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Owner on Behalf of the Ankara Bilkent City Hospital Children's Hospital

Namık Yaşar ÖZBEK

Physician in Chief

Ankara Bilkent City Hospital, Children's Hospital, Ankara, Türkiye

Head Office

Emel KAYMAZ, Başak YALÇIN BURHAN, Musa TURHAN

Ankara Bilkent City Hospital, Children's Hospital, Türkiye

Telephone: +90 (312) 552 60 00 / 401506

editorial@turkjpediatrdis.org

Press Office

FABRİKA MATBAACILIK

Tic. Sic. No: 393545, Mersis No: 0384 0359 0820 0013

İvedik O.S.B. Mah. 1372 Sk. No: 23 Yenimahalle / *Ankara*, Türkiye

info@fabrikabaskida.com, www.fabrikabaskida.com

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Original Article

Mobile media exposure in early childhood: patterns, risks, and parental insights

Metin Yiğit[1], Ahmet Alptuğ Güngör[1], Furkan Kalaycı[1], Saliha Şenel[2]

[1]Department of Pediatrics, Ankara Bilkent City Hospital, Ankara, Türkiye
[2]Department of Pediatric Emergency, Ankara Bilkent City Hospital, Yildirim Beyazit University, Ankara, Türkiye

ABSTRACT

Objective: This study aimed to assess the extent and patterns of mobile media exposure in children aged 1–24 months and examine the parental practices and beliefs associated with its use. Understanding these factors is crucial for developing preventive strategies and informing public health policies.

Material and Methods: A cross-sectional study was conducted at Ankara Bilkent City Hospital, including 404 parents of children aged 1–24 months. Data were collected using a 48-item self-administered questionnaire addressing demographics, mobile media usage patterns, and parental attitudes. Statistical analysis was performed using SPSS 23.0, with chi-square and non-parametric tests applied to identify significant associations.

Results: Mobile media exposure was reported in 65.8% of children, with 10.9% exposed as early as 3 months. Daily usage increased with age, with 9.8% exceeding two hours. Children with siblings had significantly higher exposure rates (p=0.020). Despite 91.4% of parents recognizing the potential harms of mobile media, 63.2% perceived its educational benefits. Notably, parental education and income levels did not show significant associations with exposure, whereas parental awareness about media risks correlated with reduced screen time usage (p = 0.010). Video calls were a frequent exception, with 86.8% of parents engaging in them, considering them less harmful.

Conclusion: Mobile media exposure in children under two years is alarmingly high, often surpassing recommended limits. These findings highlight the urgent need for comprehensive public health policies focusing on parental education and awareness programs. Pediatricians should play a proactive role in counseling families about screen time risks and appropriate digital engagement. Considering the widespread use of video calls, updated guidelines may be necessary to differentiate their impact from passive screen exposure. Future research should explore broader socioeconomic and environmental factors to refine intervention strategies.

Keywords: Early childhood, Mobile media exposure, Screen time

INTRODUCTION

Mobile technologies have become increasingly prevalent in children's lives, with mobile devices, particularly smartphones, playing a significant role (1). In the United States, children aged 8–12 spend an average of 4–6 hours per day on screen media, while adolescents aged 12 and above spend 7–10 hours daily (2–4). While appropriate content and educational programs can support the development of cognitive and social skills, excessive screen time is associated with problems.

Excessive mobile media exposure in early childhood has been associated with adverse biological and psychosocial outcomes. Studies suggest that early and prolonged screen exposure may disrupt neurocognitive development, particularly executive functions, language acquisition, and attention regulation (5). Additionally, excessive screen time has been linked to sleep disturbances, increased obesity risk, ocular health issues, and posture-related concerns (6). From a psychosocial perspective, excessive mobile media use may reduce parent-child interaction, hinder socio-emotional development, and contribute to behavioral issues such as impulsivity and emotional dysregulation (7). Furthermore, limited real-world social engagement in favor of screen-based interactions may negatively impact empathy and peer relationships (8). Given these potential risks, parental guidance and structured media use policies are essential in mitigating adverse developmental consequences (5,6).

To address these concerns, scientific organizations, including the American Academy of Pediatrics (AAP), the World Health Organization (WHO), and the Italian Pediatric Society, have issued guidelines discouraging mobile media exposure in children under two years old (9–13). The AAP explicitly

Correspondence Address:
Metin Yiğit
e-mail: metinyigit.md@gmail.com

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recommends that children younger than 18 months should avoid screen media use, except for video chatting, and for children aged 18–24 months, digital media should only be introduced with high-quality content and under parental supervision (12,14). Similarly, the Centers for Disease Control and Prevention (CDC) advises against screen time for children under 2 years, emphasizing that early childhood development is best supported through hands-on play and social interactions with caregivers rather than passive media consumption (15).

Despite these recommendations, research indicates that many parents permit screen exposure as early as the first year of life, reflecting a trend of over-tolerance (4,16–19). Similarly, a study by Kılıç et al. (20) in Türkiye found that parents introduce their children to mobile devices at an early age. This aligns with national data, as reports from the Turkish Statistical Institute (TÜİK) indicate a sharp increase in internet usage among children, rising from 82.7% in 2021 to 91.3% in 2024. Notably, internet usage among boys increased from 83.9% to 92.2%, while for girls, it rose from 81.5% to 90.3% over the same period (21). These findings highlight the growing digital exposure among young children, emphasizing the need for stricter parental guidance and public health interventions.

Understanding early mobile media exposure is critical for shaping preventive public health policies aimed at promoting the well-being of young children. This study seeked to evaluate mobile media (mobile phones and tablets) exposure in children aged 1–24 months, a population for whom mobile media use is not recommended. The findings aimed to provide insight into the underlying factors contributing to early exposure and inform strategies for intervention.

MATERIALS and METHODS

This cross-sectional survey study was conducted at Ankara Bilkent City Hospital's Children's Hospital between November 1, 2022, and January 20, 2023, involving children aged 1–24 months and their parents. Parents were informed about the study, provided informed consent, and voluntarily completed a supervised questionnaire without interference. No financial incentives were offered. If parents had multiple children meeting the inclusion criteria, they completed the questionnaire for the youngest child. Exclusion criteria included children with physical, developmental, neurological, or psychological disorders, as well as cases where a non-parent guardian accompanied the child.

The sample size was determined through a power analysis using GPower software. With a significance level of 0.050 and a statistical power of 90%, the minimum required sample size was calculated as 384 participants. To compensate for possible missing data, a total of 477 participants were recruited, and after exclusions, data from 404 participants were analyzed.

A self-completion 48-item questionnaire in the Turkish language that was adapted from previous studies was used to collect data from parents (4,16,17,20,22,23). The questionnaire included open-ended, yes/no, and multiple-choice questions. The questionnaire was reviewed by a senior faculty member (SS) for clarity and comprehensibility; however, formal validity and reliability testing were not conducted, as it was a survey designed to assess parental practices rather than a standardized scale.

The questionnaire captured demographic data including the child's age and gender, parents' ages and education levels, monthly income (categorized as income equal to, less than, or more than expenditure), and total number of children in the family.

To evaluate children's mobile media usage (e.g., mobile phones and tablets), questions addressed the types of devices used, whether more than one device was used simultaneously, the primary device of use, exposure to video calls, and the duration of usage.

Mobile media habits were assessed by inquiring when children first began using devices, average daily usage time, autonomy in choosing games or videos, and whether they stopped using the device independently.

Parents' perspectives and practices regarding mobile device use were explored through questions about daily usage limits, content monitoring, the presence of non-Turkish content, attention to age-appropriate material, and criteria for selecting suitable content. Additional inquiries included parents' views on device use, contexts where usage was permitted (e.g., during meals, bedtime, or outings), reasons for allowing usage, challenges in convincing children to stop, and the perceived impact on parent-child relationships.

Finally, parents were asked whether they felt sufficiently informed about children's mobile media use, consulted pediatricians on the matter, or had specific age-related recommendations for device introduction.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics, including frequencies, means, medians, ranges (minimum–maximum), standard deviations, and percentages, were calculated. Categorical variables were compared using the chi-square test, while the Kolmogorov-Smirnov test was applied to assess the normality of numerical variables. For comparisons between two independent groups, the Mann-Whitney U test was used, and the Kruskal-Wallis test was employed for multiple group A Spearman correlation analysis was conducted to ascertain the relationship between the child's age and their daily screen time. Statistical significance was set at $p < 0.050$.

RESULTS

The questionnaire was completed by 404 parents after excluding 73 due to missing or incomplete data.

Demographics of participants

The mean age of the children was 13.53±7.64 months. The mean ages of mothers and fathers were 29.36±5.02 and 32.7±5.49 years, respectively. Among mothers, 41.8% had a university or higher education, compared to 42.6% of fathers. Regarding economic status, 61.4% of parents reported that their expenditure was equal to their income. The demographic characteristics were summarized in Table I which provides demographic information of the participants, including parental education levels, income status, and the presence of siblings. These variables were examined for associations with children's mobile media exposure but were not found to be significantly related.

Children's mobile media exposure

Overall 65.8% of children were exposed to mobile media. Mobile media exposure was 19.5% in children younger than 3 months, 39.1% in 3 to 5 months, 49.4% in 6-11-months, 65.5% in 12-17-months and 88.7% in 18-24 months. Figure 1 summarizes the mobile media exposure rates across different age groups. It visually illustrates the progressive increase in screen exposure as children grow older, with a particularly sharp rise observed after 12 months of age. This figure underscores the critical early period during which media exposure becomes more frequent.

Initial exposure to mobile media occurred within the first three months of life in 10.9% of children. Figure 2 presents the distribution of children's first exposure to mobile media by age. This figure highlights that a notable proportion of children are introduced to mobile devices within the first 6 months of life, raising concerns about early and potentially inappropriate screen exposure.

Of the children, 65.8% were exposed to mobile media (cell phones or tablets). No significant correlation was found between mobile media use and parental education levels, parental ages, or economic status (0.082, 0.123 and 0.221 respectevily). However, children with older siblings had a significantly higher rate of mobile media use compared to those without siblings (p=0.020), although no difference was observed in daily usage durations (p>0.062).

Table I: The participants' demographic characteristics

Children's age (month)*	14 (6.25-20.75)
Mothers' age (year)*	29 (26-32.75)
Farhers' age (year)*	32 (28-36)
Sibling†	
None	153 (37.9)
Yes	251 (62.1)
Mothers' education level†	
Less than high school degree	119 (29.5)
High school degree	116 (28.7)
College degree	146 (36.1)
More than college degree	23 (5.7)
Fathers' education level†	
Less than high school degree	120 (29.7)
High school degree	112 (27.7)
College degree	145 (35.9)
More than college degree	27 (6.7)
Monthly income†	
Expenditure more than income	96 (23.8)
Expenditure equal to income	248 (61.4)
Expenditure less than income	60 (14.9)

***:** *(median, IQR),* **†:** *n(%)*

Table II: Children's screen exposure times, by age

Age (Months)	Mobile media exposure time (minutes)*				
	None	<30 min	30-59 min	60-120 min	>120 min
<3	33 (80.5)	3 (7.3)	1 (2.4)	4 (9.8)	0 (0)
3-5	28 (60.9)	11 (23.9)	4 (8.7)	3 (6.5)	0 (0)
6-11	40 (50.6)	20 (25.3)	13 (16.5)	2 (2.5)	4 (5.1)
12-17	20 (23.0)	41 (47.1)	14 (16.1)	7 (8.0)	5 (5.7)
18-24	17 (11.3)	46 (30.5)	44 (29.1)	27 (17.9)	17 (11.3)

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

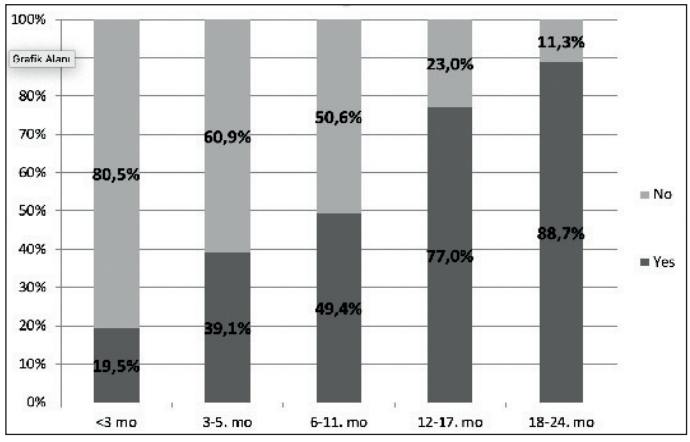

Figure 1: Mobile media usage rates of children by age groups.

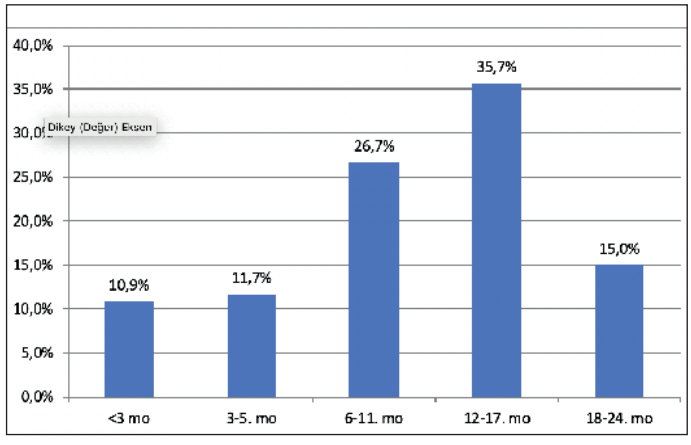

Figure 2: Distribution of children's first use of mobile media, by age.

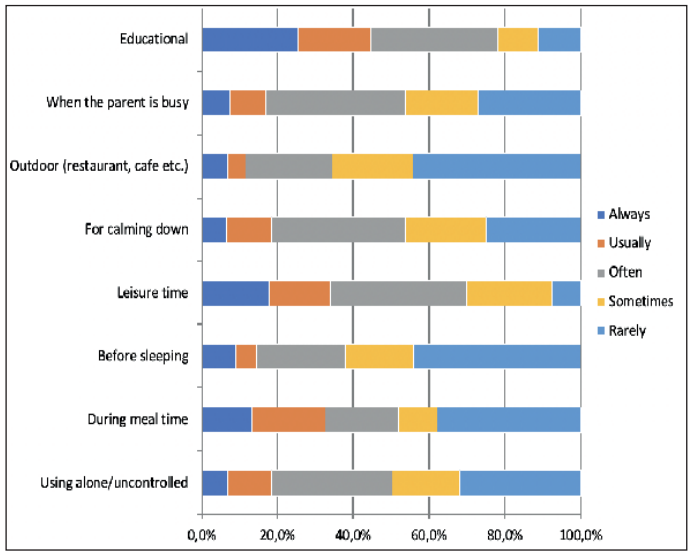

Figure 3: Parental permission patterns for children's mobile media usage.

Daily usage durations were reported as follows: 45.5% used it for less than 30 minutes, 28.6% for 31–60 minutes, 16.2% for 61–120 minutes, and 9.8% for more than two hours. Table II details children's mobile media exposure durations across different age groups. This table supports the finding that screen time generally increases with age, and it also shows that even in the youngest age group (<3 months), some children are already exposed to screens—demonstrating early media use trends. A significant positive correlation was found between the child's age and daily screen time ($p < 0.001$, $r = 0.494$).

Among children using mobile media, 40.1% wanted to choose their own content, while 45.7% of parents reported needing to convince their children to stop using devices.

Parental attitudes about mobile media

Among parents of children using mobile media, 65.6% reported setting time limits, although these limits did not significantly impact the duration of mobile media use ($p > 0.084$). The most common limits were under 30 minutes (60.1%), 30–60 minutes (27.7%), and over 120 minutes (1.2%). Parents allowed mobile media use primarily for educational purposes, entertainment, to occupy children while busy, or to calm them. Parents generally avoided permitting device use outdoors or before sleep. Figure 3 shows the contexts in which parents permit mobile media use, such as during meals, bedtime, or outings. The figure reveals that despite many parents reporting screen time restrictions, mobile devices are still commonly used in routine daily settings—pointing to a possible mismatch between parental intention and practice. Regarding co-viewing habits, 36.8% of parents reported "always" watching content with their child, 19.5% "frequently," 29.3% "sometimes," 8.6% "rarely," and 5.6% "never." Interestingly, 45.5% of parents noted an increase in mobile media exposure during pandemic-related social restrictions.

Parental beliefs about mobile media

Although 91.4% of parents believed mobile media use was harmful, 63.2% acknowledged its educational potential. Among these, 94.7% reported ensuring age-appropriate content, focusing on educational value (39.5%), entertainment (33.8%), non-violent material (12.8%), and calming properties (10.2%). Additionally, 57.1% of parents encouraged foreign language content, a preference significantly associated with maternal education level ($p < 0.001$). When asked about their knowledge of mobile media use in children, 54.5% of parents believed they were sufficiently informed. Children of parents who felt informed had significantly lower exposure to mobile media ($p = 0.010$). However, only 14.3% of parents reported receiving advice from a pediatrician, and no significant difference in exposure rates was observed based on receiving such advice ($p > 0.138$). Parental opinions on appropriate age for mobile media use varied: 6.7% believed it was appropriate before 6 months, 2.5% between 6–12 months, 21.5% between 12–24 months, 24.3% between 24–36 months, and 45% only after 36 months. Despite these beliefs, 74.8% of parents reported that mobile media reduced family interaction time, while only 5.2% believed it increased family bonding.

Video calls

Of the parents, 86.8% engaged in video calls with their children, and 78.7% reported that video calls captured their children's attention. Among these, 82.5% spent 15–30 minutes per session. Interestingly, 76.3% of parents who restricted mobile media use still engaged in video calls, although they did not perceive this as part of mobile media exposure.

DISCUSSION

The updated We Are Social 2021 report revealed a 6% increase in internet users in Türkiye, with 77.7% of the population using the internet and mobile connections reaching 90.8% of the total population as of January 2021 (24). Increased internet, social media, and device usage were observed across all categories. Among individuals aged 16–65, the average daily mobile internet usage was reported as four hours and 19 minutes (24). Our study identified alarmingly high rates of mobile media exposure in children under 24 months, with some exposed during their first months of life. This exposure steadily increased with age, reaching nearly 90% in children by 24 months. While this study did not examine factors such as parental media use, household device ownership, or environmental influences, it is plausible that these high rates reflect the pervasive use of mobile media in Turkish society. Compared to other studies in the literature, the frequencies observed in our study were strikingly higher, with nearly 10% of children exposed to mobile media for over two hours daily(18,19,25–27). These findings underscore the need for targeted and structured public health policies to mitigate early childhood mobile media exposure. Specifically,

national health authorities should implement standardized parental education programs as part of routine pediatric check-ups, focusing on evidence-based strategies to limit screen time, encourage alternative activities, and promote mindful media consumption. These programs should include practical tools such as mobile media exposure guidelines, parental workshops, and digital literacy training to equip caregivers with effective management techniques.

Studies report varied findings on the relationship between children's mobile media exposure and demographic characteristics (4,20,25,28). In our study, no significant relationship was observed between mobile media exposure and family monthly income, potentially due to the widespread availability of mobile devices across different socioeconomic levels. Similarly, no association was found between mobile media exposure and parental educational level. However, children of mothers with higher educational attainment were more likely to engage with foreign-language content.

Parental educational motivation, rule-setting practices, and strict monitoring have been shown to reduce mobile media exposure and positively influence children's academic, social, and physical development (9,23,29,30). In this study, children of parents who reported having sufficient knowledge about mobile media were exposed less frequently and for shorter durations. However, nearly half of the parents who permitted mobile media use did not monitor their children during exposure, and an equal proportion allowed children to choose their own content. Although over 90% of parents acknowledged the harmful effects of mobile media exposure and nearly two-thirds believed it reduced family time, this study reported the highest frequency of mobile media exposure among young children in the literature. These findings highlight the need to improve parental knowledge regarding the developmental and health-related consequences of mobile media exposure and promote effective behavioral strategies. Furthermore, the finding that only one in four parents had received guidance from a pediatrician emphasizes the necessity of increasing pediatricians' awareness and involvement, as they are often the first point of contact in the healthcare system for young children. Hence pediatricians should take a proactive role in media counseling, integrating discussions on mobile media exposure into well-child visits and emphasizing the developmental risks associated with excessive screen time. Standardized screening tools should be incorporated into pediatric practice to assess children's media exposure levels and guide tailored recommendations. In addition, national pediatric associations should advocate for age-specific digital media policies, setting clear recommendations on appropriate content, co-viewing practices, and screen time limits for infants and toddlers.

In line with previous studies, our findings indicate that parents primarily allow mobile media use for educational purposes, entertainment, and calming their children (31–33). Similar trends have been reported in various international studies, where parents often perceive mobile devices as a valuable educational tool, particularly for language learning and cognitive stimulation (34,35). However, research suggests that while some digital content may support learning, passive screen exposure without active parental engagement provides limited developmental benefits and may even hinder language and social skill acquisition (12). Additionally, the use of mobile media as a calming tool aligns with findings that parents frequently rely on screens to manage children's behavior and reduce distress, particularly in situations requiring quiet or distraction (36). However, studies have warned that this approach may lead to increased screen dependency and reduced self-regulation skills, as children become accustomed to using digital devices as a primary coping mechanism for emotional discomfort (7). Moreover, cross-cultural research indicates that socioeconomic and parental education levels play a role in shaping attitudes toward mobile media use, with higher-educated parents more likely to curate content and set usage limits (37). Given these findings, there is a need for parental guidance programs that emphasize structured and interactive media use, ensuring that screen exposure complements, rather than replaces, essential face-to-face interactions and self-regulation development. Future research should focus on longitudinal analyses to determine how parental motivations for mobile media use influence children's cognitive and socio-emotional outcomes over time.

Our findings align with previous research indicating that mobile media exposure is widespread among infants and toddlers, with usage increasing as children grow older. Similar to studies conducted in Türkiye and internationally, early and prolonged screen exposure has been associated with delayed language acquisition, largely due to reduced parent-child verbal interactions and limited conversational turn-taking (38,39). The observation that many children in our study autonomously selected content further supports concerns that passive engagement may replace interactive learning, which is crucial for vocabulary development. Additionally, our results reinforce prior evidence linking excessive screen use to socio-emotional challenges, including increased impulsivity, emotional dysregulation, and reduced attention span (7,40). Studies suggest that excessive screen time at a young age may contribute to difficulties in emotional self-regulation, potentially leading to heightened frustration and behavioral issues. Furthermore, the frequent use of mobile media during meals and before sleep, as observed in our study, is consistent with findings that such practices disrupt eating behaviors and impair sleep quality due to prolonged blue light exposure (6).

McClure et al. (40) reported that children under two years frequently participated in video chats, with parents perceiving this form of media as less harmful compared to other types. The study also highlighted that video calls were the most common medium parents used to maintain contact with family members. Emerging research suggests that interactive video chats can

support young children's social development by facilitating real-time communication, emotional connection, and language exposure-especially with non-resident family members. Unlike passive screen use, video calls offer opportunities for responsive interactions that may benefit cognitive and socio-emotional growth (40). Similarly, in our study, the majority of parents, including those who otherwise restricted mobile media exposure, engaged in video calls with their children. Given the positive effects of video calls on children's social interactions and the common perception that video chats do not constitute mobile media exposure, there may be a need to develop updated guidelines addressing this specific use. Future guidelines should differentiate between passive screen exposure and interactive digital engagement. Policies should provide age-appropriate recommendations on video calls, recognizing their potential social benefits while ensuring they do not contribute to excessive screen time.

This study has several limitations. First, the use of a self-developed questionnaire rather than a validated scale may limit the comparability of our findings with other standardized assessments. Second, we did not examine parents' own media use habits, which could play a significant role in shaping children's exposure and screen-related behaviors. Similarly, the presence and number of media devices in the household were not assessed, which may have influenced the accessibility and frequency of children's mobile media use. Third, although sibling presence was noted, we did not collect detailed data on the media use patterns of siblings, which might have provided further insights into family dynamics and modeling behaviors. Fourth, developmental assessments of the children were not conducted, limiting our ability to directly link screen exposure with developmental outcomes. Finally, as the study was conducted in a single tertiary center, the generalizability of the results to broader populations is constrained. Future studies should aim to incorporate multi-center designs, include detailed assessments of household media environments, and evaluate both parental and sibling media use in relation to child outcomes.

CONCLUSION

Exposure to mobile media is strikingly high among children aged 1–24 months, reaching nearly 90% by 24 months. Children of parents with greater awareness of mobile media risks were found to have lower exposure in both frequency and duration. Educational efforts should focus on increasing parental awareness about the developmental and health impacts of mobile media and encouraging effective monitoring practices. Considering the potential benefits of video calls for social interaction and parental perceptions, updated guidelines may be necessary. Future research using validated tools to explore parental behaviors and environmental factors will be critical in shaping policies that support the healthy development of young children.

Ethics committee approval

This study adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee and Institutional Review Board of Ankara Bilkent City Hospital (E2-22-1197; 05/10/2022).

Contribution of the authors

Yiğit M: Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. **Güngör A:** Constructing the hypothesis or idea of research and/or article, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. **Kalaycı F:** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Taking responsibility in necessary literature review for the study. **Şenel S:** Planning methodology to reach the conclusions, Reviewing the article before submission scientifically besides spelling and grammar.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Multifactorial influences on constipation in children with cerebral palsy: a cross-sectional study of diet, motor function, and spasticity

Hakan Toğuç[1], Hakan Aydın[2], Zehra Fidan[3]

[1]Department of Nutrition and Dietetics, İnonu University, Malatya, Türkiye
[2]Department of Physiotherapy and Rehabilitation, Lokman Hekim University, Ankara, Türkiye
[3]Department of Physiotherapy and Rehabilitation, İstanbul Aydin University, İstanbul, Türkiye

ABSTRACT

Objective: Constipation is an important problem in cerebral palsy (CP) and its exact cause is not known. The aim of this study was to investigate constipation and related factors in children with cerebral palsy.

Material and Methods: This cross-sectional study was conducted with 68 children with CP between October 2024 and January 2025. Socio-demographic data, Gross Motor Function Classification System (GMFCS) scores, Functional Independence Measure for Children (WeeFIM), Modified Ashworth Scale (MAS), 24-hour food intake records, anthropometric measurements, and Bristol Stool Scale evaluations were collected.

Results: It was found that constipation complaints increased with higher GMFCS scores, while constipation complaints decreased with improved WeeFIM scores and increased carbohydrate intake (p=0.013; p=0.040; p=0.031, respectively). Additionally, constipation severity worsened as spasticity in the right and left adductor muscles increased (p=0.001; p=0.002, respectively). Malnutrition, as indicated by the upper mid-arm circumference z-score and Body Mass Index z-scores, was associated with increased constipation (p=0.019; p=0.040, respectively). Sixty-four point seven percent (64.7%) of the mothers reported using dried apricots to alleviate constipation in their children.

Conclusion: Managing constipation in CP requires a multidisciplinary approach, integrating nutritional counseling, motor rehabilitation, and spasticity control. This study highlights the need for comprehensive interventions, moving beyond diet modifications to include physical therapy and functional independence strategies for effective constipation management in CP.

Keywords: Cerebral palsy, Constipation, Diet, Spasticity, Malnutrition

INTRODUCTION

Cerebral palsy (CP) is a neurodevelopmental disorder resulting from brain damage that occurs prenatally, during birth, or in early childhood, leaving lasting effects on muscle control, movement, and posture. CP, which is seen in approximately 1 to 4 in 1000 live births worldwide, is considered one of the most common motor disorders in childhood (1). While motor dysfunctions caused by CP significantly affect the quality of life, gastrointestinal problems such as constipation, which are common in these individuals, further reduce the quality of life (2).

Constipation is a complex condition characterized by issues such as decreased bowel movements, difficulty with defecation, and painful defecation in children with CP. Constipation, which usually has a multifactorial aetiology, is directly related to factors such as dietary habits, motor dysfunctions and spasticity (3). These problems impact children's physical and psychosocial health and lead to difficulties in daily activities (2).

Dietary habits play a critical role in the development of constipation. Deficiencies in fibre consumption, inadequate fluid intake, and feeding difficulties increase the incidence of constipation (4). Children with CP are reported to have specific dietary needs and often experience difficulty consuming solid foods. Inadequate fiber intake has been observed to exacerbate constipation by increasing stool hardness, which negatively affects bowel movements (1).

Motor function limitations make defecation processes difficult by negatively affecting intestinal motility. Constipation is more

Correspondence:
Hakan Toğuç
e-mail: hakan.toguc@inonu.edu.tr

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common in children with low levels of gross motor function and limited independent movement worsens this situation (5). In addition to motor dysfunctions, spasticity also increases the risk of constipation by making it difficult to control intestinal muscles (6). It has been observed that as spasticity severity increases, bowel movements slow down, and stool stays in the intestine longer, becoming harder (7).

Constipation management in children with CP requires a multidisciplinary approach. A combination of high fibre diets, increased physical activity and medical treatments is very important in this process (8).

Although several studies address nutritional or constipation issues in children with CP, studies that combine these factors and associate them with functional independence levels are insufficient. Therefore, this study aimed to investigate constipation and its related factors in children with CP.

MATERIALS and METHODS

Ethical dimension of the research

This cross-sectional study was conducted with 68 children with CP between October 2024 and January 2025. Since the participants did not have sufficient cognitive capacity for consent, their parents were informed in detail about the purpose and procedures of the study and their written informed consent was obtained.

Sample calculation

Based on 56 people who applied to the centre between June and September 2024 and met the inclusion criteria, the sample size was determined as 49 with 95% reliability and 5% margin of error. Within the scope of the study, 72 participants were reached and 4 participants wanted to leave the study and as a result, 68 participants completed the study. The conditions for participation in the study were determined as being diagnosed with cerebral palsy between the ages of 3-15 years and accepting to participate voluntarily.

Data collection tools

Socio-demographic data, Gross Motor Function Classification System (GMFCS) scores, Functional Independence Measure for Children (WeeFIM), Modified Ashworth Scale (MAS), 24-hour food intake records, anthropometric measurements, and Bristol Stool Scale evaluations were collected.

Gross motor functions of the participants were measured with the Gross Motor Function Classification System (GMFCS) developed by Palisano et al. (9). The system consisting of 5 grades was used to determine the degree of independence of motor skills of children and young people in activities of daily living.

Functional independence of children was measured with the WeeFIM scale adapted into Turkish by Tur et al. (10).This scale is a standardised tool used to assess functional independence of children in activities of daily living. This scale covers basic life activities such as how effectively children can eat, drink, dress, bathe and use the toilet on their own. The scale contains 18 items in total and each item assesses the child's ability to perform an activity independently with a scoring system from 1 to 7.

The Modified Ashworth Scale is widely used in the clinic to determine hip adductor muscle spasticity. This measurement method measures the resistance of the muscle during passive movement of the involved limb. The MAS was developed by adding a '1+' value to the assessment range of the Ashworth Scale between 0 and 4 and is one of the most widely used methods for spasticity assessment (11-13).

For food consumption records, food consumption records for the last 24 hours were obtained from the mothers. In addition, the participant mothers were asked what they consumed in case of constipation in their children.

Body weight of the participants was measured with a scale, and height and upper mid-arm circumference were measured with a non-flexible tape measure. For anthropometric measurements, body mass index (BMI) z-score, height-for-age (HFA) z-score and mid-upper arm circumference (MUAC) z-score were calculated according to World Health Organization (WHO) data (14).

Bristol scale was used for constipation measurements and mothers were asked to select the defecation option they observed in their children. According to the options, 1 was ranked as the most severe constipation and 7 as liquid stools (15).

Statistical analysis

The data were analysed using IBM Statistical Package for the Social Sciences, version 22.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). Food consumption records were evaluated using BeBIS 8.2 software. Descriptive statistics were presented as arithmetic mean, standard deviation, frequency and percentage. Histograms and Q-Q plots were used to assess whether the values for normal distribution, skewness, and kurtosis were within ±1.00. Analysis of variance and Kruskal-Wallis tests were used to determine differences between independent groups. Variance homogeneity was assessed using the Levene test, and Bonferroni test were applied for multiple comparisons. Additionally, Pearson and Spearman correlation tests were used to examine the linear relationship between variables. A p-value of <0.050 was considered statistically significant.

