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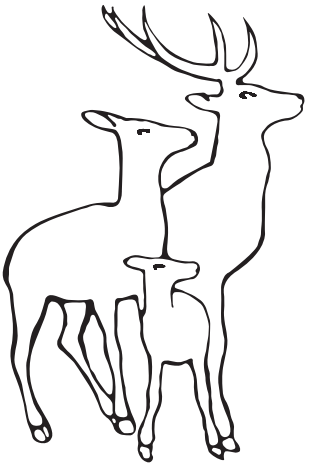

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The Turkish Journal of Pediatrics 2024; 66: 265-274
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Original Article

The treatment journey of children with moderate to severe atopic dermatitis in Türkiye: unmet needs

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ABSTRACT

Background. Atopic dermatitis (AD) substantially burdens individuals, families, and healthcare systems. We aimed to document the treatment journey of pediatric patients with moderate-to-severe AD in a referral center based in our country.

Methods. This retrospective study reviewed patients aged 1-18 years diagnosed with AD, seeking systemic treatment recommendations from the "pediatric allergy and dermatology multidisciplinary team meeting".

Results. Over the 14-month study period, 30 (12.5%) of 240 AD patients were evaluated in the pediatric dermato-allergy team meetings. The median age of the patients was 13.66 years (Q1-Q3: 7.94-17.27), of whom 60% were male. The median annual healthcare visits for AD were 4 (Q1-Q3: 1.00-8.75). Among the study group, 70% were sensitized to aeroallergens, and admission markers included total IgE (median: 1980 IU/mL, Q1-Q3: 794.50-5446), and eosinophil counts (median: 650, Q1-Q3: 275-1275). All patients utilized intermittent and/or continuous topical corticosteroids (CS), with 56.6% employing short-term/long-term topical tacrolimus. Over the past two years, systemic CSs were utilized in 93.3% of the patients, whereas 57.1% received more than one course. Approximately 43.3% of the patients agreed to receive systemic cyclosporine treatment, with only 30.8% benefiting and 3.3% reporting adverse effects (hypertrichosis and cellulitis). Three patients self-funded dupilumab, all benefiting without adverse effects. Omalizumab, mycophenolate mofetil and narrow-band ultraviolet (UV) treatments were used in one patient each, with limited benefit observed. Health insurance did not grant approval for a Janus kinase inhibitor for one patient.

Conclusions. Managing moderate to severe AD is complex and costly, considering disease heterogeneity, comorbidities, care pathways, and health system challenges. Addressing the unmet needs should be a priority in Türkiye's healthcare systems.

Key words: adolescent, atopic dermatitis, children, healthcare, systemic, treatment.

Atopic dermatitis (AD) is a chronic inflammatory skin disease that can cause a great deal of discomfort and distress for patients, their families, and the healthcare system.[1,2] It is particularly challenging to manage the moderate-to-severe spectrum, where patients often require systemic medications to control their symptoms.[3,4]

Managing AD involves proper skin care and trigger avoidance, with primary treatment using corticosteroids (CS) and calcineurin inhibitors during flare-ups, proven effective and safe in the short term.[5] In resistant or recurrent cases, a proactive approach may be considered. Severe AD is characterized by extensive body surface involvement, resistant lesions, and permanent skin changes.[6] Another definition is treatment necessity, considering it is unresponsive to

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topical treatments.[7] For severe AD, systemic immunosuppressants, narrow-band ultraviolet B (UVB), biologic therapies like dupilumab, or Janus kinase (JAK) inhibitors may be necessary. However, these pose greater responsibility, with increased risks and costs compared to first-line treatments. Caution is crucial, especially when prescribing to pediatric patients. Systemic steroids, effective in controlling severe flare-ups, are only used for short courses due to their potential adverse effects.

Türkiye is home to a diverse population with a wide range of healthcare needs. However, there is a lack of data on the treatment journey of pediatric patients with moderate-to-severe AD in this region. Therefore, the results of this study will be valuable for clinicians, policymakers, and other stakeholders who are working to improve the care of pediatric patients with moderate-to-severe AD in this region. This study aims to fill this gap by providing insights into the treatment patterns and outcomes of these patients.

Methods

This retrospective study was conducted in a tertiary care center in Türkiye to document the clinical characteristics and treatment journeys of pediatric patients with moderate-to-severe AD. The study cohort included children and adolescents aged 1-18 years who were assessed for AD during pediatric allergy-dermatology team meetings between August 1, 2021, and October 1, 2022. These patients were referred due to inadequate control of their AD with topical treatments, prompting the need for evaluation for systemic treatment options. Pediatric allergy-dermatology multidisciplinary team meetings focused on the evaluation and management of children and adolescents (aged 1-18 years) with AD refractory to topical treatment or experiencing frequent relapses, indicating a potential need for systemic therapy. These complex cases were presented to a multidisciplinary team of consultants, fostering collaborative discussion and shared decision-making.

Patient data collection

The patient information that was analyzed included their age, gender, age at the initial diagnosis of AD, details of topical and systemic treatments administered for eczema, concurrent comorbidities, levels of specific and total immunoglobulin E (IgE), blood eosinophil counts, healthcare visit frequency, coexisting respiratory and food allergies, as well as any alternative or complementary drug therapies employed. This information was gathered through both face-to-face interviews with patients and their parents and electronic medical records. Clinical data reported by patients and parents were cross-referenced with the records maintained by emergency and allergy units within the healthcare system.

