertensive patients in our cohort, particularly across CAH subtypes, age-adjusted or partial correlation analyses were not performed. Future studies incorporating pubertal staging and larger sample sizes are warranted to better disentangle the independent contributions of age, treatment exposure, and disease duration to blood pressure regulation in CAH. In addition, blood pressure levels showed moderate correlations with follow-up duration and body mass index, further supporting a cumulative effect of long-term disease burden and treatment exposure. These findings suggest that hypertension in CAH may evolve as a chronic complication over time rather than being determined solely by early disease characteristics. The weak correlations observed with age at CAH diagnosis further support the notion that long-term disease burden, treatment exposure, and growth-related changes may be more relevant determinants of hypertension in this population.

Target organ involvement was assessed in hypertensive patients, with hypertensive cardiomyopathy identified in 40%, whereas no cases of proteinuria or hypertensive retinopathy were detected. This finding highlights the potential for early cardiovascular remodeling and underscores the importance of timely blood pressure monitoring in patients with CAH.

Limitations

Several limitations of this study should be acknowledged. The retrospective design and single-center setting may limit generalizability. Blood pressure classification was based on office measurements obtained during routine visits rather than ambulatory blood pressure monitoring, which precluded the assessment of white-coat and masked hypertension. Plasma renin levels were not available for analysis. In addition, the relatively small number of hypertensive patients limited the ability to perform more extensive multivariable analyses. Nevertheless, the strengths of this study include a well-characterized cohort with long-term follow-up and a detailed evaluation of CAH subtypes and treatment-related variables.

Conclusion

Hypertension is a clinically relevant finding in children with CAH. In this study, hypertension was closely associated with CAH subtype—particularly 11β-hydroxylase deficiency—and appeared to be influenced by long-term disease burden and glucocorticoid exposure rather than mineralocorticoid dose alone. The presence of early cardiac involvement in a subset of hypertensive patients highlights the importance of regular blood pressure assessment during follow-up. These findings support the value of etiological classification and individualized treatment strategies when evaluating cardiovascular risk in patients with CAH.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Child Health Hematology-Oncology Training and Research Hospital Ethics Committee (11.06.2019, reference number: 2019-180).

Contribution of the authors

Study conception and design: Mİ, GB; data collection: BA ,ZA; analysis and interpretation of results: Mİ, SAU, FŞÇ; draft manuscript preparation: Mİ, USB. All authors reviewed the results and approved the final version of the article.

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Case Reports

Gallbladder adenomyomatosis presenting with nausea in an adolescent: A case report

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Abstract

Gallbladder adenomyomatosis is characterized by invagination of the gallbladder mucosal epithelium into the muscularis propria, which results in the formation of an intramural diverticulum. It primarily affects adults and rarely impacts children and is generally considered a benign disorder. The increased use of high-resolution ultrasonography in children has facilitated the diagnosis of gallbladder lesions in young patients. Various imaging modalities can be utilized to achieve a definitive diagnosis. We report a 17-year-old adolescent girl who presented with nausea and was diagnosed with adenomyomatosis. Although abdominal ultrasonography initially suggested a choledochal cyst, magnetic resonance cholangiopancreatography (MRCP) confirmed that the lesion represented gallbladder adenomyomatosis rather than a choledochal cyst. Following consultation with a pediatric surgeon, a cholecystectomy was planned. This case contributes to the limited pediatric literature on gallbladder adenomyomatosis.

Keywords: Adolescent, gallbladder adenomyomatosis, nausea

Introduction

Gallbladder adenomyomatosis is characterized by mucosal hyperplasia that leads to mucosal invagination into the thickened muscle layer, forming Rokitansky-Aschoff sinuses (1). The cause of this benign gallbladder wall disease is unknown (2). Patients are mostly clinically asymptomatic and the disease is detected incidentally when ultrasonography is performed for another reason. Although predominantly affecting adults, rare pediatric cases have been reported (3). Imaging modalities, particularly ultrasonography, are essential for diagnosis (4). Ultrasonography, computed tomography, and magnetic resonance imaging are commonly utilized imaging modalities (2).