RESULTS

In this study, which was conducted with a total of 68 participants, general information of children with CP is given in table I. The mean age of the children was 8.44±3.66 years. Among the

Table I: General information

Variable	Values
Age*	8.44±3.66 (6-11)
Birth weight*	2353.68±1060.65 (1650-3000)
Gender†	
Famale	32 (47.1)
Male	36 (52.9)
Type of birth†	
Vaginal delivery	29 (42.6)
C-section	39 (57.4)
Number of sibling†	
None	5 (7.4)
1	15 (22.1)
2	40 (58.8)
3	5 (7.4)
4	1 (1.5)
5	2 (2.9)
Father's education status†	
Illiterate	2 (2.9)
Primary education	29 (42.6)
High school	14 (35.3)
University	13 (19.1)
Mother's education status†	
Illiterate	5 (7.4)
Primary education	33 (48.5)
High school	23 (33.8)
University	7 (10.3)
Family income status†	
Income exceeds expenses	3 (4.4)
Income and expenditure equal	32 (47.1)
Income less than expenditure	33 (48.5)
GMFCS†	
Grade-I	29 (42.6)
Grade-II	4 (5.9)
Grade-III	14 (20.6)
Grade-IV	11 (16.2)
Grade-V	10 (14.7)

***:** *mean±SD (min-max),* **†:** *n(%),* ***GMFCS:** Gross motor function classification system*

participants, 47.1% were female and 52.9% were male. Primary school was the highest level of education completed by 42.6% of fathers and 48.5% of mothers. The family income of 48.5% of the participants was less than their expenses.

The distribution of GMFCS grades, food consumption, WeeFIM and adductor spasticity of the participants according to Bristol Stool Scale Score is given in table II. Accordingly, it was found that constipation complaints of CP patients increased with increasing GMFCS grades. It was found that GMFCS grade 2 had a significantly higher Bristol score compared to grades 4 and 5, thus grades 4 and 5 had significantly higher severity of constipation than grade 2. (p=0.013). In the relationship between the participants' food consumption and Bristol Scale score, a weak positive significant relationship was found between carbohydrate intake and Bristol Scale score (p=0.031). In addition, no significant relationship was found between the amount of fibre consumed and the amount of liquid consumed

Table II: Distribution of GMFCS levels, food consumption, WeeFIM and adductor spasticity according to Bristol Stool Scale Score

Variable	mean±SD	r/rs*	p
Bristol Stool Score by GMFCS			
Grade I (n=29)	3.83±1.65		
Grade II (n=4)	5.50±1.73[a]	-	
Grade III (n=14)	3.79±1.12		0.013†
Grade IV (n=11)	2.73±1.49[b]		
Grade V (n=10)	2.70±1.70[b]		
Total Score (n=68)	3.57±1.65		
Nutrient components			
Energy	1208.63±359.29	0.224	0.067‡
Carbonhydrat	130.00±55.89	0.262	0.031‡
Protein	45.47±15.27	0.162	0.186‡
Lipid	54.39±16.39	0.085	0.488‡
Fiber	13.16±7.21	0.163	0.186‡
Antioxidant	1.65±1.57	-0.014	0.908‡
Water	1675.91±651.72	-0.103	0.405‡
WeeFIM score			
Self-care	11.06±13.12	0.055	0.656‡
Sphincter control	5.65±7.43	0.157	0.202‡
Transfers	7.74±10.72	0.107	0.383‡
Locomotion	8.57±6.94	0.036	0.771‡
Communication	12.35±10.23	0.064	0.605§
Social cognition	10.35±7.71	0.256	0.035§
Total score	16.47±12.78	0.249	0.040‡
Adductor spasticity			
Right	1.53±1.49	-0.401	0.001‡
Left	1.46±1.43	-0.368	0.002‡

***:** *Correlation coefficients between the Bristol Stool Scale Score and the related variables,* **†:** *One-Way ANOVA test,* **‡:** *Spearman correlation test,* **§:** *Pearson correlation test,* **[a/b]:** *Different superscript letters indicate statistically significant differences between groups,* ***GMFCS:** Gross Motor Function Classification System,* ***WeeFIM:** Pediatric Functional Independence Measure*

and the Bristol Scale score (r=0.163; p=0.186). A correlational analysis between the Bristol Stool Scale Score and WeeFIM scores in individuals with cerebral palsy revealed low but statistically significant positive correlations with social cognition (r = 0.256, p = 0.035) and total functional independence scores (rs = 0.249, p =0 .040), suggesting that increased functional abilities are modestly associated with improved bowel function and reduced constipation. A moderate statistically significant negative correlation was observed between adductor spasticity and the Bristol Stool Scale Score, indicating that higher spasticity in the right (rs= –0.401, p = 0.001) and left (rs = –0.368, p = 0.002) adductors was associated with lower stool scores and thus increased constipation severity.

In evaluations based on MUAC z-scores, those with severe malnutrition (< -2 SD) were found to have significantly higher right and left adductor spasticity than those in the low-normal range (-1 SD to 0 SD) (p=0.002 and p=0.006, respectively). Constipation severity was found to be significantly lower in those with high/possible overnutrition (>+2 SD) compared to those in the normal (0 SD to +1 SD) and severe malnutrition (< -2 SD) groups (p=0.019).

Table III: The relationship between MUAC, HFA and BMI z-scores and bristol stool scale, adductor spasticity

	Adductor spasticity				Bristol Stool Scale	
	Right		Left			
	mean±SD	p	mean±SD	p	mean±SD	p
MUAC Z-SCORE						
Severe malnutrition (< -2 SD)	2.70±1.06[a]		2.70±0.82[a]		2.90±1.37[b]	
At risk of malnutrition (-2 SD to -1 SD)	1.67±1.51		2.00±1.67		3.33±2.16	
Low-normal range (-1 SD to 0 SD)	0.80±1.15[b]	0.002*	0.90±1.12[b]	0.006†	4.00±1.89	0.019*
Normal (0 SD to +1 SD)	2.00±1.41		1.71±1.38		3.48±1.25[b]	
Mildly elevated (+1 SD to +2 SD)	2.33±1.50		2.00±1.50		3.00±1.00	
High / Possible overnutrition (>+2 SD)	0.00±0.00		0.00±0.00		7.00±0.00[a]	
HFA Z- SCORE						
Severe malnutrition (< -2 SD)	2.11±1.40[a]		2.07±1.30[a]		3.71±1.51	
At risk of malnutrition (-2 SD to -1 SD)	1.75±1.45	0.044†	1.55±1.43	0.041†	3.65±2.13	0.863†
Low-normal range (-1 SD to 0 SD)	0.67±0.87[b]		0.56±0.73[b]		3.44±1.42	
Normal (0 SD to +1 SD)	1.78±1.72		1.78±1.64		3.33±1.32	
Mildly elevated (+1 SD to +2 SD)	0.00±0.00		0.50±0.71		2.50±0.71	
BMI Z- SCORE						
Severe malnutrition (< -2 SD)	1.45±1.53		1.59±1.53		3.18±1.65	
At risk of malnutrition (-2 SD to -1 SD)	1.31±1.54		1.25±1.48		4.19±2.10	
Low-normal range (-1 SD to 0 SD)	1.91±1.70	0.422*	2.09±1.58	0.471*	4.45±1.29[a]	0.040*
Normal (0 SD to +1 SD)	2.27±0.79		1.91±0.54		3.18±0.98	
Mildly elevated (+1 SD to +2 SD)	2.67±0.58		0.67±1.15		1.67±0.58[b]	
High / Possible overnutrition (>+2 SD)	1.80±1.64		2.00±1.41		3.40±0.55	

***:** *Kruskal Wallis,* **†:** *One Way ANOVA test,* **[a/b]:** *Different superscript letters indicate statistically significant differences between groups,,* ***MUAC:** Mid-upper Arm Circumference,* ***BMI:** Body Mass Index,* ***HFA:** Height for Age*

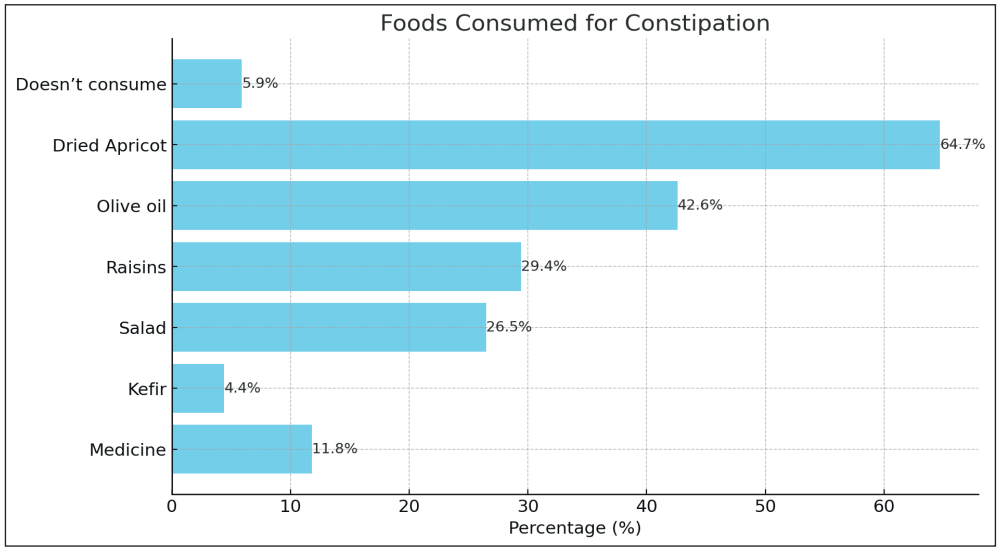

Figure 1: Food consumed for constipation

According to HFA z-scores, right and left adductor spasticity was significantly higher in those with severe malnutrition (< -2 SD) compared to those in the low-normal range (-1 SD to 0 SD) (p=0.044 and p=0.041, respectively).

In evaluations based on BMI z-scores, constipation severity was found to be significantly higher in those with mildly elevated (+1 SD to +2 SD) compared to the low-normal range (-1 SD to 0 SD) (p=0.040).

Information about the alternative methods used by the families of the participants against constipation complaints is shown in figure 1. Accordingly, 64.7% of the mothers stated that they consumed dried apricots, 42.6% olive oil and 29.4% raisins when their children complained of constipation.

DISCUSSION

Our study found that constipation complaints increased with higher GMFCS grades in children with CP. The difference between GMFCS grade 2 and grades 4 and 5 was significant (p=0.013), indicating that children with higher GMFCS grades experienced more severe constipation. As GMFCS grades rise

from one to five, decreased mobility, increased muscle tone and spasticity, and feeding difficulties may exacerbate constipation complaints. Particularly, the differences between grade 2 and grades 4 and 5 are notable, with constipation complaints being less severe in grade 2. These findings align with similar studies in the literature, highlighting that loss of motor function significantly impacts constipation in children with CP.

As the participants' social and functional independence scores increased, their Bristol scale scores also increased, indicating a decrease in constipation complaints. This finding was also supported by Günaydın and Tuncer (5) who found a significant negative relationship between functional independence and constipation (18). This suggests that psychological factors related to functional independence and social independence with increased mobility may help reduce constipation (18,19).

Constipation and adductor spasticity are distinct conditions that significantly impact quality of life. Constipation is marked by infrequent or difficult bowel movements, while adductor spasticity involves involuntary contraction of the thigh adductor muscles. Research suggests a potential link between these conditions, especially in neurodegenerative disorders. Enteric neurodegeneration, affecting gastrointestinal nerves, has been linked to constipation in aging populations (20). Spasticity, including adductor spasticity, can be influenced by non-neural factors such as soft tissue changes and muscle fatigue (21). A proposed mechanism involves age-related changes in vagal afferents, sensory nerves that innervate the gastrointestinal tract, leading to distortions in the reflex loop and contributing to both gastrointestinal and motor symptoms (22,23). In this study, a significant negative correlation was found between increased adductor spasticity and Bristol scale scores, indicating that higher adductor spasticity is associated with more severe constipation.

Our findings show a significant relationship between carbohydrate consumption and Bristol scale score. In the literature, constipation is frequently linked to diet, particularly carbohydrate intake, as carbohydrates—especially those rich in fibre—have significant effects on intestinal health (24). However, in our study, while total carbohydrate intake was associated with defecation frequency, no significant relationship was found between fibre consumption and Bristol scale scores. This discrepancy suggests that the effect of fibre on constipation management may be influenced by factors such as the type and quality of fibre consumed or individual variability in the gut microbiome (25,26). In particular, the fermentation capacity of dietary fibre and its interaction with the gut microbiota may play a key role in modulating fibre's effect on constipation. These interactions may explain why fibre intake alone did not result in significant changes in Bristol scale scores in our study. Furthermore, other dietary and lifestyle factors, such as physical activity, may have contributed to the observed results, highlighting the complex relationship between diet and constipation. However, no significant association was found between fluid intake and constipation in this study. Previous studies in healthy adults without constipation showed that decreased fluid intake led to reduced defecation frequency, with similar findings observed in studies of individuals with cerebral palsy (27, 28). This suggests that fluid intake may influence constipation, but other variables could mediate this effect in individuals with specific health conditions.

The relationship between MUAC z-score, HFA z-score and BMI z-score, which are the parameters by which malnutrition is measured in patients with CP, and constipation was analysed and it was found that constipation became more severe as weight gain increased according to MUAC z-score and BMI z-score. Similar results were found in a study conducted by Budokhane et al. (29) on CP patients in North Africa. In addition, it has been reported that inadequate food intake decreases intestinal transit time and is associated with constipation (30). Furthermore, it was found that adductor spasticity increased with increasing weakness according to MUAC z-score and HFA z-scores. Scarpato et al. (31) reported that malnutrition led to a decrease in muscle mass and impaired muscle function. This may lead to increased spasticity in adductor muscles.

Among the mothers who participated in the study, 64.7% used dried apricots, 42.6% used olive oil and 29.4% used raisins for constipation. Similarly, in Ghana, Capsicum frutescens L. and Citrullus lanatus were used as a solution to children's constipation complaints (32). In a study conducted among cancer patients in Türkiye, 39.4% used dried apricots and 28.8% used olive oil supplements for constipation (33). These food preferences are influenced by the diversity of endemic plants in the regions where they live and the presence of foods commonly consumed in Türkiye. This suggests that local flora is a determining factor in traditional medicine practices and daily diets.

CONCLUSION

In conclusion, the importance of a multidisciplinary approach in managing and treating constipation in children with CP is emphasised. Rehabilitation programmes that promote functional and social independence, along with nutritional counselling, may play a key role in reducing symptoms. The findings may guide pediatricians and healthcare professionals in developing more comprehensive and individualised follow-up plans. Future studies should further examine these relationships with larger samples and explore additional contributing factors. A better understanding of structural and psychological influences will support the development of more effective management strategies. Raising awareness and educating parents and carers remains vital to improving children's quality of life.

Limitations of the study

This study associated constipation with various factors in children with CP but has methodological limitations. The

cross-sectional design precludes causal conclusions and the small sample size and limited geographical coverage reduce generalisability. The reliance on mothers' reports and a 24-hour dietary record leads to potential bias. Furthermore, the assessment of spasticity only in the adductor muscles may not reflect its overall effect on gastrointestinal function.

Despite these limitations, the study provides valuable information by combining dietary intake, motor function and spasticity. The use of validated scales and nutritional status indicators improves data reliability and clinical interpretation, making the study suitable for interdisciplinary care.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. Ethical approval was obtained from Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee in accordance with the Declaration of Helsinki (Ref. No: 2024/5887).

Contribution of the authors

Toğuç A: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Aydın H:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Biological materials, taking responsibility of the referred patients. ***Fidan Z:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Providing personnel, environment, financial support tools that are vital for the study.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Pediatric rheumatologists' perspective on next-generation: virtual reality revolution

Ayşenur Doğru[1], Gülşah Kavrul Kayaalp[1], Selen Duygu Arık[1], Fatma Gül Demirkan[2], Özlem Akgün[1], Bengisu Menentoğlu[1], Büşra Başer Taşkın[1], Nuray Aktay Ayaz[1]

[1]Department of Pediatric Rheumatology, İstanbul University Faculty of Medicine, İstanbul, Türkiye
[2]Department of Pediatric Rheumatology, Kanuni Sultan Süleyman Research and Training Hospital, İstanbul, Türkiye

ABSTRACT

Objective: This study assessed pediatric rheumatologists' (PRs) knowledge, attitudes, and experiences regarding virtual reality (VR) technology in medical education, clinical management, patient education, and research.

Material and Methods: A web-based survey was conducted among pediatric rheumatologists (PRs) in Türkiye. Participants were categorised based on self-reported VR knowledge. Group 1 included participants who considered themselves knowledgeable about VR, while Group 2 included those who did not perceive themselves as knowledgeable about the technology. Demographics, attitudes, and behaviors related to VR were compared. The influence of social media and telemedicine experience on VR awareness was also evaluated.

Results: Eight one participants, 49.3% were pediatric rheumatology (PR) fellows, 27.1% faculty members, and 23.6% PR specialists. Overall, 67.9% had VR knowledge (Group 1), while 32.1% did not (Group 2). Group 1 demonstrated significantly greater awareness of telemedicine and health technologies ($p=0.003$, $p<0.001$). VR equipment knowledge ($p<0.001$) and prior experience ($p<0.001$) were also higher in Group 1. Awareness of VR applications in pain management was more prevalent in Group 1 (43.6%) than in Group 2 (15.3%, $p=0.018$). Hesitancy towards clinical VR implementation was reported by 90.9% of Group 1 and 61.5% of Group 2 ($p=0.199$).

Conclusion: PRs show an increasing interest in VR technology, indicating a promising trajectory for its integration into clinical and educational settings.

Keywords: Autoimmune diseases, Digital health technologies, Rheumatology, Social media, Telemedicine, Virtual reality

INTRODUCTION

Pediatric rheumatology is a subspecialty of pediatrics focusing on inflammatory and non-inflammatory disorders of the connective tissues, joints, muscles, and vessels. Although it is a relatively new branch of pediatrics, there have been great advances in the diagnosis and treatment of pediatric rheumatic diseases in the last two decades. With the emergence of biologics as therapeutic agents, the goal of complete recovery and total well-being for children with rheumatic conditions are not far away.

In addition to the developments in diagnostics and pharmaceuticals, new technologies to improve the quality of care (patient education, exercise, and pain management) and for education and professional networking are endorsed and being used with increasing enthusiasm.

Virtual reality (VR) is a significant development, initially used for entertainment and gaming. However, over the last 20 years, the accessibility and applicability of VR technology have increased (1). The technology allows users to experience real-world sensations in a virtual world created with special equipment. A head-mounted display connected to a mobile phone or computer is the most essential piece of equipment (2). Hand controllers, sensory detectors, gloves, and clothing are also used to enhance reality. This creates a three-dimensional, multi-sensory, and immersive environment.

Virtual reality technology appears to be emerging as a game changer in medical education and practical training, clinical

Correspondence Address:
Nuray Aktay Ayaz
e-mail: nurayaktay@gmail.com

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management, patient education, training, and research (3). Since pain is one of the most important symptoms in patients with rheumatic diseases, this comprehensive technology could be a new tool for pain relief. Although limited data is available, the beneficial effects of VR technology in managing pain and anxiety in patients with rheumatic diseases have been demonstrated (4). Few applications using VR technologies are being developed for the training of healthcare professionals and medical students about inflammatory arthritis (3,5). However, there may be some negative aspects, when immersed in the virtual environment, the line between the virtual and the real may become blurred as the virtual and the real become intertwined. In addition, all information about people can be accessed through the inputs and outputs of VR devices. Therefore, ethical issues such as confidentiality of personal information, personal freedom and privacy may arise as their use becomes more widespread (6).

Due to the lack of data on the use of VR, today's new but essential technology, we aimed to evaluate the knowledge, attitudes, usage trends, and experiences of pediatric rheumatologists regarding virtual reality technology in clinical practice.

MATERIALS and METHODS

The present study was conducted between June and August 2024, targeting pediatric rheumatologists (PRs) practicing in Türkiye. A web-based survey was prepared by the Google Forms software (Google Forms, Albuquerque, New Mexico, USA) and conducted to all 143 PRs in Türkiye via a WhatsApp link by mobile smartphones and e-mail addresses. After removing the pilot responses, we found that 81 physicians gave informed consent by opening the questionnaire and completing the survey anonymously, resulting in a response rate of 56.64%.

The electronic survey consisted of 27 questions, divided into three sections. The first section collected demographic information, including age, gender, academic title, center of affiliation, and experience in pediatric rheumatology.

The second section assessed participants' use of technology, including social media, internet, and telemedicine, as well as their knowledge, attitudes, and behaviors towards these technologies. Participants were asked about the frequency of social media use, their knowledge of telemedicine, whether they had assessed patients via telemedicine, their familiarity with health technologies, the proportion of literature searches related to health technologies, and their frequency of internet use related to rheumatology.

The third section focused on participants' knowledge, experience, and opinions regarding VR and its potential applications in medical practice. In this section, participants were asked whether they considered themselves to be knowledgeable about VR, with a binary response option. This section then explored their knowledge and training in VR technologies, sources of information, experiences and opinions regarding the use of VR in pain management, treatment, and exercise therapy, and their likelihood of prescribing VR technologies. It also assessed concerns about the suitability and applicability of VR technology in the hospital setting and the reasons for these concerns. The full set of survey questions can be found in the supplementary document.

Participants were categorized into two groups based on their self-assessment of knowledge regarding VR technology. Group 1 included participants who considered themselves knowledgeable about VR, while Group 2 included those who did not perceive themselves as knowledgeable about the technology. First, comparisons were made between the two groups on factors that might indirectly influence VR knowledge, such as demographic characteristics, technology use, and internet and telemedicine use. Subsequently, comparisons were made regarding factors that could directly influence VR knowledge, including participants' experiences with VR, their sources of information, and their understanding of VR applications in medical practice, in order to identify the underlying sub-factors that determine the overall knowledge of VR and their contribution to the differences between the groups.

Statistical analysis

Survey data were collected using Microsoft Excel (Microsoft Corporation, Redmond, WA) and analyzed using SPSS 29.0 (IBM Corp., Armonk, NY, USA). Minimum, maximum, and median descriptive statistics were calculated according to the distribution of numerical variables. Categorical variables were analyzed as frequency and proportion. The normality of the baseline data was examined using the Kolmogorov Smirnov test. The Mann-Whitney U test was used to compare non-normally distributed numerical variables, and the Chi-square test was used to compare categorical variables. A p-value <0.050 was considered statistically significant.

RESULTS

The survey was completed by 81 clinicians working in pediatric rheumatology in Türkiye. Sixty-seven of the PRs (82.7%) were female. The median (min-max) age of the PRs was 37 years (31-64). The study group consisted of 40 PR fellows (49.3%), 22 faculty members (27.1%), and 19 PR specialists (23.6%). Of the participants, 73 PRs (90.1%) work in an academic institution (university or training and research hospital), 7 PRs (8.6%) in a state hospital, and 1 PR (1.3%) in a private clinic. When assessing the participants' experience in pediatric rheumatology, 53 (65.4%) had 1-5 years, 18 (22.2%) had 6-15 years, and 10 (12.4%) had more than 15 years of experience.

Among the cohort, 55 PRs (67.9%) claimed to be well-versed in VR technology (group 1) and 26 PRs (32.1%) did not consider themselves knowledgeable about this technology (group 2). The

Table I: Comparison of demographic characteristics of the participants in Group 1 and Group 2

	Group 1 (n=55)	Group 2 (n=26)	p
Female*	47 (85.5)	20 (76.9)	0.343‡
Age (years)†	38 (31-64)	36.5 (31-56)	0.206§
Academic title*			
PR fellow	23 (41.8)	17 (65.4)	0.164‡
PR specialist	15 (27.3)	4 (15.4)	**0.048**‡
PR specialist (Faculty)	17 (30.9)	5 (19.2)	
Center of affiliation*			
Academic institution	50 (90.9)	23 (88.5)	0.461‡
State hospital	5 (9.1)	2 (7.7)	
Private clinic	0 (0)	1 (3.8)	
PR experience*			
1-5 years	34 (61.8)	19 (73.1)	0.333‡
6-15 years	13 (23.6)	5 (19.2)	
>15 years	8 (14.6)	2 (7.7)	

***:** n(%),**†:** median (min-max),**‡:** Chi-square,**§:** Mann-Whitney U test **PR:** Pediatric rheumatology, Bold p value for the comparison between fellows and all specialists (including specialists and faculty members)*

Table II: Comparison of social media, telemedicine, and health technology knowledge and use of participants in Group 1 and Group 2

	Group 1 (n= 55)	Group 2 (n= 26)	p*
Social media†			
Usage	53 (96.4)	24 (92.3)	0.590
Frequency			
Everyday	43 (81.1)	22 (91.7)	
2-3 days/week	5 (9.4)	0 (0)	
<2-3 days/week	5 (9.4)	2 (8.3)	0.403
Telemedicine†			
Knowledge	48 (87.3)	15 (57.7)	0.003
Experience	14 (25.5)	6 (23.41)	0.817
Knowledge about health technology*	51 (92.7)	16 (61.5)	<0.001
Frequency of internet use in their speciality†			0.730
Everyday	50 (90.9)	23 (88.5)	
2-3 days/week	5 (9.1)	3 (11.5)	
The percentage of literature reviews on health technologies in total literature reviews†			
≤20%	30 (54.5)	23 (88.5)	0.003
>20%	25 (45.5)	3 (11.5)	

***:** Chi-square,**†:** n(%)*

gender distribution between the two groups was similar, with 47 females (85.5%) in Group 1 and 20 females (76.9%) in Group 2, showing no statistically significant difference (p=0.343). The median (min-max) age of group 1 was 38 (31-64) years and that of group 2 was 36.5 (31-56) years and both groups were similar in terms of age (p=0.206). Detailed demographic data are shown in Table I.

When the participants were categorized according to academic title as PR fellows and specialists (including both practicing specialists and faculty members), the proportion of specialists was significantly higher in Group 1 (n=32, 58.2%) than in Group 2 (n=9, 34.6%) (p=0.048). When asked about the frequency of internet use in rheumatology, 50 PRs (90.9%) in Group 1 and 23 PRs (88.5%) in Group 2 reported using the internet every day (p=0.730). PRs who reported good knowledge of VR technology were significantly more informed about telemedicine (n=48, 87.3%) and health technologies (n=51, 92.7%) compared to those who felt less knowledgeable about VR technology. The differences were statistically significant for both telemedicine and health technologies (p=0.003 and p < 0.001, respectively) (Table II).

When the entire cohort was divided into fellows and specialists (including faculty members) based on academic title, 25 fellows (62.5%) and 38 specialists (92.7%) had knowledge about telemedicine (p=0.001), while 4 fellows (10.0%) and 16 specialists (39.0%) had evaluated patients via telemedicine (p=0.002).

The groups were asked to indicate the proportion of health technology reviews among their total literature reviews. In Group 1, 30 PRs (54.5%) reported this proportion as ≤20%, whereas in Group 2, 23 PRs (88.5%) reported the same. This difference was statistically significant (p=0.003) (Table II). Participants in group 1 had more knowledge of VR equipment (n=49 89.1%) compared to group 2 (n=8, 30.7%) (p<0.001). In group 1, 29 PRs (52.7%) had experience with VR technology, whereas no PRs in group 2 had such an experience. Table III provides a detailed assessment of the source of VR experience, knowledge of technology, and knowledge of VR equipment.

Table III: Comparison of the information sources and experiences of the examined PRs on VR according to groups

	Group 1 (n:55)	Group 2 (n:26)	p*
VR experience†	29 (52.7)	0(0)	<0.001
Source of VR experience†			
Educational application	19 (34.5)		
Medical congress	8 (14.5)		
Patient treatment	5 (9)		
Tecnology fairs	4 (7.3)		
Knowledge of VR equipment†	49 (89.1)	8 (30.7)	<0.001
VR equipment†			
Smartphones	36 (65.5)	6 (23.1)	
Computer	39 (70.9)	7 (26.9)	
Hand controller	6 (10.9)	6 (23.1)	
Head-monted display	39 (70.9)	5 (19.2)	
Source of information for VR technologies†			
Other healthcare professional	27 (49.1)	7 (26.9)	
Medical congress	16 (29.1)	7 (26.9)	
Scientific articles	23 (41.8)	5 (19.2)	
Technology fairs	5 (9)	2 (7.7)	
Social media	20 (36.4)	6 (23.1)	

***:** Chi-square,**†:** n(%), **VR:** Virtual reality*

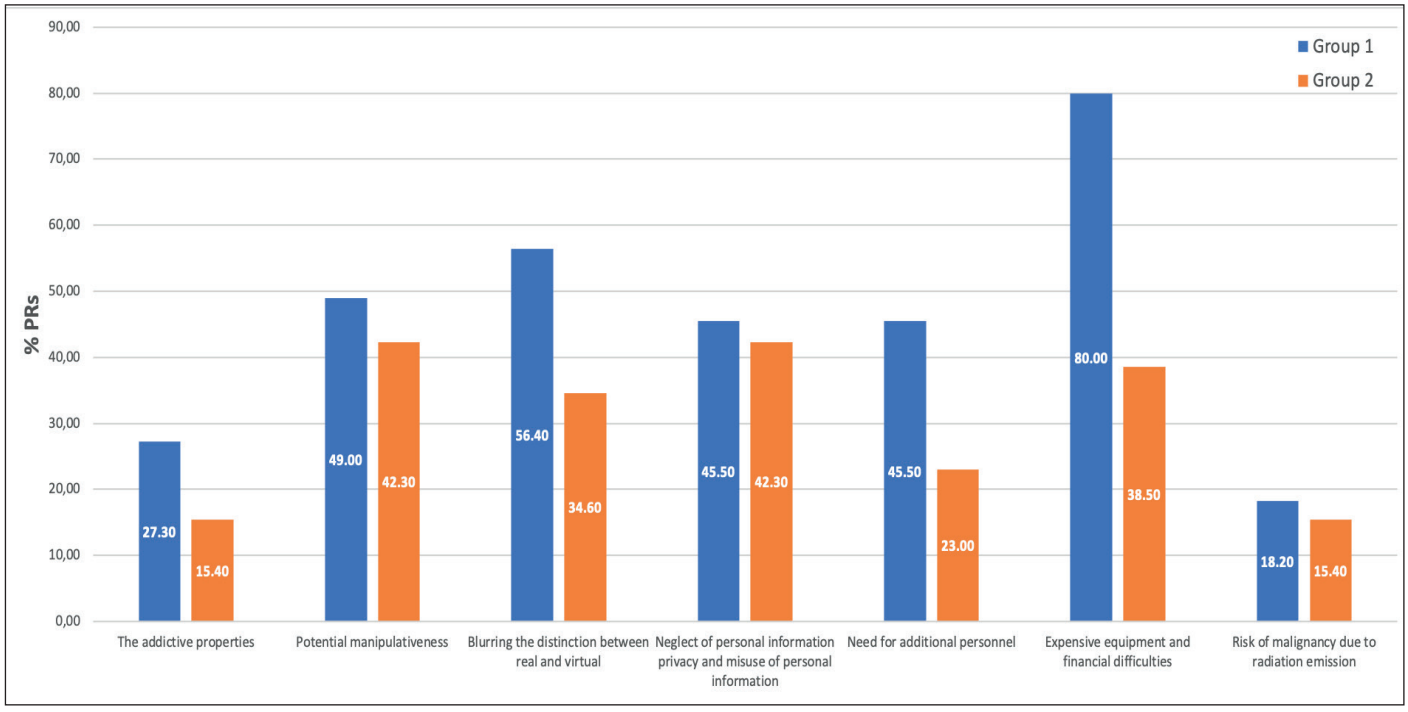

Figure 1: Percentage distribution of reasons for hesitation regarding the application of virtual reality techniques in Group 1 and Group 2

Among the participants in group 1, 47 PRs (85.4%) stated that they could use VR technology for patient education, 44 PRs (80.0%) for practical applications, 39 PRs (70.9%) for theoretical education, 37 PRs (67.3%) as a treatment method, and 1 PR (1.8%) for remote consultation. One PR (1.8%) in group 1 stated that he would not use VR technology in his practice. In group 2, 17 PRs (65.4%) stated that they could use VR technologies for patient education, 15 PRs (57.7%) for practical applications, 12 PRs (46.2%) as a treatment method, and 11 PRs (42.3%) for theoretical education. Twenty-four PRs (43.6%) in group 1 and 4 PRs (15.3%) in group 2 were aware that virtual reality applications are in use for pain management (p=0.018). Forty-six PRs (83.6%) in group 1 and 17 PRs (65.4%) in group 2 believed that virtual reality applications would be effective in pain management (p=0.887). There were 54 PRs (98.2%) in group 1 and 19 PRs (73%) in group 2 who believed that VR applications could be used in exercise therapy (p=0.743).