Diagnosis of the atopic disease

The patients were diagnosed with AD according to the Hanifin and Rajka criteria. The inclusion criteria for the study were moderate-severe AD, inadequate control with topical treatments and involvement of at least 25% of the body surface area. Objective SCORAD scores of the patients were recorded to evaluate the degree of atopic eczema. Diagnoses of allergic rhinitis and asthma were made by following international guidelines.[8-10]

Skin prick tests, serum total, and specific IgE measurements

Skin prick tests (SPTs) were administered according to the patient's clinical history, including respiratory allergies and suspected food allergies. Common aeroallergens and cross-reactive food allergens were tested, as previously described.[2,11] SPTs were conducted using histamine (10 mg/mL) and saline controls. Wheal size was measured after 15 minutes. The diagnosis of food allergy depended on demonstrating IgE sensitization through an SPT (≥ 3 mm) and/or a positive specific IgE (sIgE) level (≥ 0.30), in conjunction with a positive oral food challenge (OFC) or a consistent history of IgE-mediated allergy. In the absence of an OFC and consistent history, any SPT and/

or sIgE levels that exceeded the 95% positive predicted value (PPV) for clinical reactivity were considered. If the 95% positive PPV was not explicitly specified for any food, the criteria applied were sIgE ≥ 15 kU/L and/or SPT ≥ 8 mm. Resolved food allergy indicates tolerance to a previously allergenic food.[12] Total IgE levels were quantified in serum using the ImmunoCAP method (Thermo Fisher Scientific, Waltham, MA).

Healthcare use

Healthcare utilization was classified as "current" for the preceding year and "lifetime" for a lifetime and was documented in terms of hospitalization, emergency admissions, and scheduled or unscheduled healthcare visits for AD.

Ethical approval

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The study protocol received ethical approval from the Institutional Review Board of Hacettepe University (Approval Number: GO 21/871).

Statistical analysis

Statistical analyses were performed using SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Variables such as age, total IgE, and absolute eosinophil count exhibited non-normal distributions; therefore, the results were presented as medians and interquartile ranges (Q1-Q3).

Prevalence rates for all variables, including specific allergens, asthma, and allergic rhinitis (AR), were calculated based on age, gender, predominant initial symptoms, and family history of atopy. Frequencies and percentages were used to summarize these prevalence rates. A significance level of $P < 0.05$ was adopted for all statistical analyses.

Results

Characteristics of the study group

Over 14 months, 240 patients were referred to the study center for AD. Of these, 30 patients (12.5%) were presented and discussed at the dermatology-allergy team meetings, all of whom were subsequently included in this study.

The median age of the study cohort was 13.66 years, with a range of 7.94 to 17.27 years (p=0.52). Of these, 60% (n=18) were male. The mean follow-up duration at the study center for the entire group was 1.6 years (±0.9). At admission, medians for total IgE, eosinophil count, and eosinophil percentage were 1980 IU/mL (794.50-5446), 650 (275-1275), and 6.75% (3.80-13.15), respectively (p=0.43) (Table I).

Allergic comorbidities

A significant proportion of the study group, comprising 70% (n=21), exhibited sensitization to aeroallergens (Fig. 1). The predominant culprits were grass pollen, affecting half of the participants (50%, n=15), followed by tree pollens, which impacted 26.6% (n=8). Additionally, cat elicited allergies in 30% (n=9) of individuals, while house dust mites were responsible for sensitizations in 16.6% (n=5) of cases. Sensitization to Malassezia was observed in 16.6% (n=5) of participants. Four out of our 12 patients with AR reported experiencing additional exacerbations in their atopic eczema that persisted during the pollen season.

Approximately 40% (n=12) of the study cohort had received previous diagnoses of food allergies. Among those with food allergies, the most commonly implicated allergens were tree nuts (n=6), egg white (n=5), and cow's milk (n=3). Notably, three patients exhibited allergies to multiple food items. The current food allergies were present in 5 patients, including one with shellfish allergy and four with sensitivities to multiple (≥2) tree nuts.

Table I. Demographic and clinical features of patients.

	Preschool children (1-5 years)	School children (6-12 years)	Adolescents (13-18 years)	Entire group (1-18 years)
Total number of patients	6 (20%)	9 (30%)	15 (50%)	30 (100%)
Age, yr	2.6 (1.8-3.6)	8.5 (5.32-11.6)	16.0 (12.6-18.7)	13.66 (7.94-17.27)
Male gender	4 (66.6%)	4 (44.4%)	10 (66.6%)	18 (60%)
Age at initial symptoms, yr	2.44 (0.8-4.0)	6.9 (5.1-9.4)	14.0 (12.2-15.4)	8.8 (4.2-14.0)
Skin dryness, %	50 (15.5-80)	42.5 (25.5-65.5)	50 (27.5-70)	50 (25-70)
Family history of atopic dermatitis	0 (0%)	6 (66.6%)	4 (26.6%)	10 (33.3%)
Total IgE, IU/mL	762 (360-4133)	2529 (1303.50-3891)	1980 (851-6273)	1980 (794-5446)
Blood eosinophils, %	8.70 (3.37-20.85)	11.80 (8.0-14.05)	5.00 (2.60-10.90)	6.75 (3.8-13.1)
Aeroallergen sensitivity	2 (33.3%)	9 (100%)	10 (66.6%)	21 (70%)
Malassezia sensitivity	0 (0%)	2 (22.2%)	3 (20%)	5 (16.6%)
Ever asthma	0 (0%)	1 (11.1%)	4 (26.6%)	5 (16.6%)
Current asthma	0 (0%)	0 (0%)	4 (26.6%)	4 (13.3%)
Ever food allergy	2 (33.3%)	6 (66.6%)	4 (26.6%)	12 (40%)
Current food allergy	1 (16.6%)	2 (22.2%)	2 (13.3%)	5 (16.6%)
Current allergic rhinitis	0 (0%)	6 (66.6%)	6 (40%)	12 (40%)

Categorical data presented as n (%), numerical data as median (interquartile range: Q1-Q3).