Adenomyomatosis may be characterized on abdominal ultrasonography by 'comet-tail' reverberation artifacts within the thickened gallbladder wall. However, this imaging finding alone does not allow a definitive distinction as to whether the lesion represents benign adenomyomatosis or a malignant pathology. MRI and MRCP can detect wall thickening, focal sessile masses, and the hourglass configuration, and may also demonstrate the 'pearl necklace sign,' which represents fluid-filled intramural mucosal diverticula known as Rokitansky–Aschoff sinuses. This sign is highly specific (92%), although it is present in only about 70% of cases (5).

In this case report, a patient diagnosed with adenomyomatosis was initially scheduled for surgery owing to the presence of symptoms. Nevertheless, as the patient's family declined surgical intervention, follow-up was conducted through regular consultations with the pediatric surgery department.

Case Reports

A 17-year-old girl, presenting with nausea for three months, was taken to the pediatric gastrointestinal clinic. The patient's only presenting symptom was nausea, which did not show any correlation with food intake. Notably, there were no additional gastrointestinal complaints, including

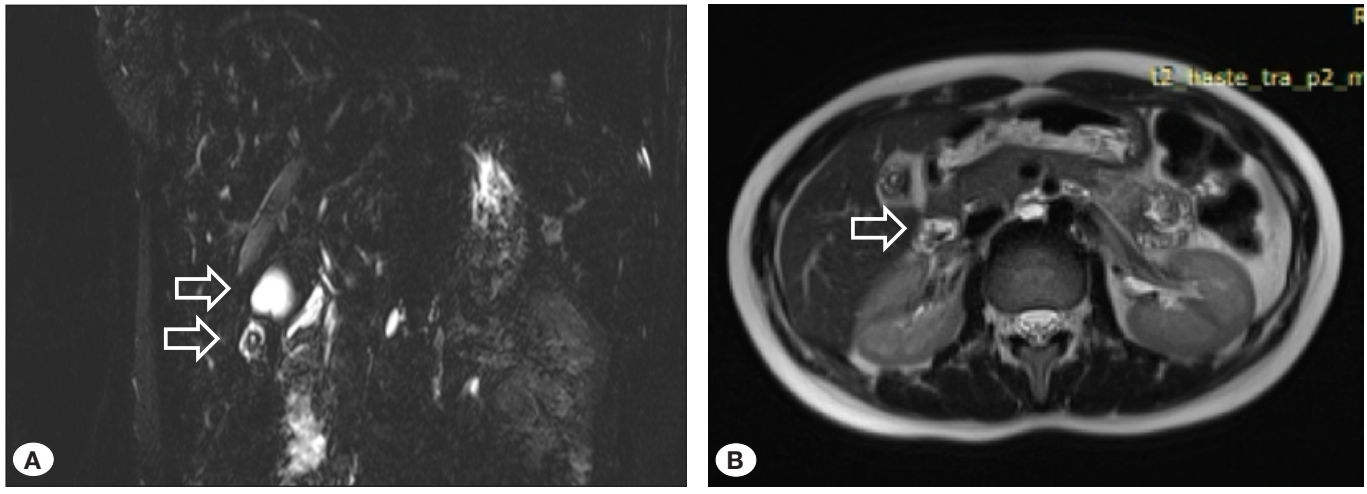

Figure 1: T2-weighted coronal view **(A)**, first arrow indicates the gallbladder, second arrow indicates adenomyomatosis; T2-weighted axial view **(B)** indicates adenomyomatosis with an arrow.

abdominal pain, vomiting, or other related symptoms. There were no notable characteristics in the patient's family history. She had a history of choledochal cyst diagnosed at age 6.

The physical examination revealed a body weight of 58.5 kg (50-75 percentile) and a height of 164.5 cm (50-75 percentile). The physical examination revealed no remarkable findings: the abdomen was soft and non-tender, with no evidence of hepatomegaly or splenomegaly. Murphy's sign was negative, and there were no stigmata of jaundice. Laboratory investigations including complete blood count, liver function tests, and lipid profile were within normal limits.