Twenty-eight PRs (50.9%) from group 1 and 10 PRs (38.4%) from group 2 thought that VR applications could be prescribed as a treatment (p=0.897). Similarly, 36 PRs (65.5%) in group 1 and 12 PRs (46.2%) in group 2 said they could prescribe virtual reality applications in a clinical setting (p=0.782) when asked if they would prefer to prescribe virtual reality applications as a treatment. Forty-four PRs (80.0%) in group 1 and 18 PRs (69.2%) in group 2 agreed that VR applications could be used in a hospital setting.

Similarly, 50 PRs (90.9%) in group 1 and 16 PRs (61.5%) in group 2 reported concerns about issues related to the VR techniques (p=0.199). In Group 1, the main concerns about VR technology were the high cost of equipment and associated financial challenges, the risk of blurring the distinction between real and virtual experiences, and the potential for manipulation and in Group 2, the main concerns were the risk of neglecting the privacy of personal data and misuse of personal information, the potential for manipulation, and issues related to the high cost of equipment and financial challenges. Figure 1 shows the percentage distribution of reasons for hesitation for both groups.

DISCUSSION

This study is the first to describe the knowledge and attitudes related to VR technology. Approximately two-thirds of the cohort indicated that they were knowledgeable about VR technology. Those who reported having such knowledge also had more information about telemedicine, health technologies, and VR equipment; they conducted more literature reviews on health technology and had more experience with VR.

There was no significant difference in age, gender, or center of affiliation between participants who considered themselves knowledgeable about VR technology and those who did not. However, the specialists and the faculty members had higher levels of knowledge about VR technology, which we attribute to the correlation between increasing professional experience and the increased likelihood of learning about new technologies through professional networks and conferences. Similarly, when physicians' perspectives on the metaverse were assessed among allergy-immunology physicians, it was found

that perspectives did not change with age, gender and place of work, but changed with increasing years of professional experience (7).

The use of social media has increased in recent years with the development of technology and the widespread use of the internet. When social media first appeared, it was for personal life and entertainment. Over time, it began to offer networking and information sharing in professional life. Medical professionals began to use social media to connect with peers, share research, discuss clinical cases, collaborate on medical projects, collect data, provide medical education, disseminate health information and educate patients about diseases, treatments and preventive measures. An international survey conducted by the Emerging EULAR Network (EMEUNET) showed that 71% of rheumatologists use social media for professional purposes, including professional networking, education, and clinical and research updates. It has been observed that those who use social media for professional purposes also use these platforms for longer periods in professional and non-professional ways (8). It is thought that the use of social media and the internet will enable people to learn more about new and widely used technologies, such as VR, through the rapid transfer of information. In our study, although not statistically significant, use of social media, frequency of use of social media, and frequency of use of the internet related to the field were higher among those who reported being more knowledgeable about VR technology.

Telemedicine has emerged with the spread of high-speed internet and portable technological devices. During the SARS-CoV-2 pandemic, the use of telemedicine has increased mainly due to the need for remote visits. Telemedicine in pediatric rheumatology practice has the potential to visit patients remotely, view patient examinations, facilitate multidisciplinary approaches, identify suspicious cases and call for face-to-face visits, and avoid problems due to social difficulties (9). Another study from our group showed that parents of pediatric rheumatology patients were quite accepting telemedicine visits (10). The convenience of telemedicine and the rapid adoption of innovations have paved the way for digital transformation in rheumatology. The ability to communicate between patients and physicians through online platforms has enabled the digitalisation of several medical practices. In our study, participants who were more familiar with VR were also more likely to be familiar with telemedicine. Specialists and faculty members were also more familiar with telemedicine and treated more patients via telemedicine.

Over the past decade, the field of rheumatology has seen significant advances through the integration of a variety of digital health technologies. These innovations enable the regular maintenance of electronic health records, enhance patient data collection through wearable technologies and mobile applications, prevent delays in diagnosis and treatment through virtual visits, use digital therapeutics, and apply artificial intelligence to make informed assumptions about patient diagnosis, treatment outcomes, and mortality (11). In our study, those who felt more knowledgeable about VR were more familiar with health technology and were more likely to include health technology topics in their clinical literature searches. It seems inevitable that the interrelationship between new developments will be overlooked. Therefore, the integration of digital technologies may open new horizons in rheumatology in the future. With the increasing use of health technologies, the use of VR in rheumatology has become more widespread and the number of people who have experienced these applications has increased. As shown in our study, knowledge about VR is growing as more people engage with it.

VR technologies have significant potential benefits for patients and rheumatologists in several areas of patient care. In pediatric rheumatology, a relatively new field compared to other pediatric subspecialties, the use of VR in education is valuable due to the current global shortage of experts. In our study, rheumatologists who were more familiar with virtual reality had more experience using it in education. VR applications are already being used for educational purposes in fields such as plastic surgery, orthopedics, and neurosurgery where manual dexterity and attention are required, as well as for the learning of anatomy and clinical ultrasound (12-16). In the field of rheumatology, an educational study was conducted in Germany where 125 participants, including healthcare professionals and medical students, were taught about inflammatory arthritis with the help of a VR application called Rheumality (3). Almost all the participants reported that the VR presentation had improved their understanding of inflammatory arthritis and expressed a desire for further training, including new case studies and information on other rheumatic diseases.

Pain management is another area where the use of VR is growing and could provide significant benefits in rheumatology. To date, it has been used in children for pain relief during dental procedures, for elective day surgery, for intravenous cannulation, and for the treatment of burns (17-20). Interestingly, in a rheumatology clinic, the application of VR-based meditation and biofeedback treatments involving 20 patients with lupus, rheumatoid arthritis, and fibromyalgia led to a reduction in pain, as evidenced by decreased Visual Analog Scale (VAS) scores (4). In our cohort, participants with a higher levels of knowledge about VR were more likely to be aware of its applications in pain management. Although the difference was not statistically significant, these participants were also more likely to believe in the effectiveness of VR for pain management. Given that pain is a prevalent symptom in rheumatic diseases, this finding underscores the potential value of VR as a tool for enhancing patient care. Despite the lack of statistical significance, the trend suggests that familiarity with VR technology may influence perceptions of its utility in clinical settings.

Digital therapeutics, another application of VR, is a subset of digital health technologies that provide evidence-based

therapeutic interventions to patients (21). These interventions are powered by advanced software programs and are designed to prevent, manage, or treat a broad spectrum of medical conditions and diseases. Many digital therapeutics undergo rigorous review and approval by regulatory agencies, such as the Food and Drug Administration (FDA), to ensure their efficacy and safety (22). In the United States, some of these products are available by prescription, and reimbursement for these treatments is anticipated to be available within a few years (22). In our study, participants who were more knowledgeable about VR were also more likely to be aware that virtual reality applications could be prescribed and were more confident in their ability to prescribe such applications. This increased awareness and confidence suggests that informed practitioners are ready to integrate digital therapeutics into clinical practice. As digital therapeutics continue to evolve, they have the potential to become a more widespread and integral part of the global healthcare system, providing innovative solutions for patient care and management.

In addition to its many potential benefits, VR applications may have some drawbacks. They may pose several potential risks, including addiction, immersive effects, and dissociative symptoms such as depersonalization, desensitization, and derealization. There are also concerns that addiction to VR applications could lead to a decrease in daily activity levels (6). Another problem is the unequal accessibility of these methods for patients and clinicians. In our study, participants' most common concerns about VR were the high cost of equipment and financial difficulties, the potential blurring of lines between reality and virtual experiences, concerns about manipulation capabilities, and the misuse of privacy and personal information. Additionally, the digital footprint, which refers to the data trail individuals leave behind while using digital devices and interacting with online services, poses a privacy risk and can make individuals susceptible to manipulation for various purposes. Therefore, it is crucial to establish comprehensive legal regulations and guidelines for virtual reality technologies and applications.

The main limitation of our study is the response rate, with approximately half of pediatric rheumatologists participating in the survey. This limited response rate limits the generalizability of our findings, as the perspectives of the non-responding half may differ. Secondly, participants who considered themselves knowledgeable about virtual reality expressed many reservations about its use. It remains unclear whether these reservations are based primarily on personal opinion or on not having experienced virtual reality first hand. Further research is needed to explore the underlying reasons for these reservations, as understanding their root causes may inform strategies to address concerns and improve the acceptance and integration of VR applications in clinical practice.

CONCLUSION

The findings suggest varying levels of familiarity with VR technology among pediatric rheumatologists, with certain demographic factors influencing comfort and knowledge regarding its use. The potential for VR to enhance both patient care and professional education in pediatric rheumatology remains promising, though further research is required to better understand its practical applications and impact on clinical practice. As VR technology evolves, it may hold considerable promise for improving the management of pediatric rheumatic diseases, depending on its integration into the field.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. Approval was obtained for the study protocol from the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (approved 02.05.2024-2541508).

Contribution of the authors

Doğru A: Constructing the hypothesis or idea of research and/or article, Taking responsibility in the writing of the whole or important parts of the study. ***Kavrul Kayaalp G:*** Planning methodology to reach the conclusions, Taking responsibility in the writing of the whole or important parts of the study. ***Arık SD:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***Demirkan FG:*** Taking responsibility in logical interpretation and conclusion of the results, Reviewing the article before submission scientifically besides spelling and grammar. ***Özlem Akgün:*** Taking responsibility in necessary literature review for the study. ***Menentoğlu B:*** Taking responsibility in necessary literature review for the study. ***Başer Taşkın B:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***Aktay Ayaz N:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Reviewing the article before submission scientifically besides spelling and grammar.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Growth response and genetic factors in SGA children: a study on rGH therapy and copy number variations

Emre Özer[1], Esra Kılıç[2], Pınar Kocaay[1], Derya Tepe[3], Aylin Kılınç Uğurlu[4], Gönül Büyükyılmaz[1], Mustafa Altan[5], Keziban Toksoy Adıgüzel[1], Mehmet Boyraz[1,6], Fatih Gürbüz[1,6]

[1]Department of Pediatric Endocrinology, Ankara City Hospital, Ankara, Türkiye
[2]Department of Pediatric Genetics, University of Health Sciences, Ankara City Hospital, Ankara, Türkiye
[3]Department of Pediatric Endocrinology, University of Health Sciences, Ankara City Hospital, Ankara, Türkiye
[4]Department of Pediatric Endocrinology, Faculty of Medicine, Gazi University, Ankara, Türkiye
[5]Department of Medical Genetics, Ankara City Hospital, Ankara, Türkiye
[6]Department of Pediatric Endocrinology, Ankara Yildirim Beyazit University, Ankara, Türkiye

ABSTRACT

Objective: Small for gestational age (SGA) is a heterogeneous condition influenced by fetal, placental, maternal, and genetic factors. While most SGA children experience catch-up growth within the first two years, up to 10-15% remain short-statured and may require growth hormone (GH) therapy. This study evaluated the clinical characteristics, genetic factors, and responses to recombinant GH (rGH) therapy in non-syndromic SGA children with persistent short stature.

Material and Methods: We retrospectively analyzed 36 non-syndromic short-statured children born SGA who were evaluated in a tertiary center. Genetic testing, including karyotyping and microarray analysis for copy number variations (CNVs), was performed. Growth response to rGH therapy was assessed in 19 patients over a three-year period.

Results: Among the 19 patients receiving rGH therapy, the mean height SDS improved from -3.04±0.58 at baseline to -2.07±0.67 after three years, with an average gain of 0.97 SDS. CNVs were identified in 6 patients (16.66%), with several pathogenic or likely pathogenic variants, including deletions and duplications in regions associated with growth and developmental disorders.

Conclusion: A significant proportion of non-syndromic SGA children with persistent short stature exhibit CNVs, underscoring the genetic complexity of this condition. rGH therapy effectively improves growth outcomes, but individual responses vary. These findings highlight the need for routine genetic screening and personalized treatment strategies to optimize care for SGA children.

Keywords: Copy number variations (CNVs), Small for gestational age, Short stature, Recombinant growth hormone (rGH)

INTRODUCTION

Small for gestational age (SGA) is defined as a condition in which the birth weight of a newborn falls below -2 standard deviation scores (SDS) relative to the reference population for the corresponding gestational age (1,2). The etiology of intrauterin growth restriction is heterogeneous, primarily associated with fetal-placental and maternal factors, with genetic factors also playing a significant role. Although there are various pathophysiological factors that can cause intrauterine growth restriction, being SGA does not necessarily indicate that a fetus is growth restricted. Some SGA fetuses may simply be constitutionally small, not necessarily growth restricted (3). While approximately 85-90% of children born SGA exhibit catch-up growth and reach the growth percentiles of their peers within the first two years of life, the remaining 10-15% experience persistent short stature (4,5). In diagnosing a child with short stature, clinicians should begin with a detailed medical history and physical examination. This is followed by targeted laboratory tests, imaging, and growth hormone (GH) evaluation. If a congenital syndrome is suspected, referral to a geneticist is often necessary. Chromosomal abnormalities, such as monosomies and trisomies, skeletal dysplasias, and malformation syndromes like Achondroplasia, as well as several single-gene syndromes, including Silver-Russell syndrome, Cornelia de Lange syndrome, 3M syndrome, and Mulibrey Nanism, are well-established causes associated with SGA and short stature (6,7). Karyotype analysis is typically the initial step in genetic testing. In cases where a genetic etiology is suspected, the choice of molecular diagnostic methods such as single-

Correspondence:
Emre ÖZER
e-mail: emre-ozer@hotmail.com

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gene analysis, gene panels, or array-based analysis varies depending on the suspected underlying cause. Furthermore, children born SGA are at an increased risk of developing long-term metabolic and cardiovascular comorbidities (8). Identifying the probable genetic causes in this patient population may provide valuable insights into assessing potential long-term health risks. Recombinant growth hormone (rGH) therapy has been approved for treating short stature in children born small for gestational age (SGA). In most countries, treatment can begin at age four and typically continues until puberty is complete. Long-term GH therapy (beyond three years) has been shown to result in sustained height improvement. Initially, there is a significant boost in growth rate during the first year of the treatment, followed by a steady and consistent growth pattern over time (9,10). Demonstrating genetic etiologies in this patient group can serve to predict treatment response to rGH therapy, also. In this study, we aimed to evaluate the clinical characteristics and responses to rGH treatment and to identify the genetic causes underlying SGA in our patient cohort.

MATERIALS and METHODS

Patient selection and study design

This study was designed as a retrospective analysis of patients under 18 years of age with a history of SGA who presented to Ankara Bilkent City Hospital with complaints of short stature. The patients born SGA who, despite being over two years of age, exhibited pathological short stature included into study. Data from the hospital system, including clinical, laboratory, and molecular results, as well as detailed medical histories, were reviewed and systematically evaluated by a research team consisting of pediatric endocrinologists and geneticists. A retrospective evaluation was conducted over a retrospective evaluation was conducted between March 2021 to March 2023.. After excluding patients with syndromic features, the remaining 36 patients with non-syndromic short stature and unknown etiology were included in the study.

GH treatment was initiated at a dose of 35 µg/kg/day in accordance with European Medicines Agency (EMA) guidelines. In the United States, initiation doses can be as high as 70 µg/kg/day according to Food and Drug Administration (FDA) recommendations (1,11). Patients were monitored every three months through routine clinical assessments, including measurements of height, weight, body mass index (BMI), growth velocity, and serum IGF-1 levels. Treatment response was assessed individually due to the wide variability in outcomes among SGA patients, and GH doses were adjusted accordingly.

Genetic analysis

For patients in whom clinical evaluation does not identify a pathology explaining short stature, karyotype analysis is routinely performed as the initial genetic test to assess chromosomal number and structure. Genetic analyses were performed using the Illumina Infinium CytoSNP-850K v1.2 BeadChip platform (Illumina, San Diego, CA, USA). DNA samples were prepared according to the manufacturer's protocol and genotyped accordingly. The raw data were analyzed using the BlueFuse Multi software (Illumina, Cambridge, UK). Copy number variation (CNV) analysis was performed based on log R ratio and B-allele frequency values, using the GRCh37/hg19 human genome assembly as reference. Identified CNVs were interpreted with reference to international databases (DGV, DECIPHER, ClinGen, ClinVar) and classified according to the 2020 ACMG guidelines for CNV interpretation. In cases where further genetic testing is indicated based on phenotypic and clinical evaluation, access to advanced genetic techniques such as gene panels, whole exome sequencing (WES), and methylation analyses is limited. Consequently, third-line genetic testing could not be performed.

Statistical analysis

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences, version 25.0 (SPSS Inc., Armonk, NY, IBM Corp., USA. The data were expressed as mean and standard deviation or as median, minimum and maximum, categorical variables were presented as frequencies and percentages.

RESULTS

Patient characteristics: This study included 36 patients with non-syndromic short stature, a history of SGA, and unknown etiology. Eighteen patients (50%) were female. The mean age at presentation was 6.05±3.81 years. The cohort exhibited a mean birth weight SDS of -3.63±1.6 and a mean gestational age of 37.25±3.06 weeks. Thirteen patients (36%) had a history of preterm born. At the initial evaluation, the mean height SDS, weight SDS, and BMI SDS were -3.19±0.69, -2.87±1.10 and -1.08±1.19 respectively. The demographic and clinical characteristics of the study cohort at initial evaluation are summarized in Table I.

Table I: Patient characteristics at initial evaluation

	n	mean±SD	min-max
Gestational age, weeks	36	37.25±3.065	29-42
Birth weight, grams	36	1784.81±500.41	800-2480
Brith weight SDS	36	-3.63±1.60	-10.88-(-2.05)
Age, years	36	6.05±3.81	1.13-13.91
Heigth SDS	36	-3.19±0.69	-4.78-(-2.17)
Weigth SDS	36	-2.87±1.10	-5.91-(-.84)
BMI SDS	36	-1.08±1.19	-3.60-1.72
IGF-1 SDS	29	-1.04±1.74	-4.21-3.14
IGFBP-3 SDS	28	0.63±0.92	0-.87-2.90

Table II: The distribution of patients with CNVs.

Patient ID	Genetic Findings	Condition/Notes
1	1q24.3_1q25.2 5.3 Mb heterozygous deletion. (GRCh38) 1q24.3_ 1q25.2(172529076_1778005552)x1	Parental array normal. May be associated with 1q24.3 microdeletion syndrome which is a rare condition characterized with growth deficiency, varying intellectual disability, and skeletal abnormalities Due to the large size of the deletion, it is likely to have clinical significance.
2	2p14-16.1 7.4 Mb deletion. (GRCh38) 2p16.1-p14(57715943_65128610)x1	Parental array normal. May be associated with 2p15p16.1 microdeletion syndrome which is characterized by growth disorders, microcephaly, and intellectual disability.
3	4p16.3-p16.1; 7.2 Mb deletion (GRCh38) 16p13.11p12.3(14820784_16777698)	Associated with Wolf-Hirschhorn syndrome which is characterized by growth disorders,"Greek warrior helmet" facies, microcephaly, seizure disorder and intellectual disability .
4	16p13.11p12.3 1.8 Mb heterozygous deletion	The 16p13.11 microdeletion syndrome is reported with a wide spectrum of neurodevelopmental disorders, including schizophrenia, autism, intellectual disability, epilepsy, behavioral disorders, and mild microcephaly. However there are limited number of patients reported and it is not commonly associated with SGA. To determine its pathogenicity, parental analysis has been planned.
5	11p15; 742 kb heterozygous duplication (GRCh38) 11p15.5p15.4(2405754_3148158)x3	Associated with arrhythmia genes, patient has arrhythmia, mother also carries the same variant with arrhythmia and short stature; possibly significant.
6	5q13.1 771 kb heterozygous duplication	Possibly significant variation. Lack of parental analysis.

Table III: Outcomes of recombinant Growth Hormone treatment

	Start of r-GH treatment (n:19)	1st year of treatment (n:19)	2nd year of treatment (n:16)	3rd year of treatment (n:6)
Heigth SDS	-3.04±0.58	-2.53±0.66	-2.26±0.66	-2.07±0.67
ΔSDS of Heigth from the r-GH initiation	-	0.50±0.30	0.76±0.43	1.28±0.51
r-GH dosage, mcg/kg/day	34.72±9.11	34.50±7.15	34.75±8.55	40.08±10.66
IGF-1SDS		0.62±2.25	0.66±1.53	1.36±1.98

Genetic results: Microarray analysis revealed copy number variations (deletions/duplications) in six patients (16.66%). Microarray analysis did not reveal any CNVs in 23 patients (63.88%) with normal results. Genetic evaluation was incomplete in seven patients (19.44%) who did not undergo microarray analysis. The distribution of patients with CNVs is summarized in Table II.

Outcomes of recombinant growth hormone treatment: A total of 19 patients received recombinant growth hormone (rGH) therapy. The age at treatment initiation ranged from 3.29 to 14.03 years, with a mean of 8.34±3.20 years. At baseline, the mean height standard deviation score (SDS) was -3.04 ±0.58 (range: -4.05 to -2.14). The detailed outcomes of GH therapy, including growth response and related parameters, are presented in Table III. Additionally, height changes over the years in patients who initiated rGH treatment are illustrated by gender in Figure 1.

DISCUSSION

This study highlights the effectiveness of rGH therapy in promoting height gain among short statured children born SGA. Additionally, CNVs were identified in one-sixth of the cohort, a significantly higher frequency than in the general population emphasizing the heterogeneity of SGA-related short stature, the influence of genetic factors, and the need for further research to better understand the underlying mechanisms and optimize treatment approaches.

The efficacy of rGH therapy in our cohort aligns with previous reports and supports its role as a cornerstone treatment for SGA-related short stature. Among the 19 patients who received rGH, we observed a mean height gain of 0.50±0.30 SDS after the first year, increasing to 0.97 SDS by the third year. This response is comparable to meta-analyses, such as Maiorana et al.'s (12), which reported a mean height gain of 0.9–1.5 SDS in rGH-treated SGA children over 2–3 years, and to Arroyo-Ruiz et al. (13), who noted a dose-dependent height increase of 1.3 SDS after three years. The initial height SDS in our cohort (-3.04±0.58) improved to -2.07±0.67 by year-3, though patients remained below population norms, consistent with the persistent growth deficit often observed in SGA populations (1). Several factors may influence this response. The mean age at rGH initiation (8.34±3.20 years) was relatively late compared to optimal recommendations of 2–4 years, potentially limiting total height gain (14,15). Studies like de Bruin and Dauber (16) suggest that earlier intervention enhances outcomes, a trend supported by our observation of a negative correlation

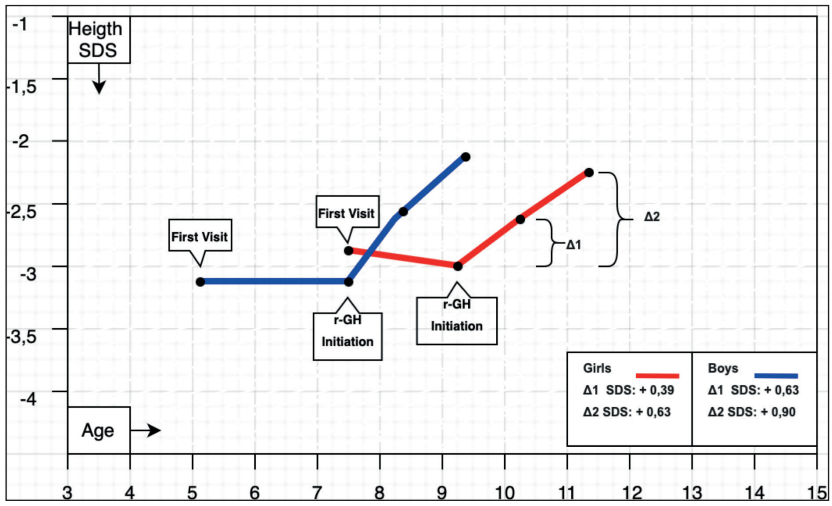

Figure 1: Height changes over the years in patients who started r-GH treatment are illustrated by gender.

between age at treatment start and height gain. Additionally, the mean rGH dose escalated from 34.72±9.11 µg/kg/day to 40.08±10.68 µg/kg/day by year-3, reflecting adjustments to maintain growth velocity, yet individual responses varied widely (e.g., IGF-1 SDS ranged from 0.62±2.25 to 1.36± 1.98). Particularly, GH therapy outcomes can be influenced by GH-IGF-1 resistance, which has been observed in some SGA children. This variability echoes findings by Jensen et al.(17), who noted heterogeneous IGF-1 responses despite consistent height gains, underscoring the need for personalized dosing strategies (13). Understanding the extent of GH-IGF-1 resistance in this population is crucial for optimizing treatment protocols and ensuring sustained growth benefits.

A key observation from this study is the notable prevalence of genetic abnormalities in our cohort. CNVs were identified in 16.66% (6/36) of patients who underwent microarray analysis, aligning with literature estimates of 10–25% prevalence of CNVs in SGA-related short stature (18-20). For instance, Homma et al. (21) identified CNVs in 14% (32/229) of patients with syndromic short stature of unknown etiology. When combined with data from other studies, the overall prevalence remains consistent at 13% (87/671). The specific CNVs identified in our cohort highlight their clinical significance. For example, Patient-1's 5.3 Mb deletion at 1q24.3-q25.2, potentially linked to 1q24.3 microdeletion syndrome, includes non-coding RNAs (DNM3OS, miR-214, and miR-199A2) implicated in skeletal development (22). Similarly, Patient-2's 7.4 Mb deletion at 2p15-p16.1, associated with 2p15p16.1 microdeletion syndrome, involves genes (USP34 and XPO1) tied to intrauterine growth restriction (IUGR). Although the exact mechanisms remain unclear, these genes are believed to influence cellular growth and development, with XPO1 potentially exerting a more dominant effect (23). Patient-3's 7.2 Mb deletion at 4p16.3-p16.1 aligns with Wolf-Hirschhorn syndrome, a well-documented cause of intrauterine growth retardation and growth failure (24). Patient-4's 1.8 Mb deletion on chromosome 16, associated with 16p13.11 microdeletion syndrome which is characterized by a wide spectrum of neurodevelopmental disorders, intellectual disability, and mild microcephaly. However, it is rarely associated with small for SGA or short stature. Only a limited number of cases have been reported in the literature (25). These findings highlight the diversity of genetic mechanisms underlying SGA and reinforce the importance of microarray analysis as a firsttier diagnostic tool in this population. However, 63.88% (23/36) of patients had normal microarray results, and 19.44% (7/36) lacked microarray and further data, suggesting that additional genetic or epigenetic factors remain undetected. This is consistent with the literature, where a significant proportion of SGA cases remain idiopathic despite standard genetic testing (7). Advanced techniques such as whole exome sequencing (WES) or methylation analysis could uncover underlying single gene mutations, imprinting defects, or polygenic contributions, as demonstrated in studies, where WES identified pathogenic variants in 25–47% of SGA patients with persistent short stature (26,27). Our findings thus advocate for a tiered genetic testing approach, progressing from karyotyping and microarray to WES when initial results are uninformative.

CONCLUSION

This study confirms the effectiveness of rGH therapy in increasing height in SGA-related short stature, with an average gain of 0.97 SDS over three years. Genetic factors played a significant role in one-sixth of cases, with CNVs emerging as a key cause, though most cases remain unexplained. This highlights the need for more advanced genetic testing. Given that chromosomal disorders are a major cause of SGA, it is essential to exclude chromosomal copy number variations, particularly before comprehensive gene panel testing or in settings where such testing is unavailable. These findings underscore the importance of targeted treatment in this diverse group while also supporting routine genetic screening for SGA patients with persistent short stature and personalized rGH treatments to account for individual differences.

Limitations

The small sample size (n=36, with only 19 on rGH) and retrospective design restrict statistical power and generalizability. The incomplete genetic evaluation in 19.44% (7/36) of patients highlights logistical challenges in comprehensive testing, while the lack of longterm follow-up to adult height precludes definitive conclusions on rGH efficacy. Additionally, the absence of epigenetic or WES data leaves potential etiologies unexplored, particularly in the 63.88% with normal microarray results. Future research should prioritize larger, prospective studies integrating WES and methylation analysis to fully elucidate SGA's genetic background.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by the ethics committee of Ankara City Hospital (E2-21-283, 24.03.2021).

Contribution of the authors

Özer E: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar, Providing personnel, environment, financial support tools that are necessary for the study, Taking responsibility for biological materials and referred patients. ***Kılıç E:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Kocaay P:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Providing personnel, environment, financial support tools that are necessary for the study, Taking responsibility for biological materials and referred patients. ***Tepe D:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study. ***Altan M:*** Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Büyükyılmaz G:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Providing personnel, environment, financial support tools that are necessary for the study, Taking responsibility for biological materials and referred patients. ***Kılınç Uğurlu A:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Providing personnel, environment, financial support tools that are necessary for the study, Taking responsibility for biological materials and referred patients. ***Toksoy Adıgüzel K:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Providing personnel, environment, financial support tools that are necessary for the study, Taking responsibility for biological materials and referred patients. ***Boyraz M:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Gürbüz F:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar, Providing personnel, environment, financial support tools that are necessary for the study, Taking responsibility for biological materials and referred patients.

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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 nutritional behaviors and dietary supplement use of preschool children: A cross-sectional study from Türkiye

Fatmanur Hümeyra Zengin[1], Esra Çetin[2]

[1]Department of Nutrition and Dietetics, Faculty of Health Sciences, Kastamonu University, Kastamonu, Türkiye
[2]Independent Researcher, Dietician, Bolu, Türkiye

ABSTRACT

Objective: This study aimed to evaluate preschool children's (aged 3-6 years) nutritional behaviors and dietary supplement usage.

Material and Methods: This descriptive, cross-sectional study was conducted between February 2024 and June 2024. The study sample consisted of 180 parents who live in the city center of Kastamonu. A questionnaire form including demographic characteristics of parents and children, children's eating habits, and information about the dietary supplements used was applied.

Results: The mean age of the children participating in the study was 60.9±9.3 months, and 35.6% of them used dietary supplements. The most commonly used supplements by children were multivitamins (15.6%), vitamin D (15.6%), fish oil (13.3%), omega-3 (11.1%), and probiotics (6.1%). As a result of multivariate logistic regression analysis, gender, number of siblings, age of the child, mother and father, education level of the mother and father, family type, and family income were not found to have a significant effect on the use of dietary supplements (p>0.050). Among the parents whose children use dietary supplements, 85.9% stated that they use them to make the child-resistant to diseases, 31.3% to make the child well-being, 26.6% to improve mental performance, and 10.9% to address a health problem.

Conclusion: Approximately one-third of parents use dietary supplements to support their children's immunity or improve their health. It should be remembered that there is very little data on the health benefits of dietary supplements in children with adequate and balanced nutrition and that unnecessary use may lead to negative consequences.

Keywords: Children, Dietary supplement, Multivitamin, Nutrition, Preschool

INTRODUCTION

Nutrition in preschool children significantly affects general health, especially brain development, both in the short and long term (1). Therefore, during the preschool period, healthy nutrition should aim to ensure proper growth and development, support cognitive development, prevent health issues associated with this age group (e.g., anemia, malnutrition), and protect against nutrition-related chronic diseases in adulthood (2). In particular, essential macro and micronutrients adequacy is critical in preschool nutrition (3). Generally, the basic nutritional needs are met through a balanced diet. However, deficiencies in certain nutrients such as iron, iodine, and vitamin D are frequently observed in a significant portion of the population (2).

Dietary supplements are orally administered products used to address nutrient deficiencies and support the diets of healthy individuals (2). In our country, legal regulations regarding dietary supplements have been prepared in parallel with the European Parliament and Council Directive No. 2002/46/EC. In line with this, the "Turkish Food Codex Supplementary Foods Communiqué" has been in force since 2013. In this communiqué, dietary supplements are defined as "products prepared in capsule, tablet, pastille, single-use powder packet, liquid ampule, dropper bottle, or other similar liquid or powder forms with a specified daily dosage, which contain concentrated extracts or the isolated forms of nutrients such as vitamins, minerals, protein, carbohydrate, fiber, fatty acid, amino acid, or other nutritional components, as well as plant-, plant-derived-, or animal-based substances, bioactive

Correspondence:
Fatmanur Hümeyra Zengin
e-mail: humeyrazengin@hotmail.com

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substances, and similar materials (4). In Türkiye, the 'Vitamin D Deficiency Prevention and Control Program' (0-1 year) and the 'Iron Like Türkiye Program' (2-12 months) are implemented nationally by the Ministry of Health. However, there is no specific vitamin and mineral supplementation program for children aged 3-6 years. In our country, there are nutritional supplements available on the market for children aged 2-4 and 4-10. For younger children, there are products that can only be used with a doctor's recommendation. Parents who wish to give supplements to their children in these age groups should check the label information of the products and ensure they do not give products intended for older children or adults to younger children (2).