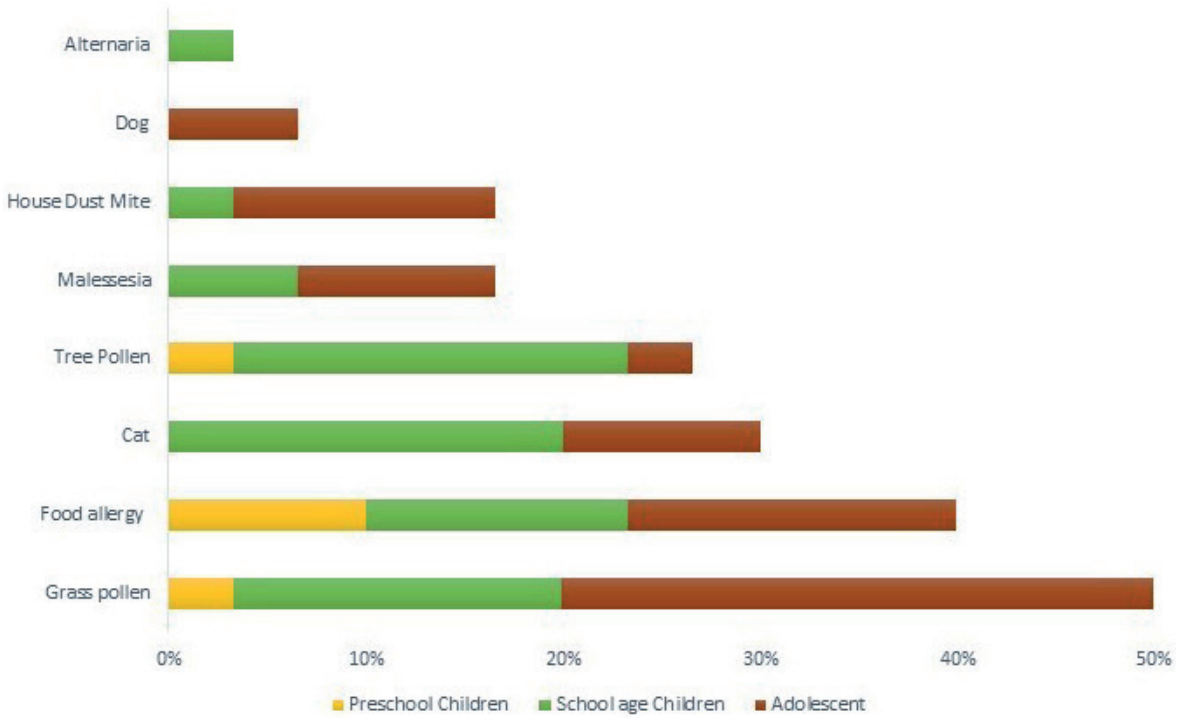

Fig. 1. Allergy frequencies in the study group.

Healthcare resource use (Fig. 2)

The median number of scheduled healthcare visits for AD during the follow-up period was 12 (Q1-Q3: 8.2-17.2). Five patients were admitted to the emergency department, four due to AD exacerbations and one due to cellulitis developed during cyclosporine therapy. Over the past 2 years, median annual healthcare visits for AD were 4 (IQR 1.00-8.75). A total of 5 patients in the study group required hospitalization due to infected AD and received parenteral antibiotic treatment during their stay.

Treatment journey (Fig. 3)

All patients used topical corticosteroids (TCS) and moisturizer intermittently or regularly. Mild-to-moderate strength TCS was used for the face and medium strength TCS was used for the body and extremities. Moderate-strength agents were more preferred as the patient's age increased.

While wet dressing treatment was recommended to half of the patients, it was accepted/tolerated by only 50%. The main concern of those who refused was the fear that the child would catch a cold due to the wet dressing. Although it worked well in almost all patients with repeated application at various intervals, subsequent applications caused adverse effects such as folliculitis. Concerns about potential systemic corticosteroid (SCS) effects, as expressed by physicians who supervised repeated administrations, also led to the discontinuation of treatment.

Our analysis unveiled a substantial dependence on SCS for managing severe AD in the past two years. Notably, 93.3% of patients necessitated a course of SCS lasting more than three days, and 57.1% used SCS on multiple occasions. The median number of SCS occasions in the group was 2.0 (2.0-4.0) per year. Despite an initial improvement observed in all SCS-receiving patients, a concerning 90% experienced relapse within a week of discontinuation. Additionally, six patients required multiple intramuscular depot CS injections, providing an average relief period of three weeks. Although all of these patients benefited from the SCS treatments, recurrence developed within one week after stopping the treatment in 90%. Additionally, 6