Radiological studies to determine the etiology revealed a 43x24 mm cyst in the common bile duct and small echogenic foci in the gallbladder lumen on a complete abdominal ultrasound. Ursodeoxycholic acid was initiated at 20 mg/kg/day. Magnetic resonance cholangiopancreatography (MRCP) was requested to confirm the diagnosis of a choledochal cyst. The MRCP examination revealed multiple sequential cystic structures in the gallbladder corpus's caudal part, suggesting adenomyomatosis (Figure 1). No other pathological findings were noted. Due to the patient's symptoms, consultations with pediatric surgery resulted in a surgical plan. The patient's family did not consent. The patient was placed under observation.

Discussion

Adenomyomatosis is characterized by mucosal epithelial invagination into the thickened muscular layer of the gallbladder (6). The presenting symptoms include abdominal pain, nausea, vomiting, and/or fever. Asymptomatic cases are incidentally diagnosed by ultrasonography during follow-up for other congenital diseases (1). Our patient primarily complained of nausea and did not report experiencing abdominal pain.

In the literature, laboratory findings are within normal limits, except for two patients with a prior history of mildly elevated serum gamma-glutamyl transpeptidase or liver enzymes (1). Our patient's liver enzymes were within normal limits.

The disease's initial observable stage is likely caused by increased intra-gallbladder pressure, which leads to smooth muscle hypertrophy due to abnormal contractions or excessive bile absorption, as well as hyperproliferation of epithelial cells in the gallbladder mucosa. This excessive proliferation causes the epithelial invagination into the muscle layer of the gallbladder, forming intramural diverticula referred to as Rokitansky-Aschoff sinuses. These diverticula may become filled with bile, bile sludge, and gallstones (7). Three forms of this disorder can be distinguished based on their morphology: diffuse, localized (typically a single nodule projecting into the lumen at the fundus, referred to as "adenomyoma" due to its polyp-like appearance on ultrasound), and segmental (a ring-like type with an "hourglass" configuration because of a transverse congenital septum in the gallbladder body) (4).

Adenomyomatosis, cancer, xanthogranulomatous cholecystitis, metastases, chronic cholecystitis, polyps, and sludge should all be taken into account when making a differential diagnosis of localized gallbladder wall thickening (5).

There might be a link between lesion's diameter and the likelihood of developing cancer; therefore, determining the diameter is important. Gallstones smaller than 5 mm typically do not create acoustic shadowing during ultrasound examinations. This situation can complicate the differentiation of polypoid lesions from gallstones when gallbladder sludge is present, and in such cases, a repeat ultrasound is recommended (8). In our patient, a cyst measuring 43x24 mm was noted in the common bile duct. When used in conjunction with MRCP, magnetic resonance imaging is a useful technique for assessing gallbladder lesions (7). During our examination of the patient using MRCP, we discovered that there were no a cyst present in the common bile duct. This finding underscores the importance of performing MRCP in similar cases.

There is limited data on the current management of gallbladder adenomyomatosis in children. While surgery is clearly indicated for symptomatic patients, the treatment of asymptomatic children remains a matter of controversy. For asymptomatic patients, monitoring with ultrasound at six-month intervals is recommended. Elective laparoscopic cholecystectomy is the suggested treatment for both adults and children, based on evidence from symptomatic patients. Additionally, preoperative MRCP assessment of the extrahepatic biliary tree anatomy is advised for these patients (4).

Conclusion

Cholecystectomy is the treatment of choice for patients with symptomatic adenomyomatosis, and preoperative imaging modalities, including US, CT, and MRI, are crucial for precise anatomical assessment. Furthermore, it is recommended that surgeons actively participate in the close follow-up of asymptomatic patients. Our experience with this particular patient highlights the need to evaluate the anatomy of the extrahepatic biliary tree with MRCP in cases where cysts are diagnosed by ultrasound examination.

The case presentation provides limited data due to involving only one patient who declined surgery. However, it demonstrates the importance of repeated imaging in patients presenting with nausea.

Contribution of the authors

Study conception and design: MT, CFO, NB,; data collection: MT, CFO, YO, YME, FC, NB; analysis and interpretation of results: MT, CFO, YO, YME, FC, NB; draft manuscript preparation: MT, CFO, YO, YME, FC, NB. All authors reviewed the results and approved the final version of the article.

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