The use of dietary supplements is widespread and increasing in developed countries (5). The most commonly used supplements are multivitamins and minerals (6-8). However, despite having specific indications, dietary supplements are often not prescribed by a healthcare professional, and there are no standardized guidelines for their use. As a result, the safety and efficacy of dietary supplements are an increasing concern for healthcare professionals. Raising awareness among healthcare professionals and parents about the use of dietary supplements and providing more information on their safety and efficacy is crucial for child health (9).

A literature review reveals a limited number of studies in Türkiye investigating the use of dietary supplements among children with certain diseases or school-aged children. However, no studies have examined healthy preschool children's nutritional habits and dietary supplement use (aged 3-6 years) (10,11). In Türkiye, comprehensive research on dietary habits and dietary supplement use in healthy preschool children needs to be improved. This study aimed to fill the gap in the literature and raise awareness for health professionals and parents. This study aimed to evaluate preschool children's (aged 3-6 years) nutritional behaviors and dietary supplement usage.

MATERIALS and METHODS

This descriptive and cross-sectional study was conducted in Kastamonu city center between February 2024 and June 2024. The sample of this study consisted of 180 parents of children aged 3-6 years attending public preschools and was selected using a random sampling method.

The sample size was calculated with G*Power 3.1 software and was determined to be at least 172. Data were collected with a questionnaire form with 46 questions, including demographic characteristics of parents and children, dietary habits of children, dietary supplements used (vitamins, minerals, and herbal supplements), purposes of using these supplements, and sources of information. The questionnaires were administered using a face-to-face interview method. Parents with children aged 3-6 years without any chronic disease who voluntarily agreed to participate were included in the study. However, parents who did not have children in this age group or were illiterate were excluded.

Statistical analysis

The study's data were analyzed and evaluated using the "Statistical Package for Social Sciences" (SPSS 25.0) program. The values of descriptive variables were given as frequency (n), percentage (%), arithmetic mean, and standard deviation (SD). Differences between categorical variables were analyzed using Pearson's chi-square test. Logistic regression analysis was used to identify the factors affecting children's use of dietary supplements.The level of significance was set at $p<0.050$ in the study

RESULTS

A total of 180 parents participated in this study. The demographic characteristics of children and parents according to the use of dietary supplements are given in Table I. The mean age of the children participating in the study was 60.9±9.3 months, and 35.6% of them used dietary supplements. The mean age of the mothers of children who used supplements (36.1±5.1 years) was higher than that of non-users (34.0±5.7 years) ($p=0.022$), but there was no difference between the ages of fathers and children ($p=0.142$). There was no difference between the gender of the child, the educational level of the parents, the number of children in the family, the income of the family, and the use of dietary supplements ($p=0.147$, $p=0.607$, $p=0.133$, and $p=0.501$ respectively). While 93.8% of dietary supplement users lived in nuclear families, 4.7% lived in extended families, and 1.6% had separated families or deceased parents. Among those who did not use dietary supplements, 80.2% lived in nuclear families, 12.1% lived in extended families, and 7.8% had separated families or deceased parents ($p=0.047$).

The children's dietary habits and physical activity status are given in Table II. While 53.1% of the children who used dietary supplements skipped meals, 30.2% of the children who did not use dietary supplements skipped meals ($p=0.002$). There was no significant difference in other eating habits or physical activity status concerning dietary supplement use ($p>0.050$).

Percentages of dietary supplement use among all participants and children using dietary supplements are given in Figure 1. Among all participants, 15.6% used multivitamins and vitamin D, 13.3% used fish oil, 11.1% used omega-3, and 6.1% used probiotic supplements. Percentages of children's dietary supplement use by gender are given in Figure 2. Girls mostly use vitamin D (10.6%), while boys (7.8%) use multivitamins.

The parent's responses to questions about dietary supplements are given in Table III. Half of the parents who do not use dietary supplements for their children refrain from doing so because they do not believe their children need them, 34.5% because their doctors do not recommend them, and 15.5% because

Table I: Demographic characteristics of children and parents according to their use of dietary supplements

	Children who use dietary supplements	Children who do not use dietary supplements	Total	p
Total participants (n)	64	116	180	-
Child's age*	62.1±8.9	60.3±9.6	60.9±9.3	0.118†
Mother's age*	36.1±5.1	34.0±5.7	34.8±5.6	0.022†
Father's age*	38.5±5.9	36.9±6.0	37.5±6.0	0.142†
Gender of the child‡				
Male	33(51.6)	71 (61.2)	104 (57.8)	0.210§
Girl	31(48.4)	45 (38.8)	76 (42.2)	
Mother's education level‡				
Primary school graduate	5 (7.8)	8 (6.9)	13 (7.2)	
Secondary school graduate	1 (1.6)	6 (5.2)	7 (3.9)	
High school graduate	13 (20.3)	40 (34.5)	53 (29.4)	0.147§
University graduate	40 (62.5)	52 (44.8)	92 (51.1)	
Postgraduate	5 (7.8)	10 (8.6)	15 (8.3)	
Father's education level‡				
Primary school graduate	1 (1.6)	6 (5.2)	7 (3.9)	
Secondary school graduate	4 (6.2)	12 (10.3)	16 (8.9)	
High school graduate	16 (25.0)	30 (25.9)	46 (25.6)	0.607§
University graduate	36 (56.3)	58 (50.0)	94 (52.2)	
Postgraduate	7 (10.9)	10 (8.6)	17 (9.4)	
Family type‡				
Nuclear	60 (93.8)	93 (80.2)	153 (85.0)	0.047§
Extended	3 (4.7)	14 (12.1)	17 (9.4)	
Parents separated/dead	1 (1.6)	9 (7.8)	10 (5.6)	
Number of children in the family‡				
1	20 (31.3)	45 (38.8)	65 (36.1)	
2	37 (57.8)	48 (41.4)	85 (47.2)	
3	6 (9.4)	12 (10.3)	18 (10.0)	0.133§
4	1 (1.6)	8 (6.9)	9 (5.0)	
5	-	3 (2.6)	3 (1.7)	
Family income status‡				
17.000 - 20.000	16 (25.0)	37 (31.9)	53 (29.4)	
20.000 - 40.000	18 (28.1)	29 (25.0)	47 (26.1)	0.501§
45.000 - 70.000	27 (42.2)	40 (34.5)	67 (37.2)	
70.001 and above	3 (4.7)	10 (8.6)	13 (7.2)	

** : mean±SD, † : Mann Whitney U Test, ‡ : n(%), § : Pearson Chi-Square Test*

they do not consider them appropriate. Among the parents who used dietary supplements for their children, 85.9% stated that they used dietary supplements to make their child-resistant to diseases, 31.3% to make them well-being, 26.6% to improve their mental performance, and 10.9% to address a health problem. Parents reported that they received the most information about the use of dietary supplements from doctors (84.4%) and the least from visual media (7.8%) and the internet (7.8%). Naturalness (57.8%) and quality (56.3%) were the factors that parents paid the most attention to when purchasing dietary supplements. Furthermore, it was found that 47.8% of parents reported being uninfluenced by advertisements when choosing dietary supplements for their children.

Table IV displays the results of the logistic regression analysis identifying determinants of dietary supplement use among children. Multivariate logistic regression analysis indicated that gender, number of siblings, age of the child, parental age and education, family structure, and household income were not significant predictors of dietary supplement use (p=0.354, p=0.343, p=0.830, p=0.205, p=0.894, p=0.401, p=0.537, p=0.818, p=0.587, p=0.209, p=0.257, p=0.372, p=0.172, p=0.060, p=0.233, p=0.331, p=0.474, and p=0.182 respectively).

DISCUSSION

Dietary supplements have become more widely used around the world in the last 20 years, and the public health crisis brought on by the COVID-19 pandemic has highlighted the importance of boosting the immune system (5,12). Cowan et al. (5) reported that the use of dietary supplements increased from 50% in 2007 to 56% in 2018. Many dietary supplements are marketed today, including various combinations of vitamins, minerals, herbal products, and single-ingredient products. They are generally used in healthy children to achieve optimal nutrition and health (13). According to the Türkiye Dietary Guidelines (TUBER) 2022, nutrient requirements can be met

Table II: Children's eating habits and physical activity status

	Children who use dietary supplements*	Children who do not use dietary supplements*	Total*	p†
Number of meals				
1-2 Meals	9 (14.1)	20 (17.2)	29 (16.1)	0.832
3-4 Meals	51 (79.7)	90 (77.6)	141 (78.3)	
5-6 Meals	4 (6.3)	6 (5.2)	10 (5.6)	
Skipping meals				
Yes	34 (53.1)	35 (30.2)	69 (38.3)	0.002
No	30 (46.9)	81 (69.8)	111 (61.7)	
Which meal did he skip?				
Morning	8 (23.5)	12 (34.2)	20 (29.0)	0.064
Noon	5 (14.7)	11 (31.4)	16 (23.2)	
Afternoon	21 (61.8)	12 (34.3)	33 (47.8)	
Evening	-	-	-	
Fast food consumption frequency				
None	3 (4.7)	12 (10.3)	15 (8.3)	0.159
One day every two weeks	16 (25)	49 (42.2)	65 (36.1)	
One day a week	29 (45.3)	22 (19)	51 (28.3)	
A few days a week	13 (20.3)	23 (19.8)	36 (20.0)	
Every day	3 (4.7)	10 (8.7)	13 (7.3)	
Snack preference				
Fruit	24 (37.5)	26 (22.4)	50 (27.8)	0.470
Nuts	9 (14.1)	17 (14.7)	26 (14.4)	0.058
Chocolate/wafer	16 (25.0)	16 (13.8)	32 (17.8)	0.911
Chips	4 (6.3)	11 (9.5)	15 (8.3)	0.048
Biscuit/cake	15 (23.4)	18 (15.5)	33 (18.3)	0.543
Ready-made fruit juice	15 (23.4)	16 (13.8)	31 (17.2)	0.808
Carbonated drinks	6 (9.4)	5 (4.3)	11 (6.1)	0.742
Milk	21 (32.8)	13 (11.2)	34 (18.9)	0.052
Tea	6 (9.4)	4 (3.4)	10 (5.6)	0.493
Wanting foods seen in advertisements				
Yes	10 (15.6)	19 (16.4)	29 (16.1)	0.290
Sometimes	15 (23.4)	39 (33.6)	54 (30.0)	
No	39 (60.9)	58 (50.0)	97 (53.9)	
Outdoor play time per day				
None	8 (12.5)	8 (6.9)	16 (8.9)	0.198
0-1 hour	20 (31.3)	27 (23.3)	47 (26.1)	
1-2 hours	23 (35.9)	60 (51.7)	83 (46.1)	
2-3 hours	10 (15.6)	19 (16.4)	29 (16.1)	
More than 4 hours	3 (4.7)	2 (1.7)	5 (2.8)	
Television watching time per day				
None	6 (9.4)	21 (18.1)	27 (15)	0.084
0-1 hour	19 (29.7)	40 (34.5)	59 (32.8)	
1-2 hours	34 (53.1)	40 (34.5)	74 (41.1)	
2-3 hours	3 (4.7)	13 (11.2)	16 (8.9)	
More than 4 hours	2 (3.1)	2 (1.7)	4 (2.2)	
Time spent on computer/tablet				
None	15 (23.4)	32 (27.6)	47 (26.1)	0.265
1-2 hours	34 (53.1)	63 (54.3)	97 (53.9)	
2-3 hours	9 (14.1)	19 (16.4)	28 (15.6)	
More than 4 hours	6 (9.4)	2 (1.7)	8 (4.4)	
Doing regular sports (swimming, basketball, folk dances, etc.)				
Yes	21 (32.8)	33 (28.4)	54 (30)	0.542
No	43 (67.2)	83 (71.6)	126 (70)	

**: n(%), †: Pearson Chi-Square Test*

with adequate and balanced nutrition. However, nutritional supplements should be used if adequate and balanced nutrition cannot be provided (2). Although there are many studies on the use of dietary supplements among adults in Türkiye, there

Table III: Parents' responses to questions about dietary supplements

	n (%)
Reasons for not using dietary supplements for their children (n=116)	58 (50)
I don't believe it's needed	
My doctor did not recommend it	40 (34.5)
I don't think it's appropriate to take dietary supplements from outside.	18 (15.5)
Reasons for using dietary supplements for their children (n=64)*	
I use dietary supplements to address my child's health problems	7 (10.9)
I use dietary supplements to make my child well-being	20 (31.3)
I use dietary supplements to improve my child's mental performance	17 (26.6)
I use dietary supplements to make my child-resistant to diseases	55 (85.9)
Primary sources of information regarding dietary supplement use (n=64)*	
Doctor	54 (84.4)
Pharmacist	24 (37.5)
Dietician	8 (12.5)
Other healthcare professionals	11 (17.2)
Circle of Friends	9 (14.1)
Visual press	5 (7.8)
Internet	5 (7.8)
Factors to consider when purchasing dietary supplements (n=64)*	
Price	4 (6.3)
Brand	20 (31.3)
Quality	37 (57.8)
Naturalness	36 (56.3)
Being domestically produced	9 (14.1)
Being affected by advertisements when choosing dietary supplements for their children (n=64)*	
Yes	27 (42.2)
No	37 (47.8)

***:** *Multiple response analysis*

is a lack of research on their use among preschool children. This study aimed to evaluate preschool children's nutritional behaviors and dietary supplement usage (aged 3-6 years). To the best of our knowledge, this is the first study in Türkiye to examine the use of dietary supplements in children aged 3-6 years.

According to the Türkiye Nutrition and Health Survey (TBSA) 2017, 9.9% of individuals aged 15 and above (6.3% of males and 13.4% of females) reported using dietary supplements. However, as the TBSA 2017 included only individuals aged 15 and older, it does not provide data on dietary supplement use among preschool children (2). In a study conducted in Türkiye investigating healthy eating behaviors and dietary supplement use in children aged 3–12, 48.2% of participants reported having previously used dietary supplements for their children (14). In another study investigating the use of dietary supplements among children aged 2 to 18 years in Türkiye, 32.5% were found to use dietary supplements (15). In Brazil, the prevalence of vitamin use among children aged 0 to 12 years is 4.8% (7). In a study conducted in Japan in 2009 among 2,125 parents of preschool children, 15% of children were found to use dietary supplements (16). A study conducted in the United States found that about one-third (32%) of children used dietary supplements, primarily multivitamins and minerals (24%) (6). Supplement use in Flemish preschool children was reported to be more than 30% (17). In a study conducted in Iranian children and adolescents (7-18 years), the prevalence of dietary supplement use was 34.1%. It was found that the prevalence of dietary supplement use increased as the age group increased (18). It was found that more than one-third (35.6%) of the children participating in this study used dietary supplements. The results of the studies may differ due to variations in the age groups included. However, all studies highlight the high use of dietary supplements among children, underlining the importance of evaluating the safety of these products for children.

According to the TBSA 2010, the most frequently used dietary supplements are reported to be 71.7% vitamin D, 46.8% iron, and 9.2% multivitamin-mineral for children aged 0-5 (19). The vitamin D (0-1 year) and iron (2-12 months) supplementation programs implemented in our country may explain why these dietary supplements are used more frequently. According to the results of the CS Mott Children's Hospital Child Health National Survey, the most commonly used dietary supplements by children aged 1-10 years are multivitamins (78%), probiotics (45%), and Omega 3 (22%) (18-20). According to the results of another study investigating the prevalence of dietary supplement use in preschool children in Australia and China, the most commonly used dietary supplements in China were calcium (58.5%) and zinc (40.4%). In comparison, the most commonly used types in Australia were multivitamins/minerals (46.2%) and fish oil (42.3%) (13). In another study conducted in the United States, the most commonly used dietary supplement was found to be multivitamin-minerals (24%) (6).

Table IV : Logistic regression analysis of factors affecting children's dietary supplement use

Predictor	B	SE	OR	95% CI for OR	p
Gender*	-0.34	0.367	0.71	0.35-1.46	0.354
Child's age	-0.018	0.019	0.98	0.95-1.02	0.343
Number of siblings	0.047	0.217	1.05	0.69-1.60	0.830
Mother's age	-0.081	0.064	0.92	0.81-1.05	0.205
Father's age	0.008	0.059		0.90-1.13	0.894
Mother's education status†					
Secondary school graduate	1.134	1.351	3.10	0.22-43.89	0.401
High school graduate	0.521	0.843	1.68	0.32-8.78	0.537
University graduate	-0.204	0.889	0.82	0.14-4.66	0.818
Postgraduate	-0.715	1.314	0.49	0.04-6.43	0.587
Father's education level†					
Secondary school graduate	-1.771	1.408	0.17	0.01-2.7	0.209
High school graduate	-1.49	1.316	0.23	0.02-2.97	0.257
University graduate	-1.189	1.330	0.31	0.02-4.13	0.372
Postgraduate	-2.026	0.064	0.13	0.01-2.4	0.172
Family Type‡					
Extended	1.324	0.704	3.76	0.95-14.94	0.060
Parents separated/dead	1.352	1.135	3.87	0.42-35.77	0.233
Family income status§					
20.000-40.000	-0.46	0.473	0.63	0.25-1.60	0.331
45.000-70.000	-0.332	0.463	0.72	0.29-1.78	0.474
70.001 and above	1.66	1.245	5.26	0.46-60.33	0.182

**** Ref:** Male, **†Ref:** Primary school graduate,**‡Ref:** Nuclear, **§Ref:** 17.000-20.000, **OR:** Odds Ratio, **CI:** Confidence Interval, **SE:** Standard Error (Cox & Snell R^2 = 0.134, Nagelkerke R^2 = 0.183, Model Accuracy = 73.3%)*

A study conducted in three Korean cities reported that vitamin-mineral supplements (77.5%) were the most commonly used dietary supplements among preschool children, followed by ginseng (49.3%) and probiotics (25.6%) (21). In another study conducted in Türkiye, similar to our data, it was found that the most commonly used dietary supplement was vitamin-mineral supplements (23.2%), and 53.9% of children using vitamin-mineral products used multivitamin-mineral, 17.2% used vitamin D, and 13.4% used multivitamin-mineral-omega 3 combinations (15). In this study, the most commonly used dietary supplements were multivitamins (15.6%), vitamin D (15.6%), fish oil (13.3%), omega-3 (11.1%) and probiotics (6.1%). Females used vitamin D the most (10.6%), while males used multivitamins the most (7.8%). These results emphasize that supplement use in children varies regionally, and the most commonly used supplements are vitamin D, multivitamin-mineral, and fish oil. Many variables, such as various societies' different health sensitivities and health policies, may influence dietary supplement choices. Although multivitamin and mineral supplements are gradually decreasing, they are still the most preferred dietary supplements (5).

The primary reasons for using dietary supplements in young children include preventing or treating nutrient deficiencies, improving and maintaining general health, preventing health problems, and strengthening immunity (8). According to NHANES 2011-2014 data, the most common reasons for dietary supplement use in children were reported to be to improve (42%) and maintain (34%) children's health and to support their diet (23%) (6). A study conducted in China found that the primary purpose of dietary supplement use in children was to increase children's immunity and support physical development rather than to support diet (22). In this study, 85.9% of parents who used dietary supplements for their children stated that they used them to make the child-resistant to diseases, 31.3% to make the child well-being, 26.6% to improve mental performance and 10.9% to address a health problem. In recent years, understanding the importance of the immune system in protecting preschool children from diseases and improving their health in the following years has led to an increased interest in dietary supplements.

In TUBER 2022, it is recommended that nutritional supplements should not be used without an assessment of nutritional status by a dietitian and evaluation of biochemical findings, and that a physician's advice should be sought (2). According to the results of the CS Mott Children's Hospital National Survey on Child Health, the majority of parents (65%) stated that they made their decisions about the use of dietary supplements based on the advice of a doctor (20). However, according to the data from many studies conducted in previous years, it has been reported that parents usually receive advice on dietary supplements from family and friends, not health professionals (6,16,21). This study observed that parents received the most information about dietary supplement use from health professionals such as doctors (84.4%) and pharmacists (37.5%). The differences in the foreign literature suggest that cultural differences play a significant role. The increased awareness of parents about

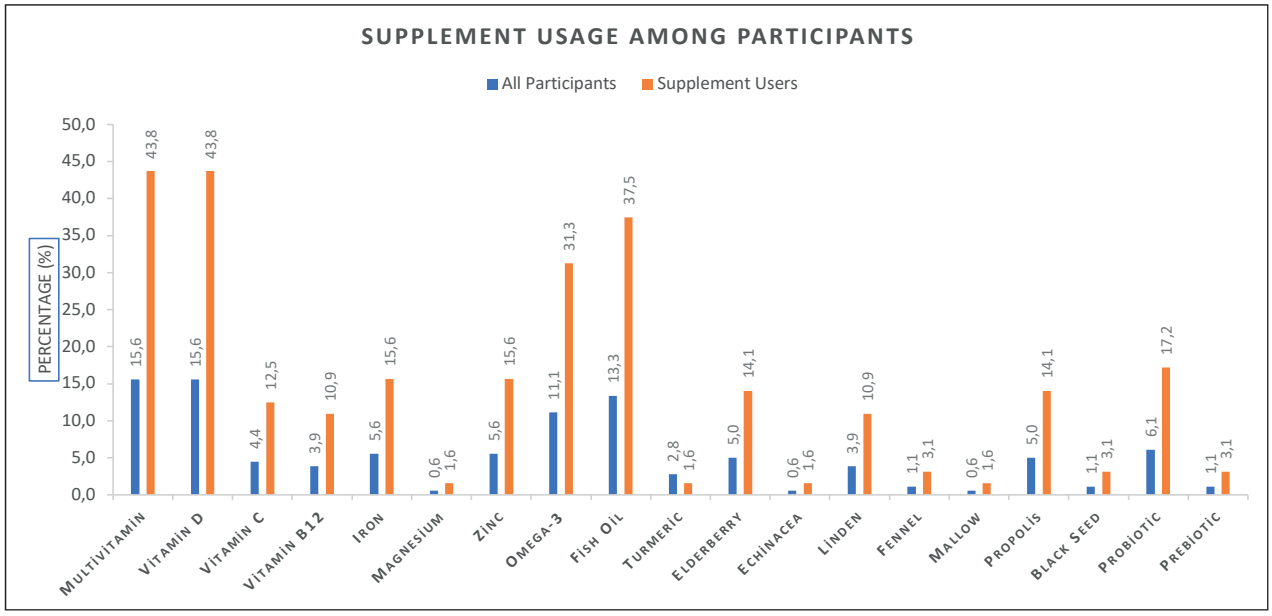

Figure 1: Percentages of dietary supplement use among all participants and children using dietary supplements. Fish oil is contains Omega-3 fatty acids (EPA and DHA), as well as Omega-6, Omega-9, and other fatty acids. Omega-3 supplements refer to supplements that contain only EPA and DHA.

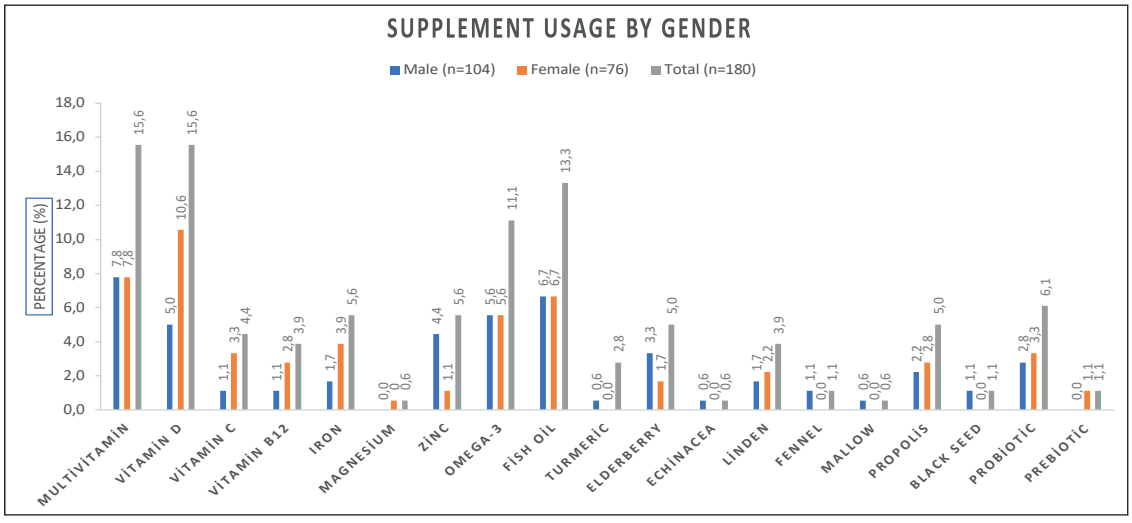

Figure 2: Percentages of children's dietary supplement use by gender. Fish oil is contains Omega-3 fatty acids (EPA and DHA), as well as Omega-6, Omega-9, and other fatty acids. Omega-3 supplements refer to supplements that contain only EPA and DHA.

dietary supplements in recent years may have contributed to parents taking into account the recommendations of health professionals more.

In addition to the positive effects of dietary supplements on health, their content has become a topic of discussion in recent years. For this reason, consumers have become more selective when purchasing dietary supplements. In a study conducted on preschool children in Japan, parents stated that they preferred dietary supplements with natural ingredients (16). In this study, naturalness (57.8%) and quality (56.3%) were the factors that parents paid the most attention to when purchasing dietary supplements. With a better understanding of the adverse effects of food additives on health, parents' interest in natural and organic foods is increasing. Although dietary supplements may seem harmless, they can contain many additives. For this reason, families are turning to more natural products.

Sociodemographic characteristics of children and their parents may affect dietary supplement use (6). In a study examining the use of dietary supplements by children aged one to ten years, it was found that parents in high-income households (>$100.000) were more likely than parents in low-income families (<$50.000) to report that their children regularly took a dietary supplement (57% vs. 44%) (20). In the study conducted using NHANES 2011-2014 data, lower age, higher income, and lower BMI were associated with higher dietary supplement use. (6). In a study examining factors associated

with supplement use in preschool children in Japan, children who used supplements tended to be older than children who did not use supplements. Still, as in this study, mothers' education level and household income were not associated with supplement use among their children (23). Another study found that "higher mother's education level" and "older age of the child" were significantly associated with supplement use for preschool children in Australia, and "higher household income" was significantly associated with supplement use in China (13). In both a study conducted among children aged 1-8 years in South Korea and another study conducted among preschool children in 3 Korean cities, supplement use was associated with household income, mother's age, and education level (21,24). In this study, multivariate logistic regression analysis revealed no significant effect of gender, number of siblings, age of the child, age of the parents, education level of the parents, family type, and family income on supplement use. Although studies generally associate supplement use with family income, mother's education, and age, this relationship was not found in this study. This may be due to the small sample size. Studies with larger sample sizes are needed to understand these relationships better.

In a study conducted on preschool children, children who used dietary supplements were likelier to skip breakfast and eat out more frequently (23). However, another study on preschool children found that supplement users had more regular meal times (21). In this study, when children's dietary habits and physical activity were analyzed according to their dietary supplement use, it was found that children who used dietary supplements skipped more meals than children who did not (53.1%-30.2%, respectively). No difference was found between the children's other eating habits and physical activity status regarding supplement use. The relationship between children's dietary habits and dietary supplement use is multifaceted and complex. Therefore, future studies should include comprehensive and holistic analyses that take into account parental attitudes, nutritional knowledge, and socioeconomic characteristics.

CONCLUSION

Adequate and balanced nutrition optimizes a child's growth and development, while an unhealthy diet can negatively affect short- and long-term health outcomes and school performance. The best way for preschool children to get the nutrients they need to be healthy is through a balanced diet with adequate amounts of fruits and vegetables, protein and fiber, and limited amounts of processed foods. However, about one-third of parents use dietary supplements to support their child's immunity or improve their health. It is important to note that there is limited evidence supporting the effectiveness of dietary supplements in improving health for children who have adequate and balanced diets, and unnecessary use may lead to negative consequences. Supplements should only be considered when children are not receiving enough nutrients from their diet, and parents should consult appropriate health professionals before using them.

Limitations of the study: This study does not fully represent the use of dietary supplements among preschool children in the country due to the small sample size and the fact that it was conducted in only one region. Additionally, dietary intake was not assessed to determine whether the overall nutrient intake of the children in our study was adequate. However, the results of this study may provide a preliminary overview of dietary supplement use among preschool children in Türkiye and could help improve parents' perceptions of dietary supplements and their purchasing behavior.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. Ethical approval for this study was obtained from Kastamonu University Clinical Ethics Committee (Date: 17.01.2024 Decision no: 2024-KAEK-6).

Contribution of the authors

Zengin FH: Idea/concept, design, control/supervision, analysis and/or interpretation, literature review, writing the article, critical review, references and fundings, materials, ***Çetin E:*** Idea/concept, design, data collection and/or processıng, literature review, references and fundings, materials

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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 malnutrition in transfusion-dependent children with beta-thalassemia major

Selma Çakmakçı[1], Kevser Gamze Daniş[2], Feyat Tunç[3], Neriman Sarı[1]

[1]Department of Pediatric Hematology-Oncology, Ankara Bilkent City Hospital, Ankara, Türkiye
[2]Department of Pediatrics, Batman Medicalpoint Hospital, Batman, Türkiye
[3]Department of Pediatrics, Batman Training and Research Hospital, Batman, Türkiye

ABSTRACT

Objective: In patients with thalassemia, factors such as low socioeconomic status, rapid erythrocyte turnover, endocrinopathy, chronic hypoxia, increased nutritional demands, multiple transfusions, and ineffective erythropoiesis may lead to malnutrition. This study aimed to investigate malnutrition and related factors in children with transfusion-dependent beta-thalassemia major (β-TM).

Material and Methods: The research group consisted of the medical records of 81 β-TM patients. Data were created by measuring the patients height (cm), body weight (kg), weight for age, mid-upper arm circumference (MUAC, cm), triceps skinfold thickness (TSF, mm) and blood parameters (e.g., hemoglobin, ferritin) before transfusion.

Results: The median age of children with β-TM was 8.8 (range, 4.6-13.0) years, 38 (47%) were male and 43 (53%) were female. The frequency of malnutrition among the children was 20.99% (4.94% moderate, 16.05% mild). The median age of those with malnutrition was higher (p=0.003) and the frequency of malnutrition was higher in children with β-TM aged 5 years and over (p=0.034). Children with and without malnutrition were similar in terms of body weight (p=0.074), MUAC (p=0.321), MUAC z-score (p=0.573), TSF (p=0.691), TSF z-score (p=0.846), TSF percentile (p=0.077), ferritin (p=0.945), vitamin B12 (p=0.119), 25-OH Vit D (p=0.995), and hemoglobin (p=0.563). Body mass index (p=0.026) and weight for age (p<0.001) were lower and albumin was higher (p=0.041) in children with malnourishment.

Conclusion: Malnutrition in children with transfusion-dependent β-TM is still a common clinical picture that needs to be tackled and prevented.

Keywords: Beta-thalassemia child, child nutrition disorders, ferritins malnutrition, iron chelating agents

INTRODUCTION

B-thalassemia major (β-TM) is an autosomal recessive type of hereditary disease in which genetic mutations affect the β-globin gene, disrupting the synthesis of functional β-globin protein. In this disease, an imbalance between α- and β-globin chains and erythropoiesis damage occur (1). Erythropoiesis injury causes premature erythrocyte destruction and causes chronic anemia with extramedullary hematopoiesis and associated bone marrow enlargement (2).

Inherited hemoglobin disorders, including thalassemia, are the most common monogenic diseases worldwide (3). Globally, it is estimated that 300.000 to 400.000 babies are born with a severe hemoglobin disorder each year (23.000 with β-TM), and up to 90% of these births occur in low or middle-income countries. Although thalassemia is common, it is most common in sub-Saharan Africa, Southeast Asia, and the Mediterranean region (4,5). The prevalence of β-TM is higher in lower-middle-income countries (e.g., India, Pakistan, Iran, and Egypt), and is lower in high-middle and high-income countries (e.g., Türkiye, Greece, the United States of America, and Canada) (6). The prevalence of β-thalassemia carriage in Türkiye is 2.1% (0.6-13.0%) (7).

In many patients with β-TM, circulating nutrient levels are reduced due to increased requirements, increased excretion, and/or malnutrition (8). In patients with thalassemia, low

Correspondence:
Selma Çakmakçı
e-mail: selmagumrukcu@gmail.com

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socioeconomic status, rapid erythrocyte turnover, long-term use of iron chelation, endocrinopathy, hypoxia due to anemia, increased body demand for energy and nutrients, and multiple blood transfusions and ineffective erythropoiesis may complicate the normal development process and lead to malnutrition (9,10).

The study aimed to evaluate the frequency of malnutrition and related factors in patients with transfusion-dependent β-TM.