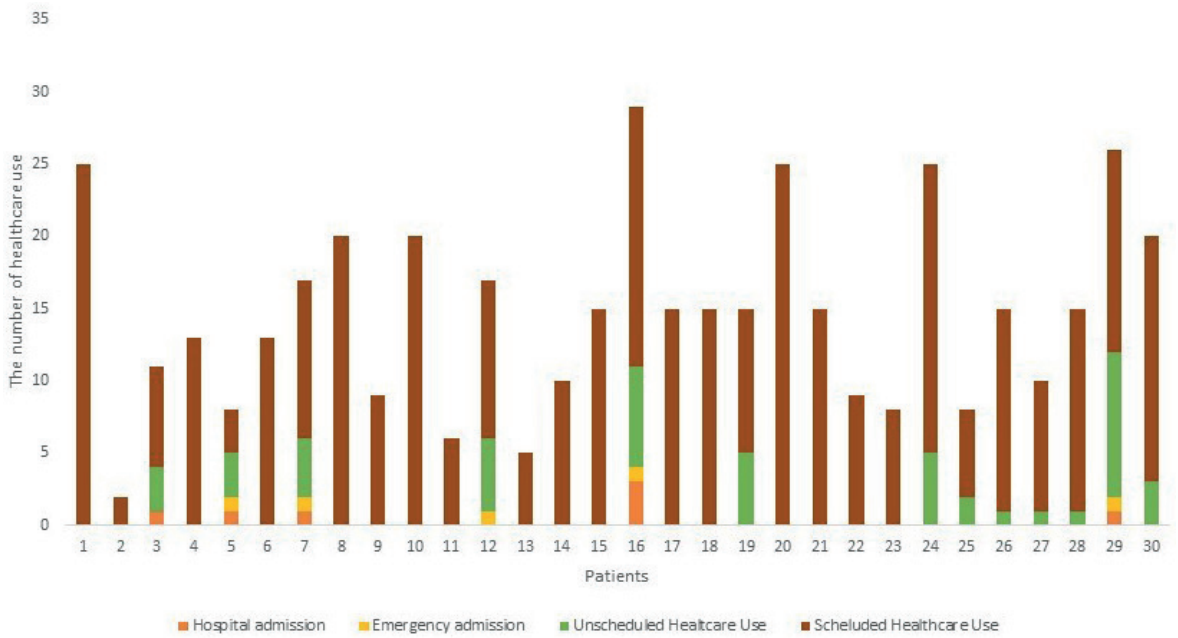

Fig. 2. Lifetime healthcare use for atopic dermatitis of each individual.

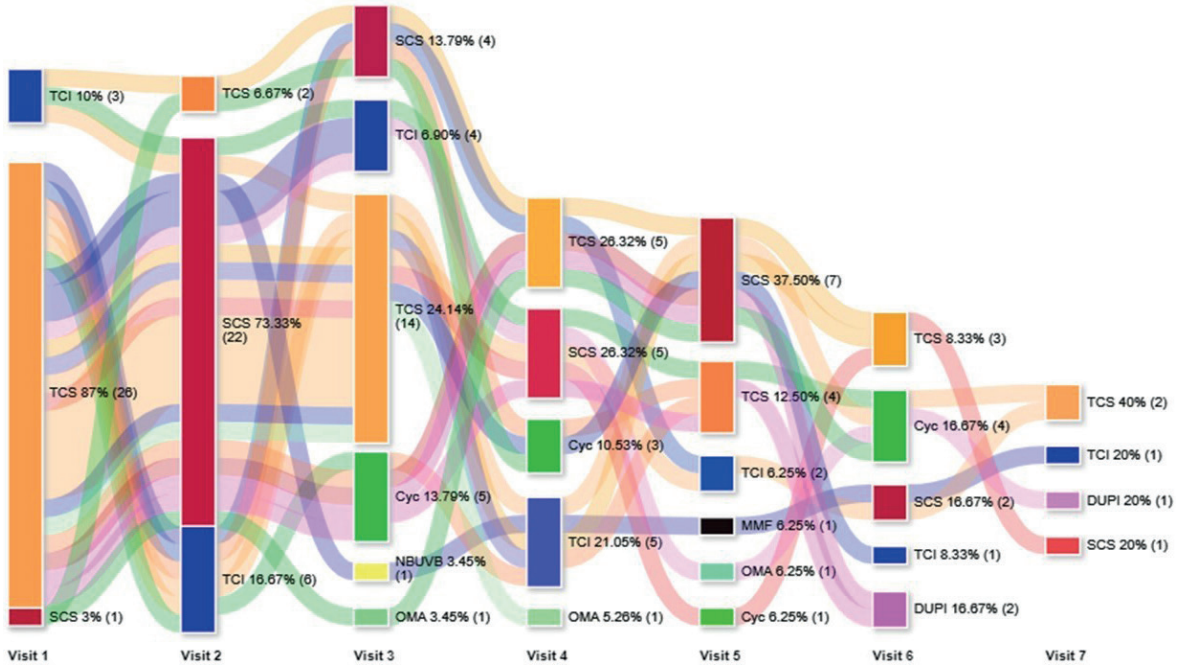

Fig. 3. Treatment journey of children of the study group.

Deciphering the Sankey diagram shows different treatments during the first two visits. First Visit: Most patients used "as-needed" topical corticosteroids, some used as-needed topical calcineurin inhibitors, and a few had a short-term systemic corticosteroid course. Second Visit: Current topical treatments continued, with additional prescriptions of either topical corticosteroids or topical calcineurin inhibitors for those not already using them. The increased use of systemic corticosteroid courses indicates potential challenges with the initial treatment plan.
(CYC: cyclosporine, DUPI: dupilumab, MMF: mycophenolate mofetil, NBUVB: narrow band ultraviolet-B, OMA: omalizumab, SCS: systemic corticosteroid, TCI: topical calcineurin inhibitor, TCS: topical corticosteroid).

patients required more than one intramuscular depot CS injection, which was effective for an average of 3 weeks.

Topical tacrolimus treatment was administered to 56.6% of the patients. Of these, 50% reported an inadequate response, and 20% could not tolerate it due to a burning sensation. Those who benefited from topical tacrolimus showed benefit within 1-2 weeks, but relapse was reported within 7-14 days when treatment was discontinued. The minimum duration of tacrolimus treatment was 9±3.4 days.

Although 17 patients were recommended to use cyclosporine, only 13 patients (43.3%) accepted this treatment and used it for an average of 6 months, and 30.8% (n=4) benefited from this treatment. Reasons for discontinuing included concerns about its long duration (15%) and the desire to avoid using the medication for more than 6 months (80%). One patient (3.3%) experienced hypertrichosis and cellulitis as adverse effects of cyclosporine treatment.

Three patients used dupilumab therapy at their own expense, as it is only reimbursed for patients over 18 years of age in our country. All of these patients had been previously treated with cyclosporine and multiple bursts of SCSs. The patients treated with dupilumab were 7, 15, and 17 years old, respectively (Fig. 4), and their mean objective SCORAD scores before and after treatment were 39.27±18.90 and 11.33±4.16, respectively. Additionally, omalizumab, mycophenolate mofetil, and narrow-band UV treatments were administered to one patient each for durations ranging from 4 to 8 months; however, they yielded minimal benefits.

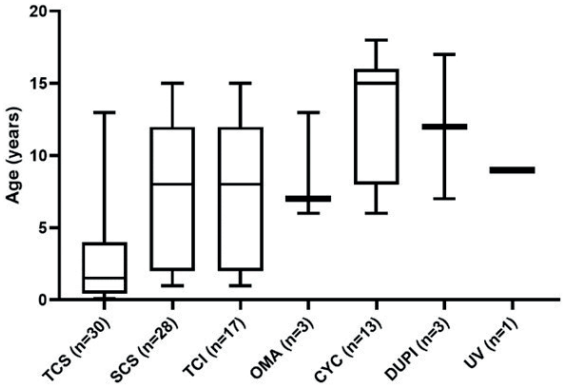

Fig. 4. Age of onset of certain treatments.
(CYC: cyclosporine, DUPI: dupilumab, OMA: omalizumab, SCS: systemic corticosteroid, TCI: topical calcineurin inhibitor, TCS: topical corticosteroid, UV: ultraviolet).

A 16-year-old female patient, despite consistent use of topical calcineurin inhibitors, TCSs, and intermittent SCS treatments, struggled to attain adequate control of the disease. Her symptoms did not respond satisfactorily to a 9-month course of cyclosporine therapy. Due to financial constraints preventing self-payment for dupilumab, the medical council chose to initiate treatment with a JAK inhibitor, specifically baricitinib. Unfortunately, the Ministry of Health declined approval for this treatment due to the patient's age. Consequently, despite the initial intention for the patient to adhere to topical treatments until reaching the age of 18 years, she successfully pursued legal action against the social security agency and transitioned to a conventional dupilumab treatment protocol, thereby achieving effective disease control.

Discussion

AD is one of the most prevalent childhood dermatologic conditions.[1] While many cases of AD can be effectively managed through topical therapies and daily skincare routines, a subset of patients require systemic treatment.[5,13] All patients were advised to follow a proactive treatment plan incorporating both TCS and calcineurin inhibitors, which proved beneficial during its application. However, low compliance emerged as a result of the demanding daily application to extensive body areas, creating challenges for both the patient and their family over time. The regimen was considered unsustainable due to the development of resistance and a decline in compliance.

This study documented the treatment experiences of pediatric and adolescent AD patients who required systemic therapies. Our findings highlight the substantial challenges faced by this patient group, characterized by high healthcare utilization, repeated SCS usage, limited benefit from available systemic treatments, and exploration of alternative/complementary therapies, a reflection of the unmet medical needs experienced by patients and their caregivers. These results underscore the pressing need for further research and consideration regarding the treatment of severe pediatric and adolescent AD patients and a clear demand for more effective and accessible treatment options tailored to this specific population.

Epidemiological insights regarding pediatric AD in Türkiye are limited. A previous multicenter study reported a cumulative prevalence of 8.1% in schoolchildren aged 9-11 years, with a point prevalence of 3.6%. Additionally, 4.3% of children with AD reported intermittent use of SCSs, and 1.4% reported regular SCS treatment.[14] This current study, conducted nearly two decades after the initial epidemiological study, reaffirms the presence of a subgroup of patients burdened by significant challenges and unmet needs. This study marks the first comprehensive exploration of the treatment journeys of pediatric and adolescent AD patients requiring systemic interventions in Türkiye.

Effective management of severe AD typically necessitates a comprehensive, multidisciplinary approach guided by dermatologists or allergists.[13,15,16] Such an approach is crucial for developing personalized treatment plans that address the unique and evolving needs of each patient. Recent advancements in therapies, such as systemic immunosuppressive medications or

biologic agents, have redefined the treatment landscape for severe AD.[17-21] These therapies have not only significantly improved healthcare utilization, disease burden, individual self-esteem, and the quality of life for patients and their caregivers but have also challenged the traditional definition of severe AD, which was based on a limited response to available treatments.

However, the high cost and complex regulatory requirements associated with these emerging therapies pose challenges for healthcare systems. The optimal approach is to incorporate these therapies into healthcare systems while implementing appropriate controls and regulations, ensuring access only for those who genuinely require them. Nonetheless, concerns about the capacity of certain countries to effectively regulate medical practices and industrial activities have led to a hesitancy toward blanket approval. This approach effectively overlooks the minority of patients with urgent needs for these treatments, and healthcare systems struggling to control pharmaceutical promotional efforts may miss valuable opportunities. Prioritizing the patients' needs while balancing accessibility to innovative therapies with cost considerations is of utmost importance.[22]

Another significant aspect of this study involves documenting the characteristics of pediatric and adolescent patients with severe AD. An important finding is that nearly half of our patients exhibited atopic respiratory comorbidities, including asthma and allergic rhinitis. Additionally, almost 70% had aeroallergen sensitization, 16.6% malassezia, and 40% had a food allergy, some of which resolved over time. These findings distinguish our study, in part, from previous investigations on severe AD.[23-26] Our study uncovered a high prevalence of aeroallergen sensitization (70%) and current food allergy (16.6%) among participants with AD. This contrasts with a multicenter study by Illi et al., where reported rates were 40% and 37%, respectively.[26] This disparity underscores potential heterogeneity in AD presentation across diverse populations. In our own research group, a separate study found a food allergy prevalence of 39% among children with AD, indicating that variability in prevalences can also exist within populations.[23] Those differences may be attributed to patient allocation from an allergy clinic.