MATERIALS and METHODS

This retrospective study was conducted at Batman Training and Research Hospital between July 2021- December 2021.

Ethics committee approval of the study was obtained from local ethics committee. Due to retrospective design of study, it is not necessary and not possible to take informed consent from recruited patients.

The medical records of 81 β-TM patients in the pediatric hematology outpatient clinic for the time period in which the research was conducted constituted the research data. All of these patients were subjected to a regular transfusion program to keep hemoglobin levels under control. Erythrocyte suspensions are administered regularly to patients at intervals of 3-4 weeks. Before transfusion, height (cm), body weight (kg), weight for age, mid-upper arm circumference (MUAC, cm), triceps skinfold thickness (TSF, mm) and blood parameters (e.g. hemoglobin, ferritin) are measured and recorded.

While measuring body weight, the caregiver was asked to remove the children's outer clothing and shoes. The children were asked to stand still on the scales with their feet slightly apart and they were measured and recorded using a calibrated scale. For height measurement, the children were asked to take off their shoes and the distance between the point marked with a board placed perpendicular to the wall and the floor was recorded when they stood upright on a flat surface (11). Mid-upper arm circumference was measured in centimeters with a non-stretched, standardized measuring tape. For measurement, the right arm was hung loosely and the midpoint between the tip of the acromion and the olecranon protrusion was determined. At this determined point, the tape was placed around the arm, preventing the soft tissue from being too tight or too loose. Two different measurements were made at a distance closest to 0.1 cm (12). The anthropometric measurement values of the children were compared with the age-appropriate World Health Organization (WHO) growth charts, and it was evaluated whether there were any malnutrition features. Children were classified according to the presence of malnutrition as mild, moderate, severe, or absent. Weight-for-height z-score values below -3 SD were classified as severe malnutrition, between -3SD and -2SD as moderate malnutrition, and between -2SD and -1 SD as mild malnutrition (13,14).

Statistical analysis

All analyses were performed using the IBM SPSS Statistics for Windows, Version 25.0 software package (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to determine whether variables were normally distributed. Data are given as mean and standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. Continuous variables were analyzed using Student's t-test or the Mann-Whitney U test depending on the normality of distribution. Categorical variables were analyzed using the Chi-square test or the Fisher-Freeman-Halton test. Statistical significance was accepted as $p<0.050$.

RESULTS

The median age of the children in the study group was 8.8 (range, 4.6-13.0) years; 38 (47%) were male and 43 (53%) were female.

The frequency of children in the study group with body mass index (BMI) z-scores between -2 SD and -1 SD was found as 16.05%, those with BMI z scores between -1 SD and 0 SD were 46.91%, and the frequency of those with BMI z-scores between 0 SD and 1 SD was 27.16%. The prevalence of malnutrition among the children was 20.99% (4.94% moderate malnutrition, 16.05% mild malnutrition). Weight for age was determined as 28 (range, 10-44), MUAC 18 (range, 16-20) cm, TSF 9 (range, 7-11) mm. The frequency of MUAC, z-score (< 5 years) -3SD to -2SD was 7.4% and -2SD to -1SD was 29.63%. The frequency of TSF, z-score (<5 years) -3SD to -2SD was 18.52% and -2SD to -1SD was 22.22% (Table I).

Among the children with transfusion-dependent β-TM, the median age of children with mild-moderate malnutrition was significantly higher than those without malnutrition (p=0.003). The frequency of mild/moderate malnutrition was 7.42% in children aged younger than 5 years, and 27.78% in children aged 5 years and over. The frequency of mild/moderate malnutrition was higher in children aged 5 years and over with β-TM (p=0.034). Children with and without malnutrition were similar in terms of sex (p=0.098), body weight (p=0.074), MUAC (p=0.321), MUAC z-scores (p=0.573), TSF (p=0.691), TSF z-score (p=0.846), TSF percentile (p=0.077), ferritin (p=0.945), vitamin B12 (p=0.119), vitamin D (p=0.995), and hemoglobin (p=0.563). Height (p=0.004) was significantly higher in children with malnutrition, and BMI (p=0.026) and weight for age (p<0.001) were significantly lower. The median albumin level was found to be higher in children with malnutrition (p=0.041, Table II).

Table I: Summary of characteristics, and anthropometric and laboratory measurements	
Age (years)*	8.8 (4.6-13.0)
<5†	27 (33.33)
≥5†	54 (66.67)
Age (months)*	105.6 (55.2-156.0)
Gender†	
Male	38 (47)
Female	43 (53)
Weight (kg)*	25.5 (17-34)
Height (cm)	127 (107-143)
Body mass index (kg/m^2)*	16.06 (15.08-18.08)
Body mass index, z-score†	
-3SD to -2SD	4 (4.94)
-2SD to -1SD	13 (16.05)
-1SD to 0SD	38 (46.91)
0SD to 1SD	22 (27.16)
1SD to 2SD	4 (4.94)
2SD to 3SD	0 (0.00)
Malnutrition†	
Absent	64 (79.01)
Mild	13 (16.05)
Moderate	4 (4.94)
Severe	0 (0.00)
Weight for age*	28 (10-44)
MUAC (cm)*	18 (16-20)
MUAC, z score (<5 years)†	
-3SD to -2SD	2 (7.41)
-2SD to -1SD	8 (29.63)
-1SD to 0SD	7 (25.93)
0SD to 1SD	10 (37.04)
1SD to 2SD	0 (0.00)
2SD to 3SD	0 (0.00)
TSF (mm)*	9 (7-11)
TSF, z-score (<5 years)†	
-3SD to -2SD	5 (18.52)
-2SD to -1SD	6 (22.22)
-1SD to 0SD	5 (18.52)
0SD to 1SD	9 (33.33)
1SD to 2SD	2 (7.41)
2SD to 3SD	0 (0.00)
Albumin (g/dL)‡	4.51±0.28
Ferritin (ng/mL)*	1138 (816-1609)
Vitamin B12 (pg/mL)*	398 (310-651)
25-OH Vit D (ng/mL)*	12 (10.2-15)
Hemoglobin (g/dL) ‡	9.27±0.93

***:** *median (1st quartile-3rd quartile),* **†:** *n(%),* **‡:** *mean±SD,* ***MUAC:** Mid-upper arm circumference,* ***TSF:** Triceps skinfold thickness*

DISCUSSION

Generally, daily consumption of nutrients is significantly lower in children with β-TM, and anthropometric measurements recorded in children with β-TM are lower compared with healthy children (15). Malnutrition, as assessed using anthropometric measures, is quite common in children with thalassemia major (16). In previous reports, there is quite a wide range of results for the frequency of malnutrition in patients with β-TM, ranging from 24% to 70%. Based on the literature review, malnutrition prevalence among children with beta thalassemia major shows considerable variation across studies, with rates ranging from a low of 19.6% in girls in the Iranian cohort to a high of 70% in the Egyptian pediatric population, demonstrating significant geographic, methodological, and demographic differences in nutritional status assessment and outcomes (17-24) (Table III). In the current study, we found the frequency of mild-moderate malnutrition as 20.99% in children with β-TM. Possible differences in factors such as age, duration of treatment, dose of treatment, available treatment options, and criteria by which malnutrition was evaluated may explain the heterogeneity of outcomes. On the other hand, although the prevalence of malnutrition found in our study is lower than that reported in previous studies, our rate is not at the desired level. New methods are needed to reduce and prevent malnutrition, which is one of the important causes of morbidity and mortality in this patient group, and has many clinical disadvantages.

Malnutrition in children with thalassemia major increases with age, regardless of gender (16). In a study evaluating children with thalassemia major aged over 5 years, it was reported that BMI decreased in patients with thalassemia major aged over 10 years (70.4%) compared with patients aged younger than 10 years (30.4%) (25). In the study of Sheikh et al. (23), it was reported that the frequency of malnutrition increased with increasing age in children with β-TM between the ages of 2 and 16 years. In the study of Biswas et al. (22), although no relationship was found between gender and malnutrition in the multivariate analysis, it was reported that age increase was a factor that predicted the presence of malnutrition independently from other factors. Similarly, in the present study, the median age of children with β-TM who had mild-moderate malnutrition was higher, and no relationship was found between gender and malnutrition. The age of patients also indicates the disease and treatment duration because thalassemia emerges from birth. Over time, the negative effects of repeated transfusions and treatments on nutritional levels may increase. The nutritional status of patients should be monitored regularly and nutritional support should be provided when necessary.

Children with β-TM have lower hemoglobin levels than healthy children due to erythropoiesis damage and rapid cycling (26). In an observational study conducted with patients with β-TM, an increase in the number of transfusions performed in the last year and a decrease in hemoglobin levels before the last transfusion were reported as independent predictors of the presence of malnutrition (22). In the present study, the mean hemoglobin level before transfusion was lower than normal (9.27±0.93) and there was no correlation between malnutrition and hemoglobin levels. Due to the continuous decrease in hemoglobin in these patients, hemoglobin levels are closely monitored and regular transfusions are attempted to ensure control.

Table II: Summary of characteristics, and anthropometric and laboratory measurements according to malnutrition

	Malnutrition		p
	Absent (n=64)	Mild and Moderate (n=17)	
Age (years)*	7.6 (4.5-12.2)	13 (11.7-14)	0.003
<5 †	25 (39.06, 92.59)	2 (11.76, 7.41)	0.034
≥5 †	39 (60.94, 72.22)	15 (88.24, 27.78)	
Age (months)*	91.2 (54-146.4)	156 (140.4-168)	0.003
Gander †			
Male	27 (42.19)	11 (64.71)	0.098
Female	37 (57.81)	6 (35.29)	
Weight (kg)*	24 (16.85-34)	32 (28-35)	0.074
Height (cm)*	123.5 (105.5-138)	143 (137-147)	0.004
Body mass index (kg/m^2)*	16.26 (15.16-18.37)	15.65 (14.92-16.65)	0.026
Weight for age*	33 (16-51.5)	2 (1-5)	<0.001
MUAC (cm)*	17.5 (15.75-20.25)	18.5 (18.0-19.5)	0.321
MUAC, z-score (<5 years) †			
-3SD to -2SD	2 (8)	0 (0)	0.573
-2SD to -1SD	7 (28)	1 (50)	
-1SD to 0SD	6 (24)	1 (50.00)	
0SD to 1SD	10 (40)	0 (0)	
1SD to 2SD	0 (0)	0 (0)	
2SD to 3SD	0 (0)	0 (0)	
TSF (mm)*	9 (7-11)	8 (7-10)	0.691
TSF, z-score (<5 years) †			
-3SD to -2SD	5 (20)	0 (0)	0.846
-2SD to -1SD	6 (24)	0 (0)	
-1SD to 0SD	4 (16)	1 (50)	
0SD to 1SD	8 (32)	1 (50)	
1SD to 2SD	2 (8)	0 (0)	
2SD to 3SD	0 (0)	0 (0)	
Albumin (g/dL)‡	4.47±0.27	4.63±0.30	0.041
Ferritin (ng/mL)*	1126.5 (806.5-1619)	1150 (878-1519)	0.945
Vitamin B12 (pg/mL)*	413.5 (323.5-680.5)	318 (290-423)	0.119
25-OH Vit D (ng/mL)*	12.0 (10.1-15.2)	12.29 (11.0-14.9)	0.995
Hemoglobin (g/dL)‡	9.24±0.99	9.39±0.64	0.563

:** *median (1st quartile-3rd quartile) (Mann-Whitney U test),* **†:** *n(%) (Pearson Chi-square test),* **‡:** *mean±SD (Student's t-test),* ***MUAC: *Mid-upper arm circumference,* ***TSF:*** *Triceps skinfold thickness,* ***Note:*** *First percentage for age in parentheses represents within-group frequency; second percentage reflects proportion in total malnutrition category.*

Table III: Summary of reported malnutrition prevalence and assessment methods in pediatric β-thalassemia major studies

Study	Country	Year	Sample Size	Age Range	Malnutrition Prevalence (%)	Measurement Criteria
Qaisar et al. (16)	Pakistan	2020	300	0-215 months	45% (0-59 months) 67.5% (60-215 months)	WHO BMI classification
Pemde et al.(18)	India	2011	154	0.5-18 yrs	24.19	BMI for age
Trehan et al. (19)	India	2015	964	0-2 yrs	26.7	Weight for age
Mirhosseini et al. (20)	Iran	2013	140	8–18 yrs	44.3 % for boys 19.6 % for girls	WHO-BMI
Fahim et al. (21)	Egypt	2013	100	N/ A	47.0	Weight for age
Biswas et al. (22)	India	2021	328	5–12 yrs	48.2	WHO-BMI
Sheikh et al. (23)	Pakistan	2017	305	2–16 yrs	58.69	CDC-BMI
Mahmoud et al. (24)	Egypt	2021	120	≤12 yrs	70.0	WHO Z-score (BMI-for-age)

Thalassemia major increases long-term extravascular hemolysis and, as a result, intestinal iron absorption. When the iron overload that comes with multiple blood transfusions is added, the amount of iron in the tissue may exceed normal limits. Excessive iron accumulation is important because it can produce hydroxyl free radicals and oxidative stress, causing progressive tissue damage in the liver, heart, endocrine glands, and other organs. Controlling serum ferritin levels with combined iron-chelating agents has been associated with a decrease in the prevalence of endocrine disorders in patients with transfusion-dependent β-TM (24,27). According to a study in mice, iron overload causes MIN6 cell dysfunction, which leads to increased fasting blood sugar, impaired glucose tolerance, and significantly reduced insulin sensitivity (28). It has been reported that the prevalence of cardiac iron overload and cardiovascular complications is high in patients with thalassemia major (29). Serum ferritin levels are higher in patients with β-TM compared with healthy children (26). In another study conducted with children with β-TM, it was reported that the mean serum ferritin level was 3326±3859 ng/mL and there was a negative correlation between the BMI percentile and mean serum ferritin levels (30). In the study of Işık et al. (31), the mean ferritin levels of patients with β-TM were reported as 2497±1469 (range, 472-8558) ng/mL (31). In a study evaluating 367 children aged 5-17 years with transfusion-dependent β-TM, it was reported that serum ferritin value was 5012 (range, 3532-6829) ng/mL, higher than normal values (32). In another study, it was reported that the median serum ferritin value in patients with β-TM was 1365 (range, 362-5996) ng/mL, and no relationship was found between ferritin levels and anthropometric measurements (33). In the present study, the median ferritin value was 1138 (range, 816-1609) ng/mL, higher than normal values, in patients with β-TM, and additionally, no relationship was found between malnutrition and ferritin. Although the ferritin value found in our study group is lower than those reported in other studies, it is above the values considered normal for ferritin. To ensure that ferritin, which is one of the leading causes of morbidity and mortality in patients with β-TM, remains within normal values in this patient group, we need new ideas about non-transfusion treatments of the disease or the effectiveness of iron chelation treatments in patients undergoing transfusions. On the other hand, insufficient compliance, which is common in current iron chelation treatments, should be taken into consideration and controls should be provided to ensure treatment compliance of patients. Higher compliance is associated with lower serum ferritin, lower risk of complications, and better quality of life (34).

Disturbances between intake and circulating nutrient levels are observed in patients with β-TM, despite apparently adequate dietary intake, for reasons such as decreased nutrient absorption, increased loss, and increased needs due to increased nutrient cycling (6,10,35). Although 25-OH Vit D deficiency is a common comorbidity in patients with thalassemia, both its prevalence and severity vary considerably in different populations (36). In the study of Fahim et al. (21), it was reported that total serum calcium and 25-OH Vit D values of patients with β-TM were significantly lower compared with healthy controls. In the study of Altıncık et al. (33), the frequency of 25-OH Vit D deficiency in patients with β-TM was reported as 54.5%, and 78.2% in the study of Işık et al. (31). In a study conducted with adult patients, it was reported that the prevalence of low 25-OH Vit D was 92.2%, and no relationship was found between malnutrition and 25-OH Vit D levels (17). Similarly, in the current study, the 25-OH Vit D level was lower than normal values and was not associated with malnutrition. Both malnutrition and 25-OH Vit D deficiency are a result of β-TM. Children with β-TM should be followed closely in terms of 25-OH Vit D levels, especially in winter, and supplements should be provided in case of deficiency.

Treatment and follow-up of β-TM with a multidisciplinary approach will be beneficial because it has the potential to cause multisystemic complications (31). Periodic close monitoring of nutritional status is needed to determine the risk of malnutrition in patients with thalassemia (37). Although the issue of nutrition is increasingly seen by caregivers for patients with thalassemia, the definition of optimal nutritional support and the means of providing this support are still unclear and need to be studied (38).

The study had some limitations. This was a retrospective single-center study that failed to establish a causal relationship between malnutrition and some factors in children with β-TM. In addition, it was performed with a small number of patients. For these reasons, the statistical significance of some relationships may have been lost and the results cannot be generalized to the general population. Another limitation is that it does not have a healthy age- and sex-matched control group. The lack of analysis of data on patients' dietary regimens is another important limitation of this study. A further limitation is the possibility of other factors affecting malnutrition that were not evaluated in the study. Despite these, this study is valuable in terms of evaluating the relationship between malnutrition and many parameters in children with β-TM.

CONCLUSION

Malnutrition in children with transfusion-dependent β-TM is still a common clinical picture that needs to be tackled and prevented. It would be useful to monitor these patients closely in terms of iron accumulation and nutritional deficiency. More comprehensive, population-based, prospective studies are needed to better understand nutritional deficiency in patients with β-TM.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. Ethics committee approval of the study was obtained from Batman Training and Research Hospital Ethics Committee (Decision date: 25.07.2023, decision no: 358).

Contribution of the authors

Çakmakçı S: Concept, Design, Data Collection and Processing, Analysis and Interpretation, Literature Review, Writing the Article, Critical Review, Supervision. ***Danış KG:*** Design, Data Collection and Processing, Literature Review, Critical Review, References and Fundings, Materials. ***Tunç F:*** Supervision, Data Collection and Processing, Analysis and Interpretation, Literature Review, Critical Review, References and Fundings. ***Sarı N:*** Supervision, Analysis and Interpretation, Writing the Article, Critical Review, Materials.

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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 subjects with exam anxiety and healthy controls using the Beier Sentence Completion Test as a projective method: a different perspective on the causes of exam anxiety

Rukiye Çolak Sivri[1], Özge Bayram[2]

[1]Department of Child and Adolescent Psychiatry, Independent Researcher, Ankara, Türkiye
[2]Department of Developmental Pediatrics, Ankara Training and Research Hospital, Ankara, Türkiye

ABSTRACT

Objective: The aim of this study was to identify factors associated with exam anxiety that may contribute to exam anxiety in children and adolescents who present to the clinic. Additionally, this study planned to compare the attitudes and behavior dynamics of individuals with exam anxiety and co-occurring psychiatric disorders with those who have isolated exam anxiety using the Beier Sentence Completion Test (BCT).

Material and Methods: The study sample consisted of girls and boys aged 8-18 who presented to the Child and Adolescent Psychiatry Outpatient Clinic of Health Sciences University Ankara Training and Research Hospital between January 1, 2019, and December 31, 2019, with complaints of exam anxiety. The BCT, the Children's Anxiety Disorder Screening Scale (SCARED), and the Children's Depression Scale (SCARED) were administered to the patients.

Results: The BCT-negative total score of the exam anxiety and comorbid diagnosis group was significantly higher than that of the control group ($p=0.001$). The BCT-neutral total score of the exam anxiety and comorbid diagnosis group was significantly lower than the control group ($p<0.001$). The distribution of the BCT self- and ability-related attitude in the exam anxiety group was significantly more negative ($p=0.008$). The distribution of the BCT attitude toward the mother in the exam anxiety group was significantly more negative ($p=0.012$).

Conclusion: Exam anxiety is a common public mental health issue in Türkiye, a country where exams and testing are frequent. Children and adolescents with exam anxiety tend to interpret external stimuli more negatively, with neutral interpretations being less frequent. The negative evaluation of one's self and abilities is an important factor that clinicians should consider. The negative attitude toward the mother in relation to parental attitudes emphasizes the role of parental attitudes in exam anxiety.

Keywords: Anxiety, Exam, Projective Techniques

INTRODUCTION

Exam anxiety is a prevalent issue that significantly impacts students' academic performance and mental health. It is defined as a psychological condition involving emotional, physiological, and behavioral responses to the perceived negative consequences of upcoming exams. This intense anxiety can impair a student's ability to effectively use their knowledge and skills, resulting in reduced performance. When disproportionate to the situation, it interferes with decision making processes, studying, and information recall, thereby affecting an individual's overall functioning (1).

Current research suggests that high test anxiety affects between 15% and 22% of the student population (2,3). Considering the early exposure to high-stakes testing in the Turkish educational system, exam anxiety represents a significant child and adolescent mental health concern, negatively influencing their social, emotional, and cognitive development, as well as their self-perception and academic identity (4). The etiology of exam anxiety is multifactorial, encompassing individual traits and environmental factors. Personal characteristics such as fear of failure, perfectionism, excessive worry, poor coping skills, and low self-esteem contribute significantly (5,6). External pressures, particularly from parents and social comparisons,

Correspondence:
Rukiye Çolak Sivri
e-mail: drrukiyecolaksivri @gmail.com

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are also influential. Parental attitudes are frequently emphasized in the literature as significant contributors to performance-related anxiety. Authoritarian parenting marked by strict rules and high expectations has been linked to elevated anxiety levels, whereas democratic parenting is associated with lower anxiety (6). Projective techniques are advantageous in revealing unconscious emotional processes that standard self-report inventories may fail to capture. Unlike traditional self-report scales, projective methods like BCT allow for a more indirect and nuanced assessment by interpreting the individual's spontaneous responses, offering a deeper clinical understanding (7). While the use of projective tools such as BCT is established in clinical settings for assessing internalizing and externalizing disorders, their application in evaluating exam anxiety remains limited. However, recent studies have begun to highlight the potential of projective tools in educational contexts to uncover subtle emotional patterns that are not easily accessed through direct questioning (8). For example, Koç et al. (8) demonstrated that BCT could effectively distinguish between adolescents with internalizing versus externalizing disorders and correlated well with self-reported anxiety and depressive symptoms. These findings suggest the relevance and utility of BCT in understanding the emotional and psychological dimensions of exam anxiety.

The primary aim of this study was to explore the psychological and emotional factors contributing to exam anxiety using the Beier Sentence Completion Test in a clinical sample of children and adolescents. Additionally, this study sought to compare the emotional and behavioral profiles of individuals with exam anxiety with and without comorbid psychiatric conditions to those of healthy controls. Our hypothesis was as follows: Children and adolescents diagnosed with exam anxiety will obtain significantly higher total negative scores on the Beier Sentence Completion Test compared to healthy controls. Additionally, among participants with exam anxiety, those with comorbid psychiatric diagnoses will exhibit higher levels of negative responses, particularly in the domains of family relationships and self-concept, compared to those with only exam anxiety.

MATERIALS and METHODS

The sample of this study consisted of male and female subjects aged 8 to 18 years who presented to the Child and Adolescent Psychiatry Outpatient Clinic of Health Sciences University Ankara Training and Research Hospital between January 1, 2019, and December 31, 2019, with complaints of exam anxiety. No comorbid physical illnesses were present among the participants included in the study. The results of the Beier Sentence Completion Test (BCT), the Children's Anxiety Disorder Screening Scale (SCARED), and the Children's Depression Scale (CDI) were accessed from the hospital's database. Comorbid psychiatric disorders were identified by the principal investigator, and the diagnoses were made retrospectively based on DSM-5 criteria. The control group consisted of children who applied for consultation in child and adolescent psychiatry but did not have a current psychiatric disorder diagnosis. Similarly, the children included in the control group did not have any physical illnesses. Moreover, no additional psychiatric disorders, including test anxiety, were present. Individuals with autism spectrum disorder, intellectual disability, or bipolar disorder were excluded from both the patient and control groups.

Beier Sentence Completion Test (BCT):

BCT is one of the projective tests commonly used in clinical practice (9). BCT is a semi-structured projective test consisting of incomplete sentences. The patient is asked to read the incomplete sentences and complete them according to their first thoughts. Its importance in the diagnostic and treatment process is heightened by its ease of use, low cost, no requirement for a certain level of education, and its ability to provide valuable additional information for psychiatric formulations. This test reflects their interests, attitudes, desires, expectations, problems, feelings, and thoughts. Each sentence in the scale expresses a behavioral dynamic. These behavioral dynamics are grouped into 11 subcategories (attitudes towards the past, attitudes towards the future, self-confidence and attitudes towards abilities/self-esteem and attitudes towards one's own abilities, attitude towards the mother, attitude towards the father, attitude towards home and family, attitude towards friends, behavior towards authority, fears and anxieties, feelings of guilt, attitude towards school and work). Interpretation of the test is evaluated by processing the analysis form. For each sentence, the value is determined as positive, negative, or neutral based on the emotional charge of the response provided by the individual. This was conducted by a second researcher who was blind to group allocation (case or control). Accordingly, sentences are marked as positive (e.g., "The best fathers are mine"), negative (e.g., "There cannot be good fathers"), or neutral (e.g., "There are both good and bad fathers"), and coded as (+), (-), or (0), respectively. Additionally, the total number of unanswered sentences is reported. In this study, the number of unanswered sentences for each subcategory was also analyzed. To minimize this bias, a second researcher independently scored the responses in a blinded manner, and the results were subsequently reviewed with the principal investigator.

Children's Depression Inventory (CDI):

The CDI is a 27-item self-report scale designed for children aged 6-17 years. The Turkish validity and reliability study was conducted by Oy (11). The test-retest reliability of the scale is 0.80, and the Cronbach alpha internal consistency coefficient is 0.77. The cutoff score for the scale is 19 (11).

The Screen for Child Anxiety Related Disorders (SCARED):

This scale consists of 41 items designed to assess anxiety in children. It is a self-report tool, with each item scored based on

the severity of the symptoms, using a scale of 0, 1, or 2 points. The recommended cutoff score is 25, which is considered indicative of an anxiety disorder. The Turkish validity study was conducted by Çakmakçı (10). The Cronbach alpha reliability values for the overall scale and subscales range from 0.88 to 0.91 (10).

Statistical analysis

IBM SPSS Statistics for Windows version 21.0 (Armonk, NY: IBM Corp., 2012) was used for statistical analysis. Categorical variables are expressed as frequency (n) and percentage (%). The normality of continuous variables was tested using the Kolmogorov-Smirnov test and is presented as mean and standard deviation. For the comparison of continuous variables between two groups, Student's t-test was used. Categorical variables were analyzed using Pearson's χ^2 and Fisher's exact tests. Pearson correlation analysis was used for SCARED Scales with BCT Subscale Totals. A significance level of $p<0.050$ was accepted.

RESULTS

The average age of the total 99 subjects was 12.1±2.7 years. The study sample consisted of 72 participants in the patient group and 27 participants in the control. The two groups were found to be similar in terms of age, gender, and educational level distribution (p=0.359, p=0.580, p=0.243 respectively, see Table I).

In the exam anxiety group (n=72), only subjects with exam anxiety represented 51.4% of the entire group (n=37), while 49.6% (n=35) had a comorbid DSM-5 diagnosis in addition to exam anxiety. Among these subjects, 29.2% (n=21) had a comorbid anxiety disorder (e.g., generalized anxiety disorder, panic disorder, etc.), 9.7% (n=7) had other comorbid disorders (e.g., tics, borderline intellectual functioning, PTSD, somatization), 5.6% (n=4) had obsessive-compulsive disorder (OCD), and 4.2% (n=3) had depression. In the scale score comparison, the CDI scores were found to be similar between the two groups (p=0.097), while the mean score of the SCARED scale was significantly higher in the anxiety group (Table II).

Analysis of the Beier Sentence Completion Test (BCT)

This test was used to examine various psychological attitudes and reactions between a group with exam anxiety and a control group. The results indicate significant differences between the two groups, with the exam anxiety group showing higher anxiety levels and more negative attitudes in various psychological areas.

BCT-Total Results:

The exam anxiety group showed a significantly higher negative mean in BCT total compared to the control group (21.2 vs. 14.3; $p<0.001$ The exam anxiety group had a significantly lower neutral mean in BCT total compared to the control group (10.7 vs. 21.4; $p<0.001$). The exam anxiety group showed a significantly higher unanswered mean in BCT total compared to the control group (6.7 vs. 2.4; p=0.016) (Table III).

Attitudes Toward the Past:

The exam anxiety group had a significantly higher negative mean regarding attitudes toward the past compared to the control group (2.1 vs. 1.4; p=0.007). The exam anxiety group showed a significantly lower neutral mean regarding attitudes toward the past compared to the control group (0.8 vs. 2.4; $p<0.001$). The exam anxiety group had a significantly higher unanswered mean in attitudes toward the past compared to the control group (0.6 vs. 0.1; p=0.010) (Table III).

Table I: Comparison of demographic and clinical scale data according to the presence of comorbid psychiatric disorders in children and adolescents presenting with exam anxiety

	Total n = 99	Exam anxiety n = 72	Control n = 27	Statistics t or χ^2	p
Age (year)*	12.1±2.7	12.2±2.7	11.6±2.5	0.921	0.359†
Gender‡					
Girl	64 (64.6)	51 (70.8)	13 (48.1)	4.421	0.058§
Boy	35 (35.4)	21 (29.2)	14 (51.9)		
Education‡					
Primary school	31 (31.3)	21 (29.2)	10 (37.0)	2.826	0.243§
Middle school	37 (37.4)	25 (34.7)	12 (44.4)		
High school	31 (31.3)	26 (36.1)	5 (18.5)		
Comorbidty‡					
No	27 (27.3)	NA	27 (100.0)	NA	NA
Exam Anxiety	37 (37.4)	37 (51.4)	0		
Exam Anxiety + The other anxiety disorder	21 (21.3)	21 (29.2)	0		
Exam Anxiety + Depression	3 (3.0)	3 (4.2)	0		
Exam Anxiety + Obsessive Compulsive Disorder	4 (4.0)	4 (5.6)	0		
Exam Anxiety + The other Scales	7 (7.1)	7 (9.7)			

***:** mean±SD, **†:** Student-t test, **‡:** n(%), **§:** Pearson chi-square test, **NA:** not-applicable*

Table II: The anxiety and depression scale scores of the exam anxiety and control groups.

	Total	Exam anxiety	Control	Statistics	
				t	p*
CDI†	34.8±9.5)	33.8±9.3	37.4±9.9	-1.677	0.097
SCARED†	33.2±17.4	37.2±17.0	22.8±14.1	3.901	<0.001

: Student-t test, †: mean±SD, **NA: not-applicable, **CDI:** Children's Depression Inventory, **SCARED:**The Screen for Child Anxiety Related Disorders*

Attitudes Toward the Future:

The exam anxiety group had a significantly higher positive mean in attitudes toward the future compared to the control group (1.9 vs. 1.1; p=0.005). The exam anxiety group showed a significantly higher negative mean in attitudes toward the future compared to the control group (1.0 vs. 0.3; p=0.001). The exam anxiety group had a significantly lower neutral mean in attitudes toward the future compared to the control group (1.7 vs. 3.3; p=0.001) (Table III).

Attitudes Toward the Self and Personal Abilities:

The exam anxiety group exhibited a significantly higher negative mean in attitudes toward the self and personal abilities compared to the control group (2.4 vs. 1.4; p=0.002). The exam anxiety group showed a significantly lower neutral mean in attitudes toward the self and personal abilities compared to the control group (1.0 vs. 2.2; p=0.000) (Table III).

Attitudes Toward the Mother:

The exam anxiety group had a significantly lower positive mean in attitudes toward the mother compared to the control group (1.8 vs. 2.4; p=0.019). The exam anxiety group showed a significantly higher negative mean in attitudes toward the mother compared to the control group (2.1 vs. 1.3; p=0.002). The exam anxiety group had a significantly lower neutral mean in attitudes toward the mother compared to the control group (0.1 vs. 0.7; p<0.001) (Table III).

Other Attitudes (Toward Father, Family, Friends, etc.):

Attitudes Toward Father: The exam anxiety group showed a significantly lower neutral mean in attitudes toward their fathers, while the unanswered mean was significantly higher.

Attitudes Toward Home and Family: The exam anxiety group showed a significantly higher negative mean and a lower neutral mean in attitudes toward home and family.

Attitudes Toward Friends: The exam anxiety group had a higher negative mean toward friends, and a significantly lower neutral mean compared to the control group.

Attitudes Toward Authority: The exam anxiety group showed a significantly lower neutral mean in their approach toward authority, but a higher unanswered mean.

Attitudes Toward Guilt: The exam anxiety group had a significantly lower neutral mean and a higher unanswered mean in their approach toward guilt.

Attitudes Toward School: The exam anxiety group showed a significantly higher negative mean and a lower neutral mean in attitudes toward school.