In this descriptive study, cyclosporine-A was the only systemic treatment with proven efficacy, and approximately half of the patients opted for this treatment. However, only 30% of them achieved the desired response. Omalizumab, mycophenolate mofetil, and narrow-band UV were also attempted as alternative options, but they showed limited effectiveness. Agents with established efficacy, such as JAK inhibitors and dupilumab, could not be prescribed before the age of 18 due to a lack of reimbursement. Based on this rationale, during the study period, three patients initiated dupilumab treatment through self-payment, while one patient commenced drug therapy by taking legal action against the social security institution.

In conclusion, the findings of this first-of-its-kind study highlight the significant burden experienced by pediatric and adolescent patients with AD requiring systemic treatment in Türkiye, including high healthcare utilization, multiple systemic corticosteroid use, and unmet needs. Additionally, there is a need for more effective and accessible treatments for this patient population.

Ethical approval

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The reason for not having family or patient consent should be written because it is a retrospective study. The study protocol received ethical approval from the Institutional Review Board of Hacettepe University (Approval Number: GO 21/871).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: BES, data collection: DIG, HU, ESA, OS, UMS, SEE; analysis and interpretation of results: DIG, BES; visualization: DIG, BES, draft manuscript preparation: BES, DIG, OS, UMS, SEE. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Has the COVID-19 pandemic negatively impacted children's development? An assessment of the neurodevelopment of premature babies born during the pandemic

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ABSTRACT

Background. Pandemics, such as COVID-19, have the potential to adversely affect children's development due to a variety of negative factors at the level of children, families, and services. In this study the effect of the pandemic on the cognitive, language and motor development of premature babies who are among the most vulnerable group, were evaluated.

Methods. The study included 236 premature infants who were followed at Hacettepe University Department of Developmental Pediatrics. The Bayley-Third Edition Developmental Assessment (Bayley III) was used to evaluate the neurodevelopment of 152 premature infants from the pre-pandemic group and 84 from the post-pandemic group at the corrected age of 18–24 months. The perinatal and sociodemographic risks were also evaluated.

Results. No difference in Bayley III scores (cognitive, language, and motor) was found between the pre- and post-pandemic groups. Furthermore, the multivariate covariance analysis displayed that regardless of the pandemic, infants with higher maternal education consistently scored higher in the cognitive, language, and motor domains; and the motor area scores of infants with moderate perinatal risk were also significantly higher than infants with high perinatal risk.

Conclusions. It is crucial to monitor the development of vulnerable children who encounter developmental risks, such as premature babies. Fortunately, no significant effect was encountered during the COVID-19 pandemic. However, this does not underweigh the need for close supervision in extraordinary circumstances. Additionally, it should be noted that severe postnatal comorbidities, perinatal risks, and social factors, such as maternal education level, interact to influence the neurodevelopmental outcomes of preterm infants.

Key words: COVID-19, premature babies, neurodevelopment, impacts.

The World Health Organization declared the COVID-19 outbreak as a pandemic on March 11, 2020, after the detection of the first case in early December 2019 in Wuhan, China.[1] Stress caused by isolation measures; school closures; restricted access to health and rehabilitation services; changes in daily routines, increased screen time, fewer physical activities; parent job losses, and increased domestic stress could be listed as negative factors at the level of children, families, and services, particularly for the health and development of the children, who are among the most vulnerable groups in a

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pandemic.[2,3] In fact, this process has been more challenging for children with special needs and their families.[4]

Restrictions caused by the pandemic have reduced access to primary healthcare and interrupted the follow-up of healthy children and pregnant women.[5] Research conducted at the beginning of the outbreak indicated that High-Risk Infant Follow-Up (HRIF) programs also needed to be enhanced since they were unable to provide effective treatment during the pandemic.[6] Furthermore, stress, anxiety, and depression symptoms were more prevalent both during the prenatal and postpartum periods in women who were pregnant during the pandemic.[7,8] On the other hand, several studies have shown that, due to pandemic measures like closures and working from home, the amount of time children spend with their parents has increased. Whereas some research suggests that children who spent more time with their parents exhibited positive learning behaviors and experienced fewer anxiety symptoms, other studies indicate that the reverse may be true due to the increased stress and chaos in the home.[9] Consequently, in the light of the bioecological framework, the pandemic processes have the potential to influence children's development with changes in the context of the parents' mental health, the home environment, family relationships, social environment, and community characteristics.[10] The COVID-19 pandemic and child development studies have resulted in a range of findings. Shuffrey et al. found that 6-month-old term infants had lower scores in gross motor, fine motor, and personal social domains compared to the historical cohort group, and it was presumed that this could be due to pandemic-related stressors or maternal anxiety during pregnancy.[11,12] In another study, comparing 6-month-old and 1-year-old term birth children who participated in neurodevelopment assessments between March 1 and May 15, 2020, in China, and a historical cohort of the same ages found that infants' development at 6 months did not differ from that of the pre-pandemic group, but that delays in communication and fine motor skills were present in the post-pandemic group of 1 year old infants.[13] In the study by Lau et al., it was discovered that there was no difference in the neurodevelopmental outcomes of premature infants at 2 years of age prior to and following the COVID-19 pandemic.[14] Nevertheless, the literature on this topic contends that long-term follow-up may reveal different developmental patterns and that initial findings do not always indicate long-term outcomes.[11,15]

There is a lack of research on the effects of the COVID-19 pandemic's altered social and environmental circumstances on the neurodevelopmental traits of premature infants. Environmental and social factors can play a protective role in preterms' neurodevelopmental trajectories; some studies show that the impact of perinatal risk factors fade over time.[16,17] However, it was found in a study comparing the influence of biological and social factors on the long-term outcomes of extremely preterm children that early neonatal complications continued to predict outcomes into adolescence and some social variables assumed increasing importance in later years, but most of them did not diminish or exceed the significant biological associations.[18] As with all the families of all the risky children monitored in our developmental pediatrics clinic throughout the pandemic, the parents of premature babies reported they reduced hospital visits due to concerns about possible COVID-19 transmission. Patient administrations were limited for the first six months, from March 2020 until October 2020, as a result of the COVID-19 cases that started to appear in Türkiye and the implementation of strict restrictions. In the first year of the pandemic, the referral pattern had caught up to the pre-pandemic period.[19] It is critical to add to the body of literature to evaluate the neurodevelopmental status of premature infants who already have developmental risks in the long-term follow-up after the pandemic. The present study aimed to evaluate the cognitive, language, and motor development of preterm infants at 18-24 months of age born and raised

during the pandemic restrictions in comparison to their counterparts born and assessed prior to the pandemic.

Materials and Methods

Participants

This retrospective study was conducted at the Hacettepe University Division of Developmental Pediatrics and the Ethics Committee of Hacettepe University approved this study (GO 22/828). The study included all 236 infants with gestational age below 37 weeks who were followed at the Developmental Pediatrics outpatient clinic between January 2018 and August 2022 and whose developmental assessments were performed using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley III) when their corrected age was between 18-24 months. The study excluded premature infants with visual and hearing impairments, as well as those who had a diagnosis or suspicion of autism spectrum disorder (Figure 1). The focus of the study was the effect of the pandemic scenario on development, instead of the consequences of the virus and disease, therefore premature babies who had intrauterine exposure to COVID-19 were not included in the study.

Republic of Türkiye Ministry of Health reported its first case of the COVID-19, on March 11, 2020. As was the case around the globe, numerous closure measures, lockdowns, and school closings were also implemented. Gradual normalization began as of May 2021, and many restrictions had been removed as of July 2021.[20] In a study in which we investigated the referral trends during the COVID-19 pandemic at the Hacettepe University Division of Developmental Pediatrics, as of July 2021, our referral trend had caught up to the pre-pandemic period.[19]

The Department of Developmental Pediatrics provides services to families and children based on family-centered strategies. The primary patient group is children aged between 0 and 6 years who have developmental risks and delays, genetic syndromes, and chronic diseases. A multidisciplinary, structured high-risk infant

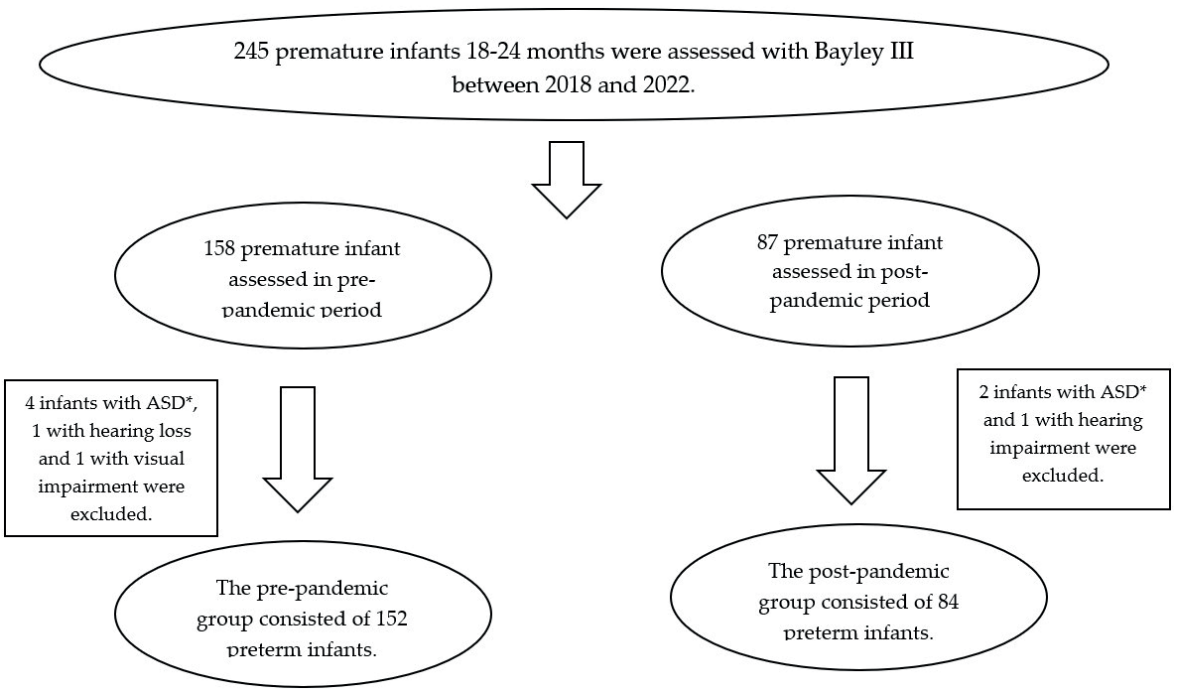

Fig. 1. The flow-chart for patients enrollment and drop-out. ASD: Autism spectrum disorder.

follow-up program is carried out by specialists from neonatology, physical therapy and rehabilitation, and developmental pediatrics for preterm infants, which constitute a sizable portion of our patient population. Based on the perinatal and social risks, patients are evaluated every three to six months with their parents. At each visit, developmental tests are carried out, risk and protective factors for development are discussed, and the necessary interventions are implemented.