Correlation Analysis

A weak negative correlation was found between the CDI score and the total scores of the Beier Sentence Completion Test in children and adolescents with exam anxiety (n=72), specifically between the BCT-Positive Total Score (r=0.363, p=0.003) (see Table IV).

In children and adolescents with exam anxiety (n=72), a weak negative correlation was observed between the SCARED score and the total scores of the Beier Sentence Completion Test, specifically between the BCT-Positive Total Score (r=0.387, p= 0.001). Additionally, a moderate positive correlation was found between the BCT-Negative Total Score (r=0.440, p<0.001).

When the total and subscale scores of the BCT test were compared by gender in children and adolescents with exam anxiety, it was found that the self-perception and positive attitude towards own abilities of girls with exam anxiety were significantly lower than those of boys (2.2 vs. 1.5; t=2.184, p=0.033). All other variables were found to be similar between the two genders (for all, p>0.050, not shown in the table).

DISCUSSION

Exam anxiety is a heterogeneous disorder with many factors in its etiology. Researchers agree on two main categories when discussing the causes of exam anxiety. It is known that young people who experience difficulties in additional study and learning skills are more likely to experience exam anxiety. The reason for this is that, in order to recall the necessary information during the exam, the information has not been sufficiently internalized, and as a result of this cognitive effort during the exam, the person experiences anxiety. In this case, the main issue is not the exam itself but rather the inadequacies in the preparation process leading up to it. The second most important cause of exam anxiety is the negative, anxiety-triggering thoughts that arise in a person's mind during the exam and the difficulty in coping with these thoughts. The foundations of these negative thoughts can stem from a variety of psychological, social, familial, and environmental factors, such as personality traits, external expectations, the person's attitudes towards themselves (either positive or negative), and their self-efficacy, along with the interactions between these factors. This study aimed to assess various aspects of individuals, including their attitudes towards themselves, their parents, life, and the environment, as well as their self-esteem, in order to identify the factors that contribute to exam anxiety.

Table III: Comparison of beier sentence completion (bct) total and subscale scores of children and adolescents with exam anxiety to the control group

Scale*	Total n = 99	Exam anxiety n = 72	Control n = 27	Statistics	
				t	p†
BCT-Total					
Positive (+)	17.4±6.2	17.2 ±6.8	17.7 ±4.3	-0.337	0.737
Negative (-)	19.2±8.2	21.2 ±8.5	14.3 ±4.7	3.932	0.000
Neutral (0)	13.8 ±7.9	10.7 ±5.9	21.4 ±7.1	-7.518	0.000
Not Response	5.5 ±7.9	6.7 ±8.6	2.4 ±4.2	2.458	0.016
Attitude towards the Past					
Positive (+)	1.2 ±1.0	1.3 ±1.0	0.9 ±0.8	1.605	0.112
Negative (-)	1.9 ±1.1	2.1 ±1.1	1.4 ±1.1	2.769	0.007
Neutral (0)	1.3 ±1.3	0.8 ±0.8	2.4 ±1.5	-6.298	0.000
Not Response	0.4 ±0.8	0.6 ±0.9	0.1 ±0.4	2.622	0.010
Attitude towards the Future					
Positive (+)	1.7 ±1.2	1.9 ±1.1	1.1 ±1.1	2.910	0.005
Negative (-)	0.8 ±0.8	1.0 ±0.7	0.3 ±0.8	3.465	0.001
Neutral (0)	2.2 ±1.5	1.7 ±1.2	3.3 ±1.6	-5.257	0.000
Not Response	0.2 ±0.6	0.2 ±0.6	0.1 ±0.4	1.063	0.291
Attitude towards Self and Own Abilities					
Positive (+)	1.8 ±1.1	1.7 ±1.1	2.0 ±1.1	-1.119	0.266
Negative (-)	2.2 ±1.4	2.4 ±1.4	1.4 ±1.0	3.211	0.002
Neutral (0)	1.3 ±1.2	1.0 ±1.0	2.2 ±1.1	-4.698	0.000
Not Response	0.5 ±1.0	0.6 ±1.1	0.2 ±0.6	1.859	0.066
Attitude towards Mother					
Positive (+)	2.0 ±1.0	1.8 ±1.1	2.4 ±0.9	-2.383	0.019
Negative (-)	1.9 ±1.1	2.1 ±1.1	1.3 ±1.0	3.030	0.003
Neutral (0)	0.3 ±0.6	0.1 ±0.3	0.7 ±0.8	-4.913	<0.001
Not Response	0.7 ±1.1	0.8 ±1.2	0.4 ±1.0	1.329	0.187
Attitude towards Father					
Positive (+)	1.7 ±1.2	1.6 ±1.3	2.0 ±1.0	-1.456	0.149
Negative (-)	1.8 ±1.3	2.0 ±1.4	1.5 ±0.9	1.493	0.139
Neutral (0)	0.5 ±0.9	0.4 ±0.8	1.0 ±1.1	-2.661	0.009
Not Response	0.7 ±1.1	0.9 ±1.2	0.4 ±0.8	2.011	0.047
Attitude towards Home and Family					
Positive (+)	2.6 ±1.2	2.6 ±1.2	2.5 ±1.2	0.069	0.945
Negative (-)	0.7 ±0.9	0.8 ±1.0	0.3 ±0.6	2.249	0.027
Neutral (0)	1.3 ±1.0	1.1 ±0.8	1.8 ±1.1	-3.581	0.001
Not Response	0.3 ±0.7	0.4 ±0.7	0.2 ±0.8	1.254	0.231
Attitude towards Friends					
Positive (+)	2.2 ±1.0	2.2 ±1.1	2.2 ±1.0	-0.202	0.841
Negative (-)	1.0 ±1.0	1.2 ±1.0	0.6 ±0.7	2.870	0.005
Neutral (0)	1.3 ±1.0	1.1 ±1.0	1.8 ±1.0	-2.955	0.004
Not Response	0.3 ±0.6	0.3 ±0.6	0.2 ±0.5	0.867	0.388
Attitude towards Authority					
Positive (+)	1.4 ±1.0	1.3 ±1.1	1.4 ±0.9	-0.384	0.702
Negative (-)	1.8 ±1.0	1.9 ±1.1	1.7 ±1.0	0.651	0.517
Neutral (0)	1.1 ±0.9	0.9 ±0.9	1.5 ±0.9	-2.656	0.009
Not Response	0.5 ±1.0	0.6 ±1.1	0.1 ±0.3	2.565	0.012
Attitude towards Fear and Anxiety					
Positive (+)	0.3 ±0.6	0.3 ±0.6	0.2 ±0.6	0.770	0.443
Negative (-)	3.0 ±1.3	3.1 ±1.3	2.7 ±1.1	1.426	0.157
Neutral (0)	1.3 ±1.1	1.0 ±1.0	1.8 ±1.1	-3.277	0.001
Not Response	0.3 ±0.7	0.4 ±0.8	0.1 ±0.5	1.468	0.146
Attitude towards Guilt					
Positive (+)	0.4 ±0.6	0.4 ±0.6	0.5 ±0.5	-0.696	0.488
Negative (-)	2.4 ±1.2	2.6 ±1.2	1.9 ±1.0	2.534	0.013
Neutral (0)	1.2 ±1.1	0.8 ±0.8	2.2 ±1.1	-6.836	<0.001
Not Response	0.8 ±1.1	1.1 ±1.2	0.2 ±0.5	3.512	0.001

Scale*	Totaln = 99	Exam anxiety n = 72	Control n = 27	Statistics	
				t	p†
Attitude towards School					
Positive (+)	1.8 ±1.2	1.8 ±1.1	2.0 ±1.4	-0.812	0.419
Negative (-)	1.2 ±1.1	1.5 ±1.1	0.7 ±0.7	3.310	0.001
Neutral (0)	1.6 ±1.1	1.3 ±1.0	2.2 ±1.3	-3.312	0.001
Not Response	0.2 ±0.6	0.3 ±0.7	0.0 ±0.1	1.853	0.067

:** *mean±SD,* **†:** *Student-t test,* ***NA: *not-applicable*

Table IV: Pearson correlation analysis of scared scales with bct subscale totals in the exam anxiety group (n = 72)

	BCT – Pozitive Total	BCT – Negative Total	BCT – Neutral Total	BCT – Not Response Total
CDI				
r*	-0.363	0.217	0.099	0.006
p	0.003	0.077	0.426	0.961
SCARED				
r*	-0.387	0.440	0.056	-0.165
p	0.001	<0.001	0.656	0.185

:** *Pearson Correlation Analysis,* ***BCT: *Beier Sentence Completion Test,* ***CDI:*** *Children's Depression Inventory,* ***SCARED:*** *The Screen for Child Anxiety Related Disorders*

Exam anxiety is not defined as an independent psychiatric disorder in the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) diagnostic system. However, exam anxiety is often associated with anxiety disorders, particularly generalized anxiety disorder or social anxiety disorder. The DSM-5 addresses such anxieties within the broader framework of anxiety disorders, but there is no specific diagnostic category for exam anxiety. Both individuals with only exam anxiety and those with an additional diagnosis alongside exam anxiety obtained significantly higher total negative scores on the BCT scale open compared to the control group. Additionally, when the distribution of total neutral scores was examined, both groups were found to have significantly lower scores than the control group. In other words, individuals with exam anxiety tend to have higher negative interpretation scores and lower neutral interpretation scores. This may provide important data in terms of highlighting the significance of the impact of adverse environmental factors in individuals with exam anxiety. Furthermore, it should be noted that the tendency of individuals with exam anxiety to interpret environmental factors negatively and report fewer neutral situations may also be a result of cognitive bias. The group with exam anxiety showed a higher rate of negative past-event interpretation compared to both the control group and the group with exam anxiety and comorbid disorders. The cognitive bias of "negative past event interpretation" or the tendency of an individual to continuously interpret past experiences in a negative light, has most commonly been studied in the context of major depression. Specifically, Beck's original cognitive model of depression explains how negative cognitive biases are prevalent across the past, present, and future, highlighting the connection between these biases and depression. Additionally, literature suggests that individuals with anxiety disorders may also exhibit a higher tendency to interpret the past negatively, a phenomenon referred to as "negative memory bias" (12-14). However, none of these studies focused specifically on individuals with exam anxiety. Upon reviewing the literature, this study is the first to identify negative past-event interpretation in individuals with exam anxiety, which is considered important for clinicians.

While it is easily predictable that individuals with exam anxiety focus on potential negative outcomes related to future exams, the finding that these individuals also exhibit a negative bias toward past experiences and prior events is significant. In comparing the two groups, the exam anxiety group had a significantly higher average negative attitude toward the future compared to the control group. In children and adolescents with exam anxiety, it should be kept in mind that anxiety disorders are often associated with selective focus on the future, excessive generalization, catastrophizing, and all-or-nothing thinking, which are all forms of negative evaluation.

In the group with exam anxiety, the negative attitude towards the self and one's abilities was found to be significantly higher compared to the control group. The literature also indicates a significant negative relationship between self-esteem and exam anxiety (15). In a comprehensive meta-analysis conducted by Nathaniel von der Embse and colleagues, which compiled 238 studies, it was concluded that self-esteem is a significant and very strong predictor of exam anxiety. The negative evaluation and perception of one's own skills and abilities, as well as the feeling of inadequacy, are considered important psychological factors contributing to exam anxiety.

Although there are studies in the literature that examine the relationship between parental attitudes and exam anxiety, these studies generally rely on scales filled out by parents and parental self-reports. The effect of how children perceive their parents, assessed through a projective method, on exam anxiety has not been explored. Most studies in the literature report that exam anxiety is higher in families with an authoritarian parenting style, while children raised in democratic families tend to experience lower levels of exam anxiety (16, 17). Beyond parenting style, the literature categorizes parent-child communication into two main types: open communication and problematic communication (18). Open parent-child communication allows for comfortable information exchange and emotional expression, promoting shared perceptions and mutual understanding (19). Studies

emphasize that the clarity of parent-child communication should help overcome problems and, in turn, alleviate exam anxiety and psychological stress. In our study, a significant negative correlation was observed between positive maternal attitudes and exam anxiety, whereas negative maternal attitudes were positively associated with higher levels of exam anxiety. These findings highlight the critical role of maternal emotional support in shaping children's stress responses, particularly in high-pressure academic contexts. As the primary attachment figure, the mother often serves as the child's initial emotional mirror, influencing their self-perception and emotional regulation. A negative relationship with the mother can undermine the child's self-esteem and foster feelings of inadequacy, which in turn may exacerbate exam-related anxiety. This aligns with previous research emphasizing the impact of authoritarian or emotionally distant parenting on internalizing symptoms in children (20,21).

Interestingly, our findings did not reveal a similarly direct association between paternal attitudes and exam anxiety. The group with exam anxiety demonstrated a lower number of neutral responses and a higher rate of non-responses regarding their father. This may reflect emotional distancing, avoidance, or a lack of perceived emotional salience in the father-child relationship, potentially indicating that paternal influence is underreported or not fully internalized by children and adolescents in this context. Prior studies have also noted the mother's comparatively stronger emotional presence in the daily lives of children as a possible explanation for this discrepancy.

Moreover, the exam anxiety group showed a tendency toward more negative and fewer neutral interpretations concerning family life. This further suggests that children's subjective perceptions of their family environment especially emotionally charged or conflictual dynamics play a pivotal role in the development of exam anxiety. These findings are consistent with literature reporting that family cohesion, emotional warmth, and parental responsiveness are protective factors against academic stress. Children with exam anxiety exhibited a different distribution of negative attitudes towards their friends. This may be the result of a combination of psychological and social factors. Anxious individuals often have lower self esteem, which is linked to having more automatic negative thoughts. Children experiencing exam anxiety may project their internal unrest onto the outside world, leading to negative interactions with those around them. Additionally, anxiety issues can create difficulties in social skills, which can result in a lack of trust in friendships or misunderstandings in communication. Anxious children often perceive social situations as more threatening, which can lead them to adopt a more defensive and negative attitude.

When comparing the total and subscale scores of the BCT test for children and adolescents seeking help for exam anxiety, girls with exam anxiety were found to have significantly lower positive attitudes towards their self-image and abilities compared to boys (2.2 vs. 1.5; t=2.184, p=0.033). All other variables were found to be similar between the genders (for all, p>0.050; not shown in the table). The literature indicates that gender differences in exam anxiety tend to be higher in girls (22-24). A recent review of the literature also found that girls have higher exam anxiety compared to boys (16). The lower self-image and positive attitudes towards their abilities in girls are considered an important mediating factor in the higher prevalence of exam anxiety in females. This finding should be taken into account by clinicians, as it may have implications for treatment formulation and psychotherapeutic interventions. Future studies should focus on identifying the psychological factors that may mediate the higher incidence of exam anxiety in girls.

CONCLUSION

This study highlights that test anxiety is a complex issue influenced by factors such as self-perception, parental attitudes, cognitive biases, and social relationships. Maternal attitudes, in particular, have a significant impact on test anxiety, while paternal attitudes show no direct effect. The findings emphasize the importance of the parent child relationship, especially the role of maternal attitudes, in shaping test anxiety. Positive maternal attitudes can help reduce anxiety, while negative ones can increase it. To address test anxiety, interventions should focus on improving cognitive biases, boosting self-esteem, and fostering positive parental attitudes. Given the prevalence of exam anxiety in Türkiye, where exams are frequent and performance-based education is common, understanding the individual and environmental factors contributing to test anxiety is crucial for effective treatment and prevention. Further longitudinal studies are needed to clarify the cause-and-effect relationships and explore gender differences in test anxiety.

Limitations

In our study, significant relationships were found between exam anxiety and maternal attitudes; however, no direct relationship was identified with paternal attitudes. It should be noted that the generalisability of these findings may be affected by several limitations. The following essay will explore the issue of subjectivity in the interpretation of projective tests. Projective tests, of which the Beier Sentence Completion Test is an example, are reliant upon the subjective interpretation of responses by the examiner. This subjectivity can influence the consistency and reliability of the results. To minimize this bias, a second researcher independently scored the responses in a blinded manner, and the results were subsequently reviewed with the principal investigator. The single-centre sampling technique constitutes a secondary limitation. Our study was conducted at a single institution, which may limit the external validity of the findings. Single-center studies are more prone to overestimating treatment effects and may not accurately reflect

broader populations. The single-centre sampling technique constitutes a secondary limitation. The study employed retrospective data collection methods, which are susceptible to recall bias. Participants' recollections of past experiences may be inaccurate or incomplete, potentially leading to misclassification and affecting the study's internal validity.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. This study has been approved by the Ethics Committee of Ankara Education and Research Hospital (E-24-251/26.09.2024).

Contribution of the authors

Çolak Sivri A: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Bayram Ö:*** Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Retrospective analysis of human metapneumovirus in hospitalized and outpatient children: Insights from a four-year experience in Türkiye

Furkan Kalaycı[1], Aslinur Özkaya Parlakay[2], Ayça Çırak[1], Ece Karaköse[1], Kaan Çelebier[1], Metin Yiğit[1,3]

[1]Department of Pediatrics, Ankara Bilkent City Hospital, Ankara, Türkiye
[2]Department of Pediatric Infectious Disease, Ankara Bilkent City Hospital, Yildirim Beyazit University, Ankara, Türkiye
[3]Department of Pediatrics, Yildirim Beyazit University, Ankara, Türkiye

ABSTRACT

Objective: Human metapneumovirus (hMPV), particularly affecting children under five, is a significant viral agent associated with a wide range of respiratory illnesses, from mild upper respiratory infections to severe lower respiratory tract involvement. This study aimed to evaluate the clinical characteristics, severity indicators, and seasonal distribution of hMPV infections over a four-year period in one of Türkiye's largest pediatric hospitals, and to assess the potential epidemic risk in the national context.

Material and Methods: This retrospective study included 345 pediatric patients diagnosed with hMPV between January 2021 and December 2024. Demographic data, clinical findings, hospitalization status, respiratory support requirements, imaging results, and outcomes were analyzed.

Results: The median age was four years; 44.6% of patients were hospitalized, and 9.2% required intensive care. Common symptoms included cough (84.1%), fever (65.8%), and rhinorrhea (59.7%). Hypoxia, tachypnea, and pulmonary infiltrates were significantly associated with hospitalization ($p<0.001$). Four patients died, three without known comorbidities. The highest case count occurred in 2022, followed by a marked decline in 2023–2024, consistent with global trends.

Conclusion: Although generally considered mild, hMPV infection can result in severe disease and mortality, even in healthy children. These findings highlight the importance of early risk identification and integration of hMPV into respiratory infection surveillance and public health strategies. No significant outbreak was observed in Türkiye during the study period.

Keywords: Children, human metapneumovirus, respiratory tract infections

INTRODUCTION

Human metapneumovirus (hMPV), first identified in 2001, affects individuals of all age groups but is particularly prevalent among children under five years of age (1). As a major viral agent of respiratory infections, hMPV can present with a wide clinical spectrum, including bronchiolitis, pneumonia, and upper respiratory tract infections (1). Although hMPV infections can occur year-round, they are most commonly observed during the winter months (2).

The most commonly observed symptoms of hMPV infections include cough, fever, nasal discharge, tachypnea, and hypoxia. However, these manifestations closely resemble those of other viral respiratory infections, thereby limiting their diagnostic specificity (2). The clinical presentation can vary widely, ranging from mild upper respiratory tract infections to severe lower respiratory tract involvement (1). It has been reported that approximately 15% of community-acquired pneumonias requiring hospitalization in children are attributable to hMPV (3). Therefore, identifying risk factors that may predict the severity of illness is critical for effective patient management.

Since its discovery, outbreaks of hMPV among children have been reported at various times (4). Notably, recent reports have indicated significant increases in hMPV cases in the northern provinces of China, which are being closely monitored due to potential public health implications (5). This surge not only highlights the importance of public health preparedness but also contributes to growing societal concern. The increasing number of cases underscores the need for robust epidemiological surveillance of hMPV.

The aim of this study was to evaluate hMPV cases detected over the past four years at one of Türkiye's largest children's

Correspondence Address:
Furkan Kalaycı
e-mail: drfurkankalayci@gmail.com

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hospitals, to elucidate their clinical characteristics, and to assess the potential epidemic risk in the country from an epidemiological perspective.

MATERIALS and METHODS

This study was conducted at Ankara Bilkent City Hospital, Children's Hospital. The study population included patients who presented to the center between January 2021 and December 2024 and were diagnosed with hMPV at the time of presentation. Data from both hospitalized patients and those managed on an outpatient basis were retrospectively analyzed. Cases in which samples were improperly collected or multiple viral or bacterial agents were detected in the same nasopharyngeal swab were excluded. Additionally, individuals presenting for reasons unrelated to respiratory symptoms or asymptomatic patients sampled for other indications were not included.

Data for this study were obtained from the electronic medical record system of Ankara Bilkent City Hospital, Children's Hospital. The retrospectively analyzed data included patients' ages, genders, dates and seasons of presentation; symptoms (fever, cough, nasal discharge, tachypnea, hypoxia); histories of chronic diseases; hospitalization status and location (general pediatric unit or pediatric intensive care unit); length of hospital stay; need for respiratory support [invasive mechanical ventilation (IMV), non-invasive mechanical ventilation (NIMV), and high-flow nasal cannula (HFNC)]; and laboratory findings. IMV and NIMV were administered in the pediatric intensive care unit. As chest radiographs were not routinely obtained upon admission, only those available were assessed. The radiographic evaluations were conducted by pediatricians. Radiographs of patients with chronic conditions were compared with previous images in the system, and new pathological findings were assessed.

Patients with chronic diseases were categorized into five subgroups based on their underlying conditions: (1) the Asthma/Wheezy Infant Group, including patients diagnosed and followed by the pediatric allergy clinic for asthma or its variants, regardless of regular inhaler use; (2) the Immunodeficiency Group, comprising patients with primary immunodeficiencies, those undergoing chemotherapy for hematologic malignancies or solid tumors, patients receiving pulse steroid or biological agent therapy, and bone marrow transplant recipients under immunosuppression; (3) the Cardiac Disease Group, which includes patients with cyanotic congenital heart diseases (e.g., Tetralogy of Fallot, Truncus Arteriosus) or other cardiac conditions associated with hemodynamic instability (e.g., myocarditis, cardiomyopathy, heart failure); (4) the Neurological and Neurometabolic Diseases Group, consisting of patients with severe neurodevelopmental impairment affecting swallowing function, including cerebral palsy, neuromuscular disorders (e.g., spinal muscular atrophy, Duchenne muscular dystrophy), sequelae of hypoxic ischemic encephalopathy, intracranial hemorrhage, or hydrocephalus, and neurometabolic disorders with significant neurological involvement (e.g., MSUD, lysosomal storage diseases, Dravet syndrome, West syndrome); and (5) the Chronic Pulmonary Disease Group, encompassing patients with structural or functional pulmonary disorders, such as bronchopulmonary dysplasia, cystic fibrosis, congenital diaphragmatic hernia, respiratory distress syndrome, pulmonary sequestration, pulmonary hemosiderosis, sequelae of congenital pneumonia, genetically undefined interstitial lung diseases, and a history of tracheoesophageal fistula or esophageal atresia surgery.

Multiplex RT-PCR Analysis

Respiratory viruses were identified using the multiplex real-time PCR (mPCR) assay (Rotor-Gene Q, QIAGEN, Germantown, Maryland, United States). This technique facilitates the detection of various pathogens, including IFV, hRSV, hCoV (Corana 229E, OC43, NL63, HKU1, SARS-COV2), hPIV, hMPV, hRV, EV, hBoV, hAdV, and human parechovirus. Additionally, bacterial pathogens including Mycoplasma pneumoniae, Bordetella pertussis, Chlamydophila pneumoniae, Haemophilus influenzae, and Streptococcus pneumoniae were also detected.

Statistical Analysis and Ethics

The Statistical Package for the Social Sciences (SPSS) 23.0 (Chicago, Illinois, USA) was implemented for the statistical analysis. The Kolmogorov-Smirnov test and the examination of histograms were used to evaluate the compliance of numerical and continuous variables with normal distribution. Numerical data with a normal distribution were expressed as the mean and standard deviation (SD), while data with a non-normal distribution were expressed as the median and interquartile range (IQR). Percentages (%) and numbers (n) were used to express categorical variables. The Mann-Whitney U test was used to compare continuous variables that did not meet the normal distribution. The Kruskal-Wallis test evaluated continuous variables from many groups that did not fit into the normal distribution. Categorical variables were analyzed with the Pearson chi-square or Fisher's Exact Test. When comparing more than one group, p values were calculated using the Bonferroni correction. The significance level was established at $p<0.050$.

RESULTS

Among 40.610 patients tested using mPCR, hMPV was detected in 371 individuals. Twenty-six patients presenting with non-respiratory symptoms were excluded, resulting in a final study population of 345 patients. The median age of the study group was 4 years (IQR: 3–7), with 59.4% being male. The median age was 3 years (IQR: 3–5) for hospitalized patients and 6 years (IQR: 4–8) for outpatients. A total of 50.1% of the cases occurred in 2022, and 68.7% of patients presented during the winter season (Figure 1).

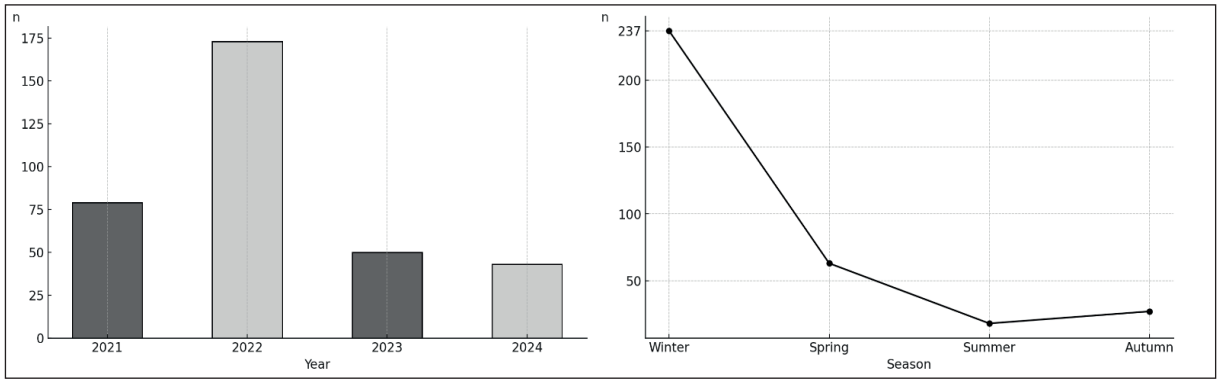

Figure 1: Distribution of metapneumovirus infections by years and seasons.

Table I: Demographic, laboratory, and chest x-ray findings in patients with and without chronic disease

	With Chronic Disease	Without Chronic Disease	Total	p
Number of patients (n)	82	263	345	-
Age*	5 (4-9)	4 (3-7)	4 (3-7)	<0.001
Gender† Male Female	 50(61) 32 (39)	 154 (58.8) 109 (41.2)	 205 (59.4) 140 (40.6)	0.899
Hospitalization† General pediatric unit Pediatric intensive care unit (PICU)	43 (52.4) 30 (69.7) 13 (30.3)	111 (42.4) 92 (88.9) 19 (11.1)	154 (44.6) 122 (55.4) 32 (20.6)	0.098
Respiratory support† Invasive mechanical ventilation Non-invasive mechanical ventilation High-flow nasal cannula (HFNC) Oxygen mask	 5 (11.6) 6 (14) 7 (16.3) 25 (58.1)	 6 (5.4) 8 (7.2) 18 (16.3) 79 (71.1)	 11 (7.2) 14 (9) 25 (16.2) 104 (67.6)	0.254
Length of hospital stay* General pediatric unit (days) Pediatric intensive care unit (PICU) (days) Total (days)	 7 (4-11) 4 (3-9) 8 (4-14)	 6 (4-10) 6 (3-9) 5 (1-9)	 6 (3-9.5) 4.5 (3-9) 7 (4-11)	 0.626 0.125 0.128
Laboratory parameters†	63 (76.8)	154 (58.6)	217 (62.9)	-
White blood cell (WBC) (×10⁶/L)*	8760 (5877-12150)	9655 (7217-12822)	9350(6870-12675)	0.361
Platelet count (PLT) (×10⁹/L)*	302 (228-398)	336 (279-472)	334 (260-444)	0.615
C-reactive protein (CRP) (mg/L)*	3.00 (1-14)	1.70 (1-5)	2 (1-6.5)	0.120
Absolute neutrophil count (ANC) (×10⁶/L)*	4340 (2615-6925)	4410 (2805-6752)	4410 (2755-6740)	0.157
Absolute lymphocyte count (ALC) (×10⁶/L)*	2750 (1380-3982)	3425 (2085-4952)	3160 (1920-4835)	0.161
Neutrophil-to-lymphocyte ratio (NLR)*	1.77 (0.97-3.79)	1.25 (0.69-3.75)	1.37 (0.74-3.70)	0.247
Alanine aminotransferase (ALT) (U/L)*	25 (18-36)	20 (15-27)	21 (15-28)	0.221
Aspartate aminotransferase (AST) (U/L)*	43 (31-56)	38 (32-51)	39 (32-51)	0.305
Lactate dehydrogenase (LDH) (U/L)*	349 (310-454)	352 (294-405)	350 (299-408)	0.142
Pulmonary infiltration† Present Absent	66 (80.5) 46 (69.7) 20 (30.3)	182 (69.2) 104 (57.1) 78 (42.9)	248 (71.9) 150 (60.4) 98 (39.6)	0.061

:** *median (IQR) (Mann-Whitney U test)* , **†:** *n(%) (Pearson chi-square),* ***White blood cell (WBC): *6600–15.600×10⁶/L,* ***Platelet count (PLT):*** *240–520 ×10⁹/L,* ***C-reactive protein (CRP):*** *<5 mg/L,* ***Absolute neutrophil count (ANC):*** *1500–8500 ×10⁶/L,* ***Absolute lymphocyte count (ALC):*** *1500–7000 ×10⁶/L,* ***Alanine aminotransferase (ALT):*** *0–41 U/L,* ***Aspartate aminotransferase (AST):*** *0–73 U/L, Lactate dehydrogenase (LDH): 0–470 U/L*

When evaluating the distribution of symptoms, 84.1% of patients (n=290) presented with cough, 65.8% (n=227) with fever, and 59.7% (n=206) with nasal discharge. Additionally, 45.5% (n=157) exhibited tachypnea, and 30.1% (n=104) showed decreased oxygen saturation (SpO_2). Overall, 44.6% of patients (n=155) were hospitalized, of whom 20.6% (n=32) required admission to the pediatric intensive care unit. At presentation, 3.2% (n=11) required IMV, 4.1% (n=14) required NIV, and 7.2% (n=25) received HFNC

support. The median total length of hospital stay was 7 days (IQR: 4–11). The median duration of stay in the general pediatric unit was 6 days (IQR: 3–9.5), while the median intensive care unit stay was 4.5 days (IQR: 3–9). Four patients died, one of whom had underlying neurological and neurometabolic disorders, while the remaining three had no chronic conditions.

According to imaging findings, 71.9% of patients (n=248) underwent chest radiography, among whom 60.4% (n=150) showed pulmonary infiltration; however, no complications such as lobar consolidation, pleural effusion, or pneumothorax were observed. Laboratory evaluations revealed a median white blood cell count of 9.350 ($\times 10^6$/L) (IQR: 6.870–12.675), a median platelet count of 334 ($\times 10^9$/L) (IQR: 260–444), a median CRP level of 2 mg/L (IQR: 1–6.5), and a median ALT level of 21 U/L (IQR: 15–28.75) (Table I).

Patients were categorized into two groups based on the presence of chronic diseases. The majority, 76.2% (n=263), had no history of chronic conditions, while 23.8% (n=82) had at least one chronic disease. Among those with chronic conditions, 31.7% (n=26) had neurological or neurometabolic disorders, 23.2% (n=19) had asthma or a history of wheezing in infancy, 22% (n=18) had immunodeficiency, 13.4% (n=11) had chronic lung disease, and 9.7% (n=8) had cardiac disease.

Among patients without chronic diseases, the median age of hospitalized individuals was significantly lower than that of outpatients (p<0.001). No significant association was observed between hospitalization and variables such as gender, fever, nasal discharge, or cough (p=0.998, p=0.671, p=0.393, p=0.123, respectively). However, hospitalization was significantly associated with the presence of tachypnea, low SpO_2, and pulmonary infiltration (p<0.001 for each). No statistically significant differences were found between the groups in terms of laboratory parameters.

Similarly, among patients with chronic diseases, the median age of hospitalized children was significantly lower than that of non-hospitalized patients (p<0.001). No statistically significant association was found between hospitalization and variables such as gender, fever, nasal discharge, or cough (p=0.899, p=0.129, p=0.206, p=0.863, respectively). However, hospitalization was significantly associated with tachypnea, low SpO_2, and pulmonary infiltration (p<0.001 for each).

Hospitalized patients comprised 55.1% (n=154) of the study group. When these patients were subdivided based on the presence of chronic diseases, it was found that younger children with chronic diseases had a higher hospitalization rate (p<0.001). No statistically significant differences were found between the two groups in terms of intensive care admission rates and length of stay (p=0.098, p=0.125, respectively). Additionally, no significant differences were observed between the groups concerning gender, fever, cough, nasal discharge, tachypnea and lung infiltration (p=0.922, p=0.531, p=0.470, p=0.086, p=0.179, p=0.061,respectively).

DISCUSSION

Despite being identified relatively recently, hMPV is generally regarded as a less severe pathogen compared to other viral agents responsible for lower respiratory tract infections (LRTIs) in children. Nevertheless, although often overshadowed by more prominent pathogens such as IFV and RSV, hMPV has been shown to cause serious clinical outcomes, including the need for intensive care and even death. This study analyzes four years of clinical data on hMPV infections from one of the largest children's hospitals in Türkiye, assessing recent epidemic risks and providing a comprehensive clinical evaluation of hMPV cases nationwide. The findings shed light on the current epidemiological landscape in Türkiye and offer guidance for evaluating global risks and developing management strategies for hMPV.

Studies conducted in various countries have reported that hMPV infections are more frequently observed in children under five years of age (4,6–8). A pediatric study involving patients under five indicated that hospitalizations were most common in those under one year of age (9), while another study reported this threshold as under three years (6,10). In the present study, the median age of all patients was four years, and that of hospitalized patients was three years, consistent with the literature. Moreover, hospitalization rates were found to increase as age decreased, regardless of the presence of chronic conditions. Globally, hMPV accounts for approximately 11% of LRTIs in children under five and 4–13% of hospitalizations due to LRTIs (6,11,12). Although hMPV can affect all pediatric age groups, it is particularly prevalent among children under five and may lead to hospitalization, necessitating careful surveillance. As with other viral respiratory pathogens, prevention and control strategies for hMPV should be developed and integrated into public health programs.

In human metapneumovirus, as with other viral respiratory pathogens, symptoms such as fever, cough, shortness of breath, nasal discharge, and hypoxia are commonly observed (13,14). Clinical presentation may range from mild fever and cough to severe bronchiolitis and pneumonia (6). Due to the similarity of symptoms, distinguishing hMPV infections from other respiratory infections has been reported to be challenging (15,16). Fever and cough are consistently described as the most common symptoms in the literature (16). Similarly, in the present study, these two symptoms were the most frequently observed. The absence of a significant association between fever, cough, nasal discharge, and either a history of chronic disease or hospitalization suggests that these symptoms alone are insufficient to predict disease severity. In contrast, the significant association between tachypnea, decreased SpO_2, and hospitalization highlights the importance of considering all clinical signs and findings collectively during patient evaluation.

In one study, infiltration was observed in 8% of patients with hMPV infection on chest radiographs, while a review reported

this rate as 26.4% (16,17). A study conducted in China found an infiltration rate of 75.2% (18). In the present study, this rate was 60.4%. Pulmonary infiltration was found to be significantly associated with hospitalization, regardless of the presence of chronic disease. The wide variation in reported rates may be attributed to methodological differences, including patient selection and imaging criteria. Nevertheless, the high rate observed in this cohort suggests that hMPV can be a serious pathogen affecting the lower respiratory tract. Moreover, the strong association between pulmonary infiltration and hospitalization indicates that radiographic findings may serve as a useful predictor of disease severity.

In the literature, reported rates of PICU admission among patients with hMPV infection vary considerably. For example, in one study involving 78 patients, 64.1% (n=50) were hospitalized, but only two required PICU care (19). In a U.S.-based cohort study, 6% (n=12) of 200 hMPV-positive patients were admitted to the PICU, and 4% (n=8) were intubated (10). In contrast, a study of 145 patients reported no PICU admissions (18), while another study reported a PICU admission rate of 11.4% (6). In the present cohort, 9.2% of patients (n=32) required pediatric intensive care, and 3.2% (n=11) underwent intubation. These findings indicate that severe clinical presentations can occur in children with hMPV infection. The PICU admission rate observed in this study was higher than in some previous reports, possibly due to differences in patient demographics, underlying disease profiles, access to healthcare services, and diagnostic or therapeutic approaches. Therefore, careful assessment of individual risk factors and early implementation of intervention strategies are critical in the management of pediatric hMPV cases. Notably, the intubation rate was similar to those reported in the literature, suggesting that the higher PICU admission rate may be attributable to an increased need for NIV rather than IMV. The potential role of NIV in reducing the need for IMV should also be considered.

In the present study, four patients died following hMPV infection, three of whom had no underlying chronic conditions. In the literature, mortality has typically been reported in the context of co-infections, secondary bacterial infections, or serious chronic illnesses (20). However, fatal cases involving isolated hMPV infection, as observed in this study, have rarely been reported. Although limited in number, these findings suggest that hMPV infection can, in some instances, lead to complications requiring intensive care and even result in death. This underscores the need for vigilant clinical monitoring and risk stratification, particularly given that severe outcomes may occur even in previously healthy children.

Various studies have reported that hMPV infections most commonly occur during the winter season (2,21). Consistently, in the present study, the highest number of cases was recorded during the winter months, followed by spring. Outbreaks associated with hMPV in children have been reported in Norway (2002–2003), Korea (2007), and Switzerland (2021) (1). Additionally, significant increases in case numbers were observed in China and several European countries in 2022; however, reported rates declined markedly in 2023 and 2024 (5,22,23). Although a rise in cases was noted in China towards the end of 2024, the World Health Organization did not classify this as an unusual outbreak or pandemic threat (23). In this Turkish cohort, the peak number of cases was observed in 2022, followed by a notable decline in 2023 and 2024. These findings suggest that no clinically significant epidemic occurred during the study period, and the seasonal distribution of cases was consistent with global trends.

This study has several limitations. First, due to its retrospective design and single-center setting, the findings may not be representative of the general population. In addition, infection control measures implemented during and after the SARS-CoV-2 pandemic may have influenced the observed prevalence of hMPV. Although some pathogens and co-infections were excluded using multiplex PCR, the absence of sputum culture data limited the ability to rule out secondary bacterial infections. Furthermore, conducting the study in the capital city may not fully reflect the socioeconomic disparities and inequalities in healthcare access present across the country, potentially limiting the generalizability of the findings to the broader Turkish population. Nevertheless, despite these limitations, this study—conducted in one of the largest pediatric centers in Türkiye and based on a large patient cohort—offers valuable insights into the clinical course and management of hMPV infections and supports the development of effective public health strategies.

CONCLUSION

In conclusion, hMPV is a common viral pathogen, particularly affecting children under five years of age. Clinical symptoms alone are insufficient to predict disease severity; however, SpO_2, tachypnea, and pulmonary infiltrations at presentation have been identified as significant risk factors for hospitalization. Although often perceived as a mild virus, the notable proportion of patients requiring intensive care, along with four reported deaths—three of which occurred in previously healthy children—suggests that hMPV can follow a severe and potentially fatal course. These findings underscore the importance of not underestimating hMPV as a respiratory pathogen and highlight the need for its inclusion in diagnostic, monitoring, and preventive health strategies. Despite recent concerns about epidemic risk, a decrease in case numbers compared to previous years was observed. Nonetheless, given that this decline may be temporary and viral circulation patterns can fluctuate over time, the continuation of effective surveillance and prevention strategies remains essential.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. This study was conducted in accordance

with the Declaration of Helsinki and received ethical approval from the Ethics Committee of Ankara Bilkent City Hospital (24.04.2024/141).

Contribution of the authors

Study conception and design: ***FK, MY, AOP*;** data collection: ***EK, AC, KC*;** analysis and interpretation of results: ***FK,MY*;** draft manuscript preparation: ***FK, KC*;** All authors reviewed the results and approved the final version of the article.

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The authors declare that there is no conflict of interest.

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Original Article

Cardiac involvement as a gateway to the diagnosis of inherited metabolic disorders: A 16-year pediatric experience from a tertiary metabolic center

Merve Yoldaş Çelik[1], Ebru Canda[1], Havva Yazıcı[1], Fehime Erdem Karapınar[1], Ayşe Yüksel Yanbolu[1], Zülal Ülger Tutar[2], Ertürk Levent[2], Sema Kalkan Uçar[1], Mahmut Çoker[1]

[1]Department of Pediatric Metabolism and Nutrition, Ege University, İzmir, Türkiye
[2]Department of Pediatric Cardiology, Ege University, İzmir, Türkiye

ABSTRACT

Objective: Cardiac involvement is a common but often underrecognized feature of inherited metabolic disorders (IMDs), particularly in pediatric populations. Early detection is crucial, since many IMDs have disease-specific treatments that can improve outcomes. This study aimed to evaluate the frequency and spectrum of inherited metabolic disorders among pediatric patients presenting with cardiomyopathy, and to emphasize the importance of early recognition for targeted management.

Material and Methods: We retrospectively analyzed the records of 71 pediatric patients referred to a tertiary metabolic center between 2004 and 2020 due to cardiomyopathy or other cardiac findings. Demographic, clinical, and diagnostic data were reviewed, with a focus on final diagnoses and metabolic etiology.

Results: The median age at presentation was 17 months (range, 15 days-17 years). Dilated cardiomyopathy was the most common phenotype (57.7%), followed by hypertrophic (21.1%) and non-compaction cardiomyopathy (15.4%). An inherited metabolic disorder was diagnosed in 12 patients (16.9%), most commonly Pompe disease, carnitine transporter deficiency, and very long-chain acyl-CoA dehydrogenase deficiency. Parental consanguinity was present in 50% of diagnosed cases. Despite therapy, four patients died due to cardiac failure.

Conclusion: Inherited metabolic disorders account for a substantial proportion of pediatric cardiomyopathy cases. Early metabolic screening should be considered in all children with cardiomyopathy, especially when suggestive features are present. Prompt diagnosis may allow for timely intervention, genetic counselling, and improved outcomes.

Keywords: Inherited metabolic disorders, cardiomyopathy, pompe disease, fatty acid oxidation defects, mitochondrial disorders

INTRODUCTION

Inherited metabolic disorders (IMDs) are a heterogeneous group of diseases caused by defects in biochemical pathways, most of which follow an autosomal recessive inheritance pattern. These disorders often present with multisystem involvement due to the accumulation of toxic metabolites or deficient energy production. The heart, being a metabolically active organ with high energy demands, is commonly affected in IMDs. Cardiac involvement may serve as an initial manifestation or may emerge during disease progression, significantly impacting prognosis (1).

Approximately 30% of pediatric cardiomyopathy cases are attributed to IMDs (2). The most common cardiac findings associated with metabolic disorders include hypertrophic, dilated, non-compaction, or restrictive cardiomyopathy, arrhythmias, conduction defects, valvular disease, and sudden cardiac death. The heart derives nearly 95% of its ATP from mitochondrial oxidative phosphorylation, and the remainder from glycolysis and the Krebs cycle. Thus, disruption of energy metabolism in IMDs can critically affect myocardial function (3, 4).

More than 200 metabolic disorders with cardiac involvement have been described to date, including fatty acid oxidation defects, glycogen storage diseases, lysosomal storage disorders, peroxisomal disorders, mitochondrial diseases, organic acidemias, aminoacidopathies, and congenital disorders of glycosylation (2, 5-7).

Correspondence Address:
Merve Yoldaş Çelik
e-mail: drmerveyoldas@yahoo.com

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The aim of this study was to retrospectively evaluate the frequency, clinical spectrum, and diagnostic yield of inherited metabolic disorders (IMDs) in pediatric patients presenting with cardiac findings who were referred to a tertiary metabolic center.

MATERIALS and METHODS

This retrospective study was conducted in the Division of Pediatric Nutrition and Metabolism, Department of Pediatrics, Ege University Faculty of Medicine. Medical records of pediatric patients referred between January 2004 and December 2020 for cardiac involvement suggestive of an IMD were reviewed. Inclusion criteria were: 1) presence of cardiomyopathy or arrhythmia identified by echocardiography or electrocardiography, and 2) referral for evaluation of a possible IMD. Patients with structural congenital heart disease or acquired causes of cardiomyopathy (e.g., viral myocarditis) were excluded.

For each patient, demographic data (age at presentation, sex), clinical findings, cardiac phenotype, and diagnostic work-up results were collected. Specific attention was paid to features associated with inherited conditions, including parental consanguinity, family history of sudden cardiac death or similarly affected siblings, and presence of multisystem involvement (e.g., developmental delay, hepatomegaly, hypotonia, dysmorphic features).

Cardiac evaluation included electrocardiogram (ECG) and transthoracic echocardiography (ECHO), both performed at the time of referral. Patients were classified into five categories based on cardiac phenotype: dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), non-compaction cardiomyopathy (LVNC), restrictive cardiomyopathy (RCM), or arrhythmia without structural abnormality.

All patients underwent metabolic screening according to clinical suspicion, including serum lactate, ammonia, creatine kinase, acylcarnitine profile, urine organic acids, and plasma amino acids. In selected patients, enzyme assays or molecular genetic testing (e.g., next-generation sequencing, targeted gene panels, or Sanger sequencing) were performed to confirm a metabolic diagnosis. For those who underwent genetic testing, diagnoses were established based on the identified variants in accordance with ACMG (American College of Medical Genetics and Genomics) criteria.

The primary outcome was the proportion of patients who received a definitive diagnosis of an IMD. Descriptive statistics were used to summarize the distribution of clinical and diagnostic characteristics across the study population. No formal hypothesis was performed due to the observational nature of the study.

Statistical Analysis

Data were analyzed using SPSS version 25 (IBM Corp., Armonk, NY, USA). Descriptive statistics were applied; continuous variables were expressed as median (range), and categorical variables as frequencies and percentages.

RESULTS

Seventy-one patients (36 males and 35 females) were included in the study. The age at presentation ranged from 15 days to 17 years, with a median of 17 months. Parental consanguinity was noted in 27 patients (38%), and 8 (11%) had a history of sibling death, often reported as sudden or unexplained.

Cardiac manifestations at presentation included dilated cardiomyopathy in 41 patients (57.7%), hypertrophic cardiomyopathy in 15 (21.1%), left ventricular non-compaction cardiomyopathy in 11 (15.4%), restrictive cardiomyopathy in 2 (2.8%), and arrhythmia without structural abnormalities in 2 (2.8%). The distribution of cardiac phenotypes observed in the study cohort is illustrated in Figure 1.

A confirmed diagnosis of an IMD was established in 12 patients (16.9%). Table I presents the demographic and clinical characteristics, cardiac phenotypes, specific diagnoses, administered treatments, and outcomes of these patients. Of the diagnosed cases, six (50%) had a history of parental consanguinity. Five patients with hypertrophic cardiomyopathy were diagnosed with infantile-onset Pompe disease. All five received enzyme replacement therapy with recombinant human acid α-glucosidase. Three patients died during follow-up. One patient with hypertrophic cardiomyopathy was diagnosed with very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency. Nutritional therapy including medium-chain triglyceride-enriched formula and feeding strategies to avoid catabolism was initiated. The patient died in early infancy. Four patients with dilated cardiomyopathy were diagnosed with carnitine transporter deficiency. Oral L-carnitine supplementation was

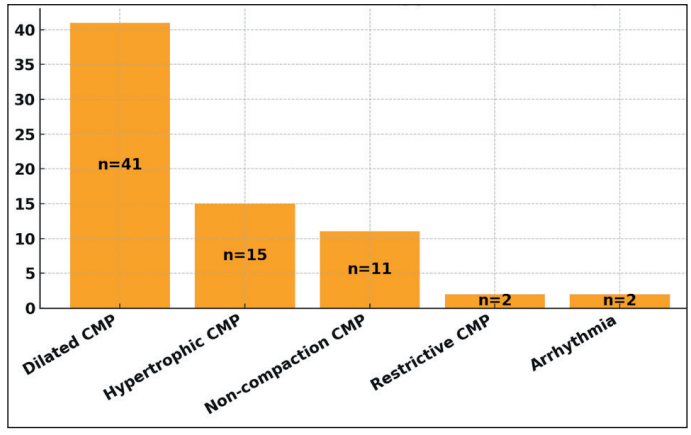

Figure 1: Distribution of cardiac phenotypes in the study cohort. CMP: cardiomyopathy

Table I: Patients diagnosed with inherited metabolic disorders presenting with cardiac involvement.

Number	Diagnosis	Gender	Consanguinity	History of Sibling Death	Age at diagnosis (months)	Cardiac Phenotype	Treatment	Outcome
1	Carnitine transporter deficiency	Female	No	No	24	Dilated cardiomyopathy	Oral L-carnitine	Alive
2	Carnitine transporter deficiency	Male	Yes	No	60	Dilated cardiomyopathy	Oral L-carnitine	Alive
3	Carnitine transporter deficiency	Male	No	No	72	Dilated cardiomyopathy	Oral L-carnitine	Alive
4	Carnitine transporter deficiency	Female	Yes	No	168	Dilated cardiomyopathy	Oral L-carnitine	Alive
5	Complex I deficiency	Female	No	Yes	10	Left ventricular non-compaction	MCS	Alive
6	Pompe disease	Female	No	No	2	Hypertrophic cardiomyopathy	ERT	Alive
7	Pompe disease	Male	No	No	3	Hypertrophic cardiomyopathy	ERT	Alive
8	Pompe disease	Female	No	No	3	Hypertrophic cardiomyopathy	ERT	Deceased
9	Pompe disease	Male	Yes	No	5	Hypertrophic cardiomyopathy	ERT	Deceased
10	Pompe disease	Female	Yes	No	7	Hypertrophic cardiomyopathy	ERT	Deceased
11	VLCAD deficiency	Female	Yes	Yes	1	Dilated cardiomyopathy	DM	Deceased
12	VLCAD deficiency	Male	Yes	Yes	3	Hypertrophic cardiomyopathy	DM	Deceased

MCS: *Mitochondrial cofactor supplementation,* ***ERT:*** *Enzyme replacement therapy,* ***VLCAD:*** *very long-chain acyl-CoA dehydrogenase,* ***DM:*** *Dietary management (MCT (medium-chain triglyceride), fasting avoidance)*

administered. Clinical follow-up indicated stable cardiac status without progression to heart failure. One patient with dilated cardiomyopathy was diagnosed with VLCAD deficiency. Nutritional management was initiated. The patient died in early infancy. One patient with left ventricular non-compaction cardiomyopathy was diagnosed with mitochondrial complex I deficiency. Supportive therapy with cofactor supplementation (carnitine, coenzyme Q10, riboflavin) was provided. Cardiac function remained unchanged during follow-up.

The median age at diagnosis among patients with confirmed IMDs was 6 months (range, 1 month-14 years). Pompe disease was diagnosed at a mean age of 4 months, and carnitine transporter deficiency at a mean age of 6.7 years. In total, five patients (three with Pompe disease and two with VLCAD deficiency) died during the follow-up period.

Fifty-nine patients (83%) remained without a confirmed metabolic diagnosis despite metabolic investigations. Earlier diagnosis was more frequently observed in cases presenting with early-onset cardiomyopathy and multisystem involvement.

DISCUSSION

Cardiac involvement is a well-recognized yet frequently underdiagnosed manifestation of IMDs, especially in pediatric populations. The myocardium's high energy requirements make it particularly vulnerable to metabolic derangements, including mitochondrial dysfunction, impaired fatty acid oxidation, and toxic substrate accumulation (8). Cardiomyopathy may be the initial or even sole presenting feature in some IMDs, early recognition of a metabolic etiology is critical (9). Timely diagnosis not only enables disease-specific interventions that may improve cardiac outcomes but also allows for family counseling and screening (2).

IMDs represent an essential and often overlooked cause of pediatric cardiomyopathies. In our cohort, 16.9% of patients presenting with cardiac findings were ultimately diagnosed with an IMD. This prevalence is comparable to rates reported in previous studies, such as 8.7% in the Pediatric Cardiomyopathy Registry (n=855 with hypertrophic cardiomyopathy) and 22.4% in the cohort reported by Bonnet et al. (n=58) (10,11).

In contrast to previous studies focusing predominantly on hypertrophic cardiomyopathy, the most common phenotype in our cohort was dilated cardiomyopathy (57.7%), followed by hypertrophic and left ventricular non-compaction types. However, among the IMD-positive cases, hypertrophic cardiomyopathy was more frequent, largely due to infantile-onset Pompe disease. This reinforces prior observations that specific metabolic disorders preferentially affect certain myocardial patterns (12, 13).

Pompe disease accounted for five out of twelve IMD diagnoses in our study. All cases manifested as early-onset hypertrophic cardiomyopathy and were treated with enzyme replacement therapy. Despite intervention, three patients died, underscoring the aggressive disease course and the limited reversibility of advanced cardiac involvement. These outcomes align with international data suggesting that prognosis in classic infantile Pompe disease is closely tied to the timing of diagnosis and treatment initiation (12, 14).

Carnitine transporter deficiency was exclusively seen in patients with dilated cardiomyopathy in our cohort. All affected individuals responded positively to L-carnitine therapy, with stabilization of cardiac function and no heart failure progression. These findings are consistent with previous reports highlighting the treatable nature of this disorder and the potential for complete reversal of cardiac symptoms when diagnosed early (15, 16).

Conversely, VLCAD deficiency was associated with a fulminant disease course in both affected patients, despite the initiation of dietary management protocols that included medium-chain triglyceride enriched formulas and avoidance of fasting. The poor outcomes highlight the high mortality risk associated with the neonatal-onset phenotype, which is known to present with early cardiac decompensation, arrhythmias, and hepatomegaly. In such cases, the window for therapeutic intervention is often narrow, and even with appropriate nutritional support, cardiomyopathy may progress rapidly to intractable heart failure (17, 18). These findings underscore the need for prenatal or newborn screening strategies in high-risk populations, especially where consanguinity is common.

Similarly, the patient with mitochondrial complex I deficiency presenting with LVNC cardiomyopathy exhibited only a modest clinical response to mitochondrial cofactor therapy, including carnitine, riboflavin, and coenzyme Q10. While such supportive regimens are widely used in clinical practice, evidence for their efficacy remains limited, particularly in cases with significant myocardial structural abnormalities. LVNC is increasingly recognized in mitochondrial disorders, likely reflecting the underlying disruption in myocardial development due to impaired oxidative phosphorylation. Given the multisystemic and progressive nature of mitochondrial diseases, early diagnosis and prognostication remain challenging, and cardiac involvement is often a significant determinant of survival (19-21).

Despite a thorough workup, 83% of patients remained undiagnosed, which reflects both the limitations of current diagnostic methods and the possibility of unrecognized or ultra-rare disorders. This highlights the potential future role of advanced tools such as whole-exome or genome sequencing in uncovering hidden etiologies.

It is important to note that the relatively high proportion of IMD diagnoses in our cohort may reflect a referral bias. Our study population consisted exclusively of patients referred to the metabolic clinic due to cardiomyopathy or unexplained cardiac findings. As such, these children represent a preselected group with an increased likelihood of having an underlying metabolic etiology. Therefore, while our findings underscore the diagnostic importance of metabolic evaluation, the reported prevalence rates should not be directly extrapolated to the general pediatric cardiomyopathy population.

Taken together, our findings support the integration of metabolic screening into the routine evaluation of pediatric cardiomyopathy. In cases with suggestive features, such as consanguinity, early-onset symptoms, or multisystem involvement, metabolic causes should be actively investigated, as early diagnosis can lead to targeted and potentially life-saving interventions. A collaborative approach between pediatric cardiologists and metabolic specialists is essential to ensure timely diagnosis, personalized treatment, and improved long-term outcomes.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ege University (02.01.2023, reference number: 22-12.2T/34).

Contribution of the authors

M.Y.Ç and ***S.K.U***; data collection: ***M.Y.Ç, E.C., H.Y., F.E.K., A.Y.Y., Z.Ü.T., R.E.L, S.K.U, M.Ç.***; analysis and interpretation of results: ***M.Y.Ç***; draft manuscript preparation: ***M.Y.Ç*** and ***S.K.U*** All authors reviewed the results and approved the final version of the article.

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Original Article

From bedside to revisit: identifying risk factors for outpatient revisits following pediatric viral lower respiratory tract infections – insights from hospitalized cases of RSV, HBoV and influenza

Kaan Çelebier[1], Metin Yiğit[1,2]

[1]Department of Pediatrics, Ankara Bilkent City Hospital, Ankara, Türkiye
[2]Department of Pediatrics, Yildirim Beyazit University, Ankara, Türkiye

ABSTRACT

Objective: Acute lower respiratory tract infections (ALRTIs) are among the leading causes of hospitalization, particularly in children under five years of age. A substantial proportion of children discharged after hospitalization for viral ALRTIs experience recurrent respiratory tract infections; however, the clinical predictors of these recurrences have not yet been fully defined. This study aimed to investigate the relationship between recurrent hospital visits due to respiratory tract infections within one year post-discharge and various clinical and demographic factors in pediatric patients hospitalized with ALRTIs caused by respiratory syncytial virus (RSV), human bocavirus (HBoV), or influenza viruses (IFV).

Material and Methods: This retrospective observational study included pediatric patients hospitalized due to RSV, HBoV, or IFV infections between January and December 2023. Demographic characteristics, clinical presentation, hospitalization details, and post-discharge follow-up data were evaluated. Recurrent hospital visits related to respiratory tract infections within one year of discharge were analyzed.

Results: A total of 519 patients were evaluated. Recurrent hospital visits due to respiratory tract infections were identified in 216 patients (41.6%) during the follow-up period. Younger age ($p = 0.028$) and the presence of chronic illness ($p = 0.011$) were found to be significant risk factors for these repeat visits. No significant association was observed between recurrent visit frequency and variables such as sex, identified viral pathogen, laboratory parameters, or radiological findings.

Conclusion: Younger age and comorbid chronic illnesses were identified as important risk factors for recurrent hospital visits following viral ALRTIs. These findings highlight the need for more structured and targeted follow-up strategies in pediatric patients at higher risk after hospital discharge.

Keywords: Human bocavirus, influenza virus, respiratory syncytial virus

INTRODUCTION

Acute lower respiratory tract infections (ALRTIs) rank among the leading causes of morbidity and mortality in children under five years of age, particularly in low-income countries (1,2). Approximately 30–50% of children hospitalized with viral ALRTIs are reported to develop recurrent respiratory tract infections (3). Therefore, identifying clinical markers to predict which children are at high risk of recurrence following hospitalization is of critical importance (4). However, despite its clinical relevance, there is limited evidence to accurately predict which children will experience bronchiolitis recurrence or require further medical care after discharge (5).

Viral ALRTIs in childhood have been associated with recurrent respiratory tract infections and episodes of wheezing (6). However, whether the infectious etiology of ALRTIs influences short-term clinical outcomes, such as post-hospitalization recurrence, remains unclear (5). Human bocavirus (HBoV), respiratory syncytial virus (RSV), and influenza viruses (IFV) have been shown to cause clinical conditions that require hospitalization in pediatric patients (7-9). In contrast, other respiratory viruses, such as metapneumovirus, rhinovirus, and parainfluenza viruses, are generally associated with milder clinical courses that do not require hospitalization and are suitable for outpatient management (10-12). Previous studies have primarily focused on the relationship between early RSV

Correspondence Address:
Kaan Çelebier
e-mail: drkaancelebier@gmail.com

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infections and the risk of recurrent hospital visits, as well as the development of asthma and allergic diseases (13). In recent years, with the availability of more sensitive molecular diagnostic methods, other common viral pathogens such as HBoV and IFV, which can lead to more severe clinical presentations, have also begun to receive attention in research studies (14).

Recurrent hospital visits are known to impose a significant burden on healthcare systems (15). In pediatric populations, the presence of chronic illnesses and various sociodemographic factors contribute to this increased risk. The aim of this study was to identify clinical predictors of recurrent hospital visits during the post-discharge period and to develop appropriate preventive strategies accordingly. The findings were intended to strengthen follow-up care for discharged children, facilitate timely interventions when necessary, and help reduce the frequency of readmissions.

MATERIALS and METHODS

The study population consisted of patients hospitalized in the Departments of Pediatrics and Pediatric Infectious Diseases at Ankara Bilkent City Hospital Children Hospital between January and December 2023. Since RSV, HBoV, and IFV infections frequently require hospitalization in pediatric patients, only those admitted with acute lower respiratory tract infections (ALRTIs) in whom a respiratory viral panel identified a single viral pathogen—RSV, HBoV, or IFV—were included in the study. Multiplex real-time PCR testing (Rotor-Gene Q, QIAGEN, Germantown, Maryland, USA) was used to detect respiratory viruses from samples obtained during hospitalization. Patients were categorized according to the identified viral pathogen. Those with multiple viral pathogens, admissions outside the specified study period, hospitalizations unrelated to ALRTIs, absence of RSV, HBoV, or IFV detection on viral panels, or incomplete clinical data were excluded.

The hospitalization courses of the patients and their recurrent hospital visits within one year post-discharge were retrospectively analyzed. All visits to the pediatric emergency department and pediatric outpatient clinics within one year after discharge due to newly developed complaints were considered hospital visits. Presenting complaints and their characteristics were determined by reviewing the examination notes available in the hospital's electronic medical records. Only visits in which the primary presenting complaint involved any respiratory symptom or sign (e.g., cough, nasal/chest congestion, wheezing, respiratory distress, or hypoxemia) were classified as respiratory tract infection–related hospital visits. Follow-up visits conducted to assess clinical recovery after the same hospitalization episode were excluded from the analysis.

The patients' demographic characteristics (age, sex), presence of chronic illness, gestational age (preterm/term), date and season of hospitalization, presenting complaints, presence of tachypnea on initial physical examination, oxygen saturation levels, presence of hypoxia, chest radiograph findings, and laboratory data were recorded. Patients with an oxygen saturation level below 92% were classified as hypoxic. Laboratory assessments included liver transaminase levels, blood gas analyses (pH, pCO_2, HCO_3, lactate), complete blood counts (white blood cell, neutrophil, lymphocyte, and platelet counts), procalcitonin, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels. In patients for whom sputum or blood cultures were obtained, the corresponding culture results were also reviewed.

Data regarding the clinical unit of admission, length of hospital stay, administration of respiratory support or inhaled therapy, and, where applicable, the specific type of respiratory support provided were retrospectively recorded. Based on all these variables, the relationship between the identified viral pathogen group and hospital visits occurring within one year after discharge was evaluated.

Statistical analysis

Data entry and analysis were performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics 25, IBM Corporation). The normality of numerical variables was assessed using the Shapiro–Wilk test. Descriptive statistics for parametric variables were reported as mean and standard deviation, whereas non-parametric variables were expressed as median values (minimum–maximum). Categorical variables were summarized as frequency and percentages. Group comparisons for categorical variables were performed using the chi-square test. For numerical variables, the independent samples t-test was applied when assumptions for parametric analysis were met; otherwise, the Mann–Whitney U test was used. A p-value ≤ 0.050 was considered statistically significant.

RESULTS

Respiratory tract infections are among the leading causes of hospital visits, particularly in childhood. In this study, pediatric patients hospitalized due to RSV, HBoV, and IFV infections—given their potential to cause severe clinical conditions requiring hospitalization—were followed for one year after discharge to evaluate recurrent respiratory tract infection–related hospital visits. Additionally, clinical and demographic factors potentially associated with these visits were assessed.

Data from a total of 519 patients were analyzed. Of these, 338 (65.1%) were male and 181 (34.9%) were female. The median age for the entire cohort was 3 years (IQR; 1–6). Based on the viral pathogens identified at the initial hospitalization, 98 patients (18.9%) were hospitalized due to RSV, 209 patients (40.2%) due to HBoV, and 212 patients (40.9%) due to IFV. Within one year post-discharge, 376 patients (72.4%) had at least one healthcare visit, 216 of which were attributed to respiratory tract infections. The median number of visits for these patients was

Table I: Sociodemographic and descriptive characteristics of the patients

Descriptive characteristic	Total	RSV	HBoV	IFV
Number of patients*	519	98 (18.9)	209 (40.2)	212 (40.9)
Gender*				
Male	338 (65.1)	70 (71.4)	144 (68.9)	124 (58.5)
Female	181(34.9)	28 (28.6)	65 (31.1)	88 (41.5)
Recurrent outpatient visit*				
Yes	376 (72.4)	67 68.3)	160 (76.5)	149 (70.2)
No	143 (27.6)	31 (31.7)	49 (23.5)	63 (29.8)
Recurrent RTI visit*				
Yes	216 (41.6)	45 (45.9)	96 (45.9)	75 (35.3)
No	303 (58.4)	53 (54.1)	113 (54.1)	137 (64.7)
Recurrent non-RTI visit*				
Yes	267 (51.4)	40 (40.8)	111 (53.1)	116 (54.7)
No	252 (48.6)	58 (59.2)	98 (46.9)	96 (45.3)
Number of recurrent RTI visit†	2 (1-3)	2 (1-3)	2 (1-3)	1 (1-3)
Number of recurrent non-RTI visit†	2 (1-2)	1 (1-2)	2 (1-2)	2 (1-2)
Age†	3 (1-6)	1 (1-2)	2 (1-4)	5 (2-8)

:** *n (%),* **†:** *median (Q_1-Q_3),* ***RTI: *Respiratory tract infection*

Table II: Laboratory parameters of patients during hospitalization

Laboratory Parameter	n	Value*
AST (U/L) 0-46	507	39 (30-57)
ALT (U/L) 0-32	507	23 (17-35)
LDH (U/L) 0-337	459	337 (293-396)
PH 7.35-7.45	381	7.43 (7.39-7.46)
PCO_2 (mmHg) 35-45	381	32.9 (28 .80-37.20)
HCO_3 (mEq/L) 22-25	381	21.4 (19.30-23.30)
Lactate (mmol/L)	381	1.95 (1.40-2 .69)
CRP (mg/L) 0-5	505	8.81 (2.98-23.30)
WBC x 10^9/L 5.4-13.8	505	8.39 (5.245-11.655)
ANC x 10^9/L 1.5-8.5	505	4.18 (2.140-6.955)
ALC x 10^9/L 2.2-8.5	505	2.39 (1.345-4.080)
PLT (/µL) 200-460	505	268.5 (221.000-405.750)

:** *median (Q_1-Q_3),* ***AST: *Aspartate Aminotransferase,* ***ALT:*** *Alanine Aminotransferase,* ***LDH:*** *Lactate Dehydrogenase,* ***CRP:*** *C-Reaktif Protein,* ***WBC:*** *White Blood Cell,* ***ANC:*** *Absolute Neutrophil,* ***ALC:*** *Absolute Lymphocyte,* ***PLT:*** *Platelet*

2 (IQR; 1–3). Additionally, 135 patients presented to healthcare facilities for both respiratory and non-respiratory reasons during the same period. The sociodemographic and descriptive characteristics of the study cohort are presented in Table I.

In the subgroup of patients who exhibited recurrent clinic visits, a comparison of the median ages of those with and without respiratory infections revealed that those experiencing respiratory infections were younger. Specifically, the median age of patients with respiratory infection was 3.42 years, compared to 4.68 years for those not suffering from such an infection, and this difference was found to be statistically significant (p = 0.028). Similarly, the relationship between presenting complaints at the initial hospitalization and subsequent recurrent visits was analyzed. Patients presenting with cough had a significantly higher rate of recurrent visits for respiratory infections (75.8 vs. 62.7; p<0.001). However, no significant association was found for fever (64.7 vs. 62.5; p=0.189) or sore throat (25.9 vs. 22.6; p=0.544). The season of initial hospitalization was not significantly associated with the need for recurrent visits (winter to autumn; 59.3, 20.8, 6.9 vs. 13.0; p= 0.112). Additionally, patient gender was not found to influence the frequency of such visits (p=0.476).

The relationship between the viral pathogens identified during hospitalization and the need for recurrent hospital visits due to respiratory tract infections was evaluated. No statistically significant difference was found among the RSV, HBoV, and IFV groups regarding the likelihood of recurrent hospital visits for respiratory tract infections (p=0.362). In contrast, a significant association was observed between the presence of chronic illness and an increased risk of recurrent visits due to respiratory tract infections (65.00 vs. 35.00; p=0.011).

No significant association was found between the presence of hypoxia during hospitalization (46.3 vs. 40.3; p=0.623) or the need for oxygen therapy via mask (58.3 vs. 47.8; p=0.217), high-flow nasal cannula oxygenation (HFNC) (25.5 vs. 26.2; p=0.478), non-invasive mechanical ventilation (NIV) (17.7 vs 18.9; p=0.474), or invasive mechanical ventilation (IMV) (p=0.238) and recurrent outpatient visits due to respiratory tract infections after discharge. Similarly, the presence of infiltrates on chest radiographs obtained during hospitalization was not associated with an increased risk of recurrent visits (71.2 vs. 67.4; p=0.610). However, when evaluated according to the site of hospitalization, patients admitted to general wards were found to have significantly higher rates of recurrent visits due to respiratory tract infections compared to those monitored in the intensive care unit (79.9 vs. 20.1; p<0.001).

The laboratory values of the entire patient group are presented

in Table II. Comparative analysis of the laboratory parameters between patients who revisit to the hospital and those who did not demonstrated no statistically significant differences ($p > 0.05$ for all comparisons).

DISCUSSION

Acute viral lower respiratory tract infections (ALRTIs) are typically self-limiting illnesses that often resolve with supportive care at home. However, a considerable number of pediatric patients require hospitalization for observation and supportive treatment (16). Approximately 30–50% of children hospitalized due to viral ALRTIs are at increased risk for recurrent respiratory illnesses (14,3). Therefore, identifying clinical parameters that can help stratify high-risk subgroups following viral ALRTIs is of substantial clinical importance (4). In this study, recurrent hospital visits due to respiratory tract infections within one year after discharge were evaluated in children hospitalized with respiratory infections caused by RSV, HBoV, and IFV. The primary aim was to investigate potential associations between these recurrent visits and factors such as patient age, sex, presence of chronic illness, hospitalization characteristics, and the identified viral pathogens.

Viral ALRTIs are among the leading causes of morbidity, mortality, and hospitalizations, particularly in younger children (2,17). Approximately 30–40% of children who experience these infections during the preschool period may develop recurrent episodes (18). Similar studies have reported that viral pathogens are most frequently identified in children under the age of four (19). The median age findings in our study are consistent with these results. Furthermore, it was demonstrated that younger children have a higher likelihood of recurrent hospital visits due to respiratory tract infections following hospitalization for ALRTIs (20). Our findings support these observations, as the rate of recurrent hospital visits due to respiratory tract infections was found to be higher in younger children. This may be related to the fact that children under the age of five—particularly those under two years—are at greater risk for ALRTIs and associated complications (21). Therefore, the risk of recurrent infections should be carefully considered during post-discharge follow-up of younger children.

A review of the literature reveals no consensus regarding the impact of viral pathogens identified in ALRTIs on long-term respiratory problems and recurrent hospital visits after discharge. In one study, RSV and non-RSV viruses were analyzed as separate groups, and it was reported that non-RSV viruses were associated with a higher risk of recurrent respiratory illnesses following infection (22). In a multicenter cohort study conducted in the United States, it was reported that in ALRTIs caused by a single viral pathogen without co-infections, the specific viral agent identified had no significant impact on recurrent hospital visits after discharge (5). The same study reported that RSV–rhinovirus co-infections were associated with increased rates of recurrent respiratory tract infection–related hospital visits. In another study, among infections caused by various viral pathogens such as RSV, HBoV, rhinovirus, metapneumovirus, IFV, and parainfluenza viruses, patients with rhinovirus infections demonstrated higher rates of recurrent respiratory tract infection visits during one-year follow-up (14). Similarly, another study reported that IFV infections were associated with higher rates of recurrent hospital visits compared to other viral agents (20). In our study, however, no significant differences were observed in the rates of recurrent respiratory tract infection–related hospital visits within one year post-discharge among the three patient groups classified according to RSV, HBoV, and IFV identified at the time of hospitalization. The literature suggests that geographical factors may influence clinical outcomes during the course of illness as well as the need for recurrent hospital visits in the post-recovery period, potentially leading to regional differences (17,15). The discrepancies between previous studies and our findings may be attributed not only to differences in patient populations but also to geographical variations among the countries and regions where the studies were conducted.

Previous studies have reported that blood gas analysis, complete blood count, and CRP results obtained during hospitalization for ALRTIs in children are associated with disease severity, the need for oxygen therapy, intensive care unit admission, and prolonged hospitalization. One study demonstrated that leukocytosis on complete blood count, elevated CRP levels, acidosis on blood gas analysis, and increased pCO_2 values were associated with intubation and intensive care unit admission (19). Another study demonstrated that elevated lactate levels were associated with prolonged hospitalization, increased disease severity, and the need for intubation (23). Although these studies identified significant associations between laboratory findings and disease severity, prolonged hospitalization, and increased need for respiratory support, their relationship with recurrent hospital visits due to respiratory tract infections after discharge was not evaluated. In our study, this issue was investigated, and it was observed that the likelihood of recurrent hospital visits could develop independently of disease severity and laboratory parameters. This finding suggests that all patients, regardless of clinical severity, should be assessed at discharge for the potential risk of recurrent visits, and appropriate follow-up planning should be implemented.

Although the majority of children with viral ALRTIs recover without serious complications after discharge, some experience clinical relapses leading to unplanned healthcare visits and rehospitalizations. The literature reports that comorbid chronic illnesses increase the likelihood of infection recurrence and the need for repeated healthcare visits following viral ALRTIs (5,24). Similarly, in our study, children with chronic illnesses were found to have a higher rate of recurrent hospital visits due to respiratory

tract infections within one year after discharge compared to otherwise healthy children. Therefore, in the follow-up of high-risk patient groups with chronic illnesses, the increased risk of infection should be considered, and this awareness should be integrated into the planning of preventive strategies.

Rehospitalization after discharge is relatively common among patients hospitalized with ALRTIs (25). Although this issue has been extensively investigated in adult patient populations, studies focusing on pediatric age groups remain limited (20). Although no clear consensus exists, recurrent hospital visits and readmissions have generally been reported to occur in the presence of chronic illnesses or following intensive care unit admissions due to severe acute illness (26). However, these studies have primarily focused on recurrent hospitalizations. In contrast, our study demonstrated that patients monitored in general wards had a significantly higher rate of hospital visits due to respiratory tract infections in the post-discharge period. This finding suggests that pediatric patients followed in general wards should also be closely monitored for recurrent respiratory tract infections.

Limitations

In this observational study, the one-year follow-up period after hospital discharge was evaluated. Therefore, treatment and follow-up practices may have varied among patients, and long-term outcomes may not have been fully captured. The study was single-center and retrospective in nature. Factors such as climate changes, variations in public awareness, public health programs, and infection prevention measures implemented during and after the SARS-CoV-2 pandemic may have influenced the seasonal distribution of viral pathogens. Furthermore, the absence of a universally accepted definition for bronchiolitis and ALRTIs may have led to inter-physician variability in clinical diagnoses (27,28). Moreover, although the study center is a tertiary care institution, patients may have sought medical care at different healthcare facilities within one year after discharge.

CONCLUSION

This study evaluated recurrent hospital visits due to respiratory tract infections within one year after discharge in pediatric patients hospitalized with ALRTIs caused by RSV, HBoV, and IFV. The findings demonstrated that such visits occurred more frequently in younger children and in those with comorbid chronic illnesses. No significant association was found between the frequency of recurrent visits and the type of viral pathogen or other clinical parameters. These results highlight the need for a more cautious and structured approach to post-discharge follow-up in children at increased risk.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (04.06.2025, reference number: 25-1341).

Contribution of the authors

Study conception and design: ***KC, MY,*** Data collection: ***KC***, Analysis and interpretation of results: ***KC, MY***, Draft manuscript preparation: ***KC, MY***

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Do hematologic parameters predict coronary artery involvement in children with Kawasaki disease? A retrospective study

Merve Küçükoğlu Keser[1], İlkay Erdoğan[2], Esra Baskın[3]

[1]Department of Pediatrics, Ankara Bilkent City Hospital, Ankara, Türkiye
[2]Department of Pediatric Cardiology, Baskent University, Ankara, Türkiye
[3]Department of Pediatric Rheumatology, Baskent University, Ankara, Türkiye

ABSTRACT

Objective: Kawasaki disease (KD) is an acute systemic vasculitis of childhood that may lead to coronary artery involvement (CAI) if not promptly treated. Early identification of laboratory predictors for coronary complications is essential. This study aimed to identify early laboratory predictors of coronary complications in KD, to help clinicians assess risk during the acute phase.

Material and Methods: We retrospectively analyzed 38 pediatric KD patients. Clinical and laboratory data—including hemoglobin (Hb), hematocrit (Htc), white blood cell count (WBC), platelet counts (PLT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), liver enzymes, and Harada scores—were collected and compared between patients with and without CAI. Receiver operating characteristic (ROC) and logistic regression analyses were performed.

Results: The mean age was 35.0±32.6 months, with 65.8% male. CAI was observed in 16 of 38 patients (42.1%). No statistically significant differences were found in the laboratory values at diagnosis between patients with and without CAI.

Conclusion: Routine hematological and inflammatory markers at admission were not predictive of CAI in KD. These findings highlight the need for high clinical suspicion in incomplete cases and suggest that incorporating clinical features and risk scores may improve early risk stratification.

Keywords: Blood cell count, coronary aneurysm, C-reactive protein, Kawasaki disease

INTRODUCTION

Kawasaki disease (KD) is an acute, self-limited vasculitis predominantly affecting children under five years of age (1, 2). It is now the leading cause of acquired heart disease in children in developed countries (3, 4). KD is characterized by fever plus a constellation of clinical signs and has a marked predilection for the coronary arteries (5). Although the exact cause remains unknown, an exaggerated immune response to an infectious trigger in genetically susceptible hosts is thought to underlie its pathogenesis (6). Timely administration of intravenous immunoglobulin (IVIG) within the acute phase dramatically reduces the risk of coronary artery aneurysms (CAA) from an estimated 20–25% in untreated cases to around 2–4% in those treated with IVIG (7, 8).

Despite appropriate therapy, a subset of children still develop coronary artery involvement (CAI). Incomplete presentations of KD, characterized by fewer diagnostic criteria, are prone to diagnostic delays and have been associated with a higher risk of CAI (9). Laboratory features of acute KD such as elevated CRP and ESR, leukocytosis, mild anemia and hypoalbuminemia reflect intense systemic inflammation but their predictive value for coronary outcomes remains unclear (10-12).

Given this uncertainty, we conducted a retrospective study of children with KD to evaluate whether baseline hematological parameters are associated with CAI. We also examined the impact of incomplete clinical presentation on coronary risk. Our aim was to identify any early laboratory predictors of coronary complications in KD, which could help guide clinicians in risk stratification during the acute phase.

MATERIALS and METHODS

This study was a retrospective observational analysis conducted at a Baskent University Ankara Hospital. We reviewed the medical records of children diagnosed with KD between 2003 and 2017. The diagnosis of complete KD was established based on the American Heart Association (AHA) criteria, which require fever for at least five days together with at least four of the five principal clinical features of KD. In cases of

Correspondence Address:
Merve Küçükoğlu Keser
e-mail: mervekucukoglukeser@gmail.com

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suspected incomplete KD, patients presented with prolonged fever and fewer than four of the principal clinical features, and the diagnosis was supported by compatible laboratory findings or echocardiographic evidence of KD in the absence of an alternative explanation (13, 14). Patients were categorized as having complete KD or incomplete KD according to these definitions. We excluded patients with known congenital heart disease or other systemic inflammatory conditions that could confound the assessment.

For each patient, we recorded demographic information and clinical presentation (complete vs. incomplete KD). Laboratory data were collected from the initial evaluation at the time of diagnosis. The parameters of interest included hemoglobin (Hb, g/dL), hematocrit (Hct, %), white blood cell count (WBC, per mm^3), and platelet count (PLT, per mm^3) at baseline, as well as in the 1st, 2nd, and 3rd weeks, and at the 1st and 2nd months of follow-up. Inflammatory markers included CRP, time to CRP normalization (days), ESR, and time to ESR normalization (days). In addition, biochemical markers such as aspartate aminotransferase (AST, U/L), alanine aminotransferase (ALT, U/L), gamma-glutamyl transferase (GGT, U/L), and serum albumin (Alb, g/dL) were assessed. Anemia was defined according to age-specific reference ranges of Hb.

Transthoracic echocardiography was performed for all patients at diagnosis (baseline) and repeated during follow-up at approximately 1 month, 2 months, and 6 months after disease onset. The coronary arteries (including the left main, left anterior descending, left circumflex, and right coronary arteries) were imaged, and their internal diameters were measured. Coronary artery Z-scores were calculated using body surface area–adjusted models. CAI was defined and classified based on Z-score criteria: normal if Z-score < 2.0, dilatation (ectasia) if Z-score ≥ 2.0 and < 2.5, small aneurysm if Z-score 2.5–5.0, medium aneurysm if Z-score 5.0–10 (and absolute diameter < 8 mm), and giant aneurysm if Z-score ≥ 10 (or absolute diameter ≥ 8 mm) (15). In our analysis, we grouped coronary outcomes into a binary variable indicating the presence versus absence of any CAI.

We calculated the Harada score for patients who presented within the first 9 days of illness. The Harada scoring system is a clinical tool developed to identify KD patients at higher risk for coronary artery complications, originally described in a Japanese cohort (16). It assigns one point for each of the following risk factors present early in the disease course: (1) age < 12 months, (2) male sex, (3) fever duration ≥ 8 days, (4) PLT count ≥ 350.000/mm^3 at presentation, (5) CRP ≥ 3 mg/dL, (6) ESR ≥ 40 mm/h, (7) WBC count ≥ 12,000/mm^3, and (8) Htc ≤ 35%. A total score ≥ 4 has been used as a threshold to predict increased risk of CAI. In our study, we applied the Harada score only to those patients who were diagnosed and treated within day 9 of illness, in line with its intended use for early risk stratification.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Shapiro-Wilk test. Data were presented as mean and standard deviation (SD) or as median with interquartile range (IQR), as appropriate. Categorical variables were summarized as counts and percentages. Group comparisons between patients with and without CAI were conducted using the independent samples t-test. To evaluate potential predictors of CAI, univariate logistic regression analyses were performed for key laboratory variables, including Hb, Htc, WBC count, PLT counts across different timepoints, CRP, ESR, liver function tests (AST, ALT, GGT, Alb) levels. Odds ratios (ORs) with 95% confidence intervals (CIs) and corresponding p-values were reported. ROC curve analyses were conducted to assess the diagnostic performance of selected variables in predicting CAI. The area under the curve (AUC) was calculated for each parameter. A p-value < 0.050 was considered statistically significant.

RESULTS

The demographic and clinical characteristics of patients with KD are presented in Table I. In 2 cases, classification could not be determined due to missing data.

Table I: Demographic and clinical characteristics

Variable	n	Values
Gender (Male)*	38	25 (65.8)
Harada Score ≥4*	38	20 (52.6)
Age (months)†	38	25.0 [11.2–55.0]
Fever (°C)‡	36	39.0 ± 0.6
Duration of fever (days) ‡	36	8.2 ± 3.4
Heart rate (beats/min) ‡	32	124.3 ± 19.7
Systolic BP (mmHg) ‡	30	94.3 ± 8.2
Diastolic BP (mmHg) ‡	30	58.8 ± 6.1
Season at diagnosis*	38	
Spring		10 (26.3)
Summer		14 (36.8)
Autumn		4 (10.5)
Winter		10 (26.3)
Diagnostic Findings*	38	
Lip and oral mucosa changes		33 (86.8)
Conjunctivitis		32 (84.2)
Rash		30 (78.9)
Extremity changes		27 (71.1)
Lymphadenopathy		26 (68.4)
Fever duration (days) ‡	36	8.2 ± 3.4
Time to diagnosis (days) ‡	37	6.4 ± 4.8
Length of hospital stay (days) ‡	35	10.2 ± 7.1
Complet KD*	38	28 (73.7)
Coronary artery involvement*	38	16 (42.1)
Harada score ‡	37	4.5 ± 1.2

: n(%), †: median (IQR), ‡: mean±SD, **IQR: Interquartile Range, **BP:** Blood pressure, **KD:** Kawasaki Disease, **CAI:** Coronary artery involvement, **Harada score:** a clinical risk score used to predict coronary artery involvement. Calculated only for patients who presented within the first 9 days of illness.*

Table II: Laboratory parameters by coronary artery involvement status

	n	Total*	CAI (+)*	CAI (-)*	p†
Hb (g/dl)	38	11.0±1.05	10.8±1.20	11.1±1.01	0.534
Hct (%)	38	32.5±2.87	31.9±2.82	32.9±2.93	0.315
WBC (x10³/mm³)	38	16.0±6.60	18.0±7.94	14.9±5.73	0.204
PLT (x10³/mm³)	38	467.11±179	471.05±173.00	321.00±169.00	0.362
1st week		682.05±271	747.60±325.00	630.32±206.00	0.405
2nd week		695.69±297	724.17±338.00	664.64±264.00	0.975
3rd week		518.62±290	565.29±267.00	482.33±368.00	0.470
1st month		431.50±123	438.29±132.00	424.71±123.00	0.902
2nd month		404.92±70	414.00±63.00	400.50±90.00	0.886
CRP (mg/L)	37	121.1±83.23	105.0±65.72	139.4±96.20	0.286
Time to CRP decrease (days)	38	13.8±11.39	12.7±8.46	14.6±14.90	0.692
ESR (mm/h)	36	75.5±25.44	73.8±25.92	77.4±25.93	0.895
Time to ESR decrease (days)	38	30.0±20.34	29.0±21.57	30.7±19.39	0.875
AST (U/L)	37	66.6±85.19	77.1±110.88	58.5±58.02	0.988
ALT (U/L)	37	88.4±96.69	110.4±130.50	71.6±47.27	0.951
Alb (mg/dl)	29	3.5±0.51	3.4±0.50	3.5±0.52	0.643
GGT (U/L)	22	94.5±88.55	115.4±87.38	73.5±100.73	0.149

***:** *mean±SD,* **†:** *Independent samplet test*, **CAI:** *Coronary artery involvement,* **Hb:** *Hemoglobin,* **Hct:** *Hematocrit,* **WBC:** *White Blood Cell,* **PLT:** *Platelet,* **CRP:** *C-reactive protein,* **ESR:** *Erythrocyte Sedimentation Rate,* **AST:** *Aspartate Aminotransferase,* **ALT:** *Alanine Aminotransferase,* **Alb:** *Albumin,* **GGT:** *Gamma-Glutamyl Transferase*

Table III: Univariate logistic regression of laboratory parameters for predicting coronary artery involvement

	n	OR	95% CI Lower	95% CI Upper	p
Hb (g/dl)	38	0.759	0.397	1.453	0.405
Hct (%)	38	0.876	0.679	1.132	0.312
WBC (x10³/mm³)	38	1.000	0.999	1.000	0.216
PLT (x10³/mm³)	38	1.000	1.000	1.000	0.651
1st week		1.000	1.000	1.000	0.621
2nd week		1.000	1.000	1.000	0.862
3rd week		1.000	1.000	1.000	0.995
1st month		1.000	1.000	1.000	0.925
2nd month		1.000	1.000	1.000	0.972
CRP (mg/L)	37	0.995	0.987	1.004	0.313
Time to CRP decrease (days)	38	0.986	0.916	1.060	0.696
ESR (mm/h)	36	0.007	–0.043	0.057	0.795
Time to ESR decrease (days)	38	1.001	0.957	1.048	0.950
AST (U/L)	37	1.004	0.994	1.013	0.453
ALT (U/L)	37	1.005	0.996	1.014	0.251
Alb (mg/dl)	29	0.417	0.083	2.089	0.287
GGT (U/L)	11	0.003	–0.007	0.014	0.535

***OR:** Odds ratios,* **CI:** *confidence intervals,* **Hb:** *Hemoglobin,* **Hct:** *Hematocrit,* **WBC:** *White Blood Cell,* **PLT:** *Platelet,* **CRP:** *C-reactive protein,* **ESR:** *Erythrocyte Sedimentation Rate,* **AST:** *Aspartate Aminotransferase,* **ALT:** *Alanine Aminotransferase,* **Alb:** *Albumin,* **GGT:** *Gamma-Glutamyl Transferase*

All patients were treated with IVIG (2 g/kg single infusion) and high-dose aspirin in the acute phase, followed by low-dose aspirin in the subacute phase as per standard protocol.

The laboratory parameters are presented in Table II. Inflammatory markers were elevated in nearly all patients.

CAI were identified in 16 out of 38 patients (42.1%). Most coronary lesions were detected either at diagnosis or during follow-up echocardiography within the first 2–6 weeks of illness. Among the affected patients, 12 had CAA only, two had coronary dilatation (ectasia) without meeting aneurysm criteria, and two patients exhibited both aneurysms and ectasia. For instance, one patient presented with a small aneurysm in the right coronary artery and diffuse ectatic changes in the left coronary system.

Table IV: Association between clinical type and coronary artery involvement

	CAI (+)*	p†
Complet KD (n:28)	11 (39.3)	
Inkomplet KD (n:8)	5 (62.5)	
Total (n:36)	16	0.422

: n(%), †: Fisher's exact test, **CAI: Coronary artery involvement, **KD:** Kawasaki Disease. Among the cases with a known classification of KD (complete or incomplete), CAI data were missing for two patients.*

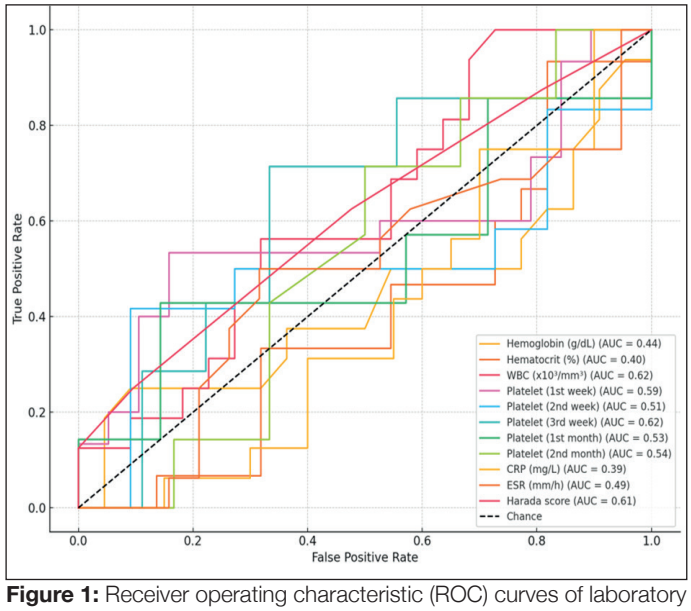

Figure 1: Receiver operating characteristic (ROC) curves of laboratory parameters for predicting coronary artery involvement in Kawasaki Disease. AUC values are shown in parentheses. WBC and platelet values in the third week showed the highest predictive performance, though no parameter exceeded an AUC of 0.65.

Based on Z-score classification, seven aneurysms were categorized as small (Z-score 2.5–5), seven as medium (Z-score 5–10 or absolute diameter 5–8 mm), and two as giant (Z-score ≥10). All patients with CAI received appropriate adjunctive therapy and were closely monitored by pediatric cardiology according to the severity of coronary findings, including continuation of aspirin therapy.

The distributions of key laboratory parameters—including Hb, Htc, WBC, PLT count at various time points, CRP, ESR, and Harada score—were compared between patients with and without CAI (Table II). No statistically significant differences were found in any of these baseline parameters.

ROC analysis was conducted to assess the predictive value of laboratory parameters for CAI (Figure 1). The highest AUC was observed for WBC count (AUC = 0.62), followed by PLT count in the third week (AUC = 0.62) and the Harada score (AUC = 0.61). However, none of the parameters demonstrated strong predictive performance (AUC > 0.70).

In univariate logistic regression analyses, none of the evaluated laboratory parameters—including Hb, Htc, WBC count, PLT count across various time points, CRP, ESR, liver enzymes (AST, ALT, Alb, GGT)—were found to be statistically significant predictors of CAI (Table III).

Among 36 patients with available data, 28 were diagnosed with complete KD and 8 with incomplete KD (Table IV). CAI was observed in 11 of the 28 complete KD cases (40.7%) and in 5 of the 8 incomplete KD cases (83.3%). Although the rate of CAI appeared higher in the incomplete group, the difference did not reach statistical significance (Fisher's exact test, p = 0.422).

DISCUSSION

In this retrospective study of 38 children with KD, we investigated whether initial hematological and inflammatory parameters are associated with the development of CAI. Our findings indicate that traditional laboratory markers measured at presentation – including Hb, Htc, WBC count, PLT count, CRP and ESR, AST, ALT, Alb and GGT – did not show a statistically significant difference between patients who developed coronary artery changes and those who did not. In other words, no routine blood parameter at diagnosis emerged as a clear predictor of coronary complications in our cohort. This is consistent with much of the existing literature, which has shown that while KD is invariably accompanied by systemic inflammation and characteristic laboratory abnormalities, these metrics alone often lack the specificity needed to predict CAI formation (12). The acute phase reactants (CRP, ESR) and blood counts reflect the intensity of inflammation but do not necessarily distinguish which children will have CAI. Our results reinforce the notion that clinicians cannot rely solely on common lab tests at presentation to assess the risk of coronary sequelae in KD.

It is worth noting that some previous studies have reported potential links between certain laboratory extremes and coronary risk, although findings have been variable. For example, extremely elevated CRP levels have been associated with increased likelihood of coronary artery lesions in some analyses (17, 18). A meta-analysis reported that for each 1 mg/L increase in CRP, the odds of coronary artery abnormality increased slightly (OR ~1.02), underscoring CRP as a continuous contributor to risk (19). Similarly, anemia and hypoalbuminemia have been observed more frequently in KD patients who develop CAA in some studies (12). Increased neutrophil counts and higher PLT counts in the subacute phase have also been proposed as risk factors in prior reports (12). However, these associations are not consistently reproducible across all populations. For instance, Rahbari-Manesh et al. (20) found no significant correlation between PLT count or ESR/CRP levels and CAI. Our findings are consistent with previous studies that question the predictive value of individual hematologic markers. The absence of significant differences in our analysis supports the notion that the pathogenesis of coronary lesions in KD is multifactorial and cannot be adequately reflected by a single laboratory parameter measured at a single time point.

The ROC analysis revealed that the WBC count had an AUC value of 0.62. Similarly, the PLT count in the third week and the Harada score showed AUC values in the range of 0.61–0.62. However, none of these parameters demonstrated adequate predictive performance (AUC > 0.70). This suggests that relying solely on laboratory values may be insufficient to predict CAI in KD.

Limitations

This study has several limitations. First, its retrospective and single-center design may limit the generalizability of the findings to broader populations. Most importantly, the sample size (38 patients) was small, which is the main limitation of our study. A small sample size reduces the statistical power to detect potentially meaningful differences, increasing the risk of type II error. In our analysis, this means subtle predictive effects of laboratory variables could have been missed. Additionally, among the cases with a known KD classification (complete or incomplete), CAI data were missing for two patients, which may have affected the analysis of the association between KD type and CAI. Although a wide range of laboratory parameters was evaluated, it should be noted that the dynamic nature of inflammation in KD may not be fully captured by measurements at a single time point. Serial measurements and trends over time might offer more meaningful predictive insights, but this aspect could not be assessed within the scope of this study.

CONCLUSION

In this retrospective study, no significant association was found between initial hematological parameters, inflammatory markers, or liver enzymes and the development of CAI in children diagnosed with KD. These results suggest that the commonly measured laboratory indices at presentation, while reflective of the systemic inflammation in KD, are not reliable predictors of which children will develop CAI. The Harada risk score and other risk factors were examined, but their predictive value in our population was limited, indicating that current risk stratification tools may need to be tailored for different populations or supplemented with additional biomarkers.

In summary, routine blood test abnormalities in KD should alert physicians to the diagnosis but do not on their own predict coronary outcomes. Clinicians should be particularly vigilant in cases of incomplete KD, as delayed diagnosis in these cases can lead to higher rates of CAI. Future prospective studies and larger multicenter analyses are needed to identify early predictors of coronary artery lesions in KD. Such research may include advanced inflammatory markers, genetic factors, or refined clinical scoring systems. Improved risk stratification would allow for more targeted therapy with the ultimate goal of further reducing the incidence of CAI in KD. With ongoing investigations into the pathogenesis and biomarkers of KD, we hope that early identification of high-risk patients will become more feasible, thereby improving outcomes for this serious pediatric condition.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study protocol was reviewed and approved by the Baskent University Institutional Review Board (date:30.07.2025, number: KA25/291)

Contribution of the authors

Study conception and design: ***MKK, İE;*** data collection: MKK; analysis and interpretation of results: ***MKK, İE, EB;*** draft manuscript preparation: ***MKK, İE.*** 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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