While the difference between the pre- and post-pandemic groups was taken to have an effect size of 0.4, it was determined that, with 80% power and 5% type 1 error levels, 149 premature cases should be included in the pre-pandemic group and 75 premature cases in the post-pandemic group to detect a change of 5 points in Bayley III scores. The pre-pandemic group consisted of 152 premature babies evaluated between January 2018 and December 2019, whereas the post-pandemic group consisted of 84 premature babies born between March 2020 and December 2020 who had not been exposed to intrauterine COVID-19 and whose developmental evaluation was completed by August 2022. After this date we did not include any more premature babies, as the pandemic restrictions had become minimal after this date.

Evaluation tools

The sociodemographic data and the mothers' Edinburgh Postnatal Depression Scale (EPDS) results were obtained from the patient files. Child health status including infant gestational age, birthweight, multiple birth, Apgar score, duration of Neonatal Intensive Care Unit (NICU) stay, severe hyperbilirubinemia, small for gestational age (SGA) or large for gestational age (LGA), additional systemic illness including congenital heart diseases and metabolic, neurological or genetic disorders, bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), mechanical ventilation during NICU stay, mechanical ventilation duration, and presence of severe sepsis were all reviewed from the patient files and medical records. Infants' health status were classified as high moderate or low risk according to the Turkish Neonatal Society (Supplementary Table I) guidelines.[21]

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

The Bayley III is one of the most widely used and reliable developmental assessment tool in the world, evaluating cognitive, language, and motor development in children aged 1–42 months. The Bayley-III has acceptable levels of reliability (test-retest reliability > 0.67; internal consistency > 0.86) and concurrent validity compared to numerous developmental diagnostic tests for American children.[22] It is age-normed and has a standard deviation (SD). Each case's distribution for the sum of scaled scores is converted to composite scores (mean = 100, SD = 15). The developmental evaluation of all infants was conducted by the same experienced child development specialist.

Statistical analysis

IBM SPSS Version 22.0 was used to perform the statistical analysis. The numerical variables were summarized as mean, SD or median [min-max], whereas categorical variables were reported as frequencies and percentages. In continuous variables, the differences between the groups were determined by an independent samples t-test or Mann-Whitney U test as appropriate. The Pearson chi-square test was used to determine these differences for categorical variables. A multivariate analysis of covariance (MANCOVA) is a statistical procedure used to analyze the relationship between multiple dependent variables and

one or more independent variables while controlling for the influence of covariates. The Bayley III composite scores were utilized for this covariance analysis. The effect of groups (preterm infants born pre-pandemic vs. during pandemic) on child development domains assessed by Bayley III was examined using the MANCOVA, which controlled the covariance of biological (child's age, birth weight, gestational age, and perinatal risk) and environmental (mother's working status and maternal educational level) variables. The homogeneity of variance-covariance matrices and multivariate normality were satisfied, which is a prerequisite for the MANCOVA. A p-value of less than 0.05 was considered significant.

Results

The demographic features of the two groups (pre-pandemic and post-pandemic born premature infants) are presented in Table I. The post-pandemic group had higher birth weight, gestational age, and child age at developmental assesments. In terms of perinatal risk factors, premature infants in both groups were comparable. Except for maternal employment status, there was no difference between the two groups' sociodemographic traits (Table I). Table II provides a detailed breakdown of the Bayley III results, which were applied in both groups when the corrected ages of the prematures were between 18 to 24 months.

Table I. Sociodemographic and clinical characteristics of the pre-pandemic and post-pandemic groups.

	Pre-pandemic group (n=152)	Post-pandemic group (n=84)	p value
	Median (min-max) / n (%)	Median (min-max) / n (%)	
Child age (months)[a]	18.55 (17.50-22.30)	20.00 (17.50-24.00)	**0.000**
Gestational age (weeks)	32 (23-36)	32.82 (24-36)	**0.004**
Birth weight (gram)	1755 (620-4430)	1895 (600-4100)	**0.024**
Infants' perinatal risk			0.163
Low risk	15 (9.8)	14 (16.6)	
Moderate risk	55 (36.1)	34 (40.4)	
High risk	82 (53.9)	36 (42.8)	
Maternal age	32 (21-50)	22 (22-50)	0.552
Maternal education			0.111
≤High school	61 (42.7)	44 (53.7)	
>High school	82 (57.3)	38 (46.3)	
Paternal age	34 (25-51)	35 (26-50)	0.752
Paternal education			0.630
≤High school	65 (45.5)	40 (48.8)	
>High school	78 (54.5	42 (51.2)	
Maternal Edinburg postpartum depressive symptoms score	7 (1-25)	6 (1-20)	0.062
Number of children at home	2 (1-4)	2 (1-4)	0.417
Number of family members	4 (1-7)	4 (3-6)	0.573
Birth order of the child	1 (1-4)	2 (1-4)	0.126
Mother's working status			**0.002**
Employed	54 (37.8)	15 (18.3)	
Unemployed	89 (62.2)	67 (81.7)	
Father's working status			0.689
Employed	142 (99.3)	81 (98.8)	
Unemployed	1 (0.7)	1 (1.2)	

[a]:Corrected age at which developmental assessment was performed were given

Table II. Bayley III scores in the pre-pandemic and post-pandemic groups.

	Pre-pandemic group (n=152)	Post-pandemic group (n=84)
	Mean ± SD (range)	Mean ± SD (range)
Cognitive composite score	93.61±10.72 (60-125)	93.98±11.18 (55-115)
Language composite score	88.31±11.35 (56-118)	88.76±12.95 (53-121)
Motor composite score	90.02±9.75 (46-110)	93.48±12.27 (46-124)
Cognitive scale score	8.72±2.14 (2-15)	8.79±2.23 (1-13)
Language scale score	15.93±3.89 (5-26)	16.09±4.43 (4-27)
Receptive language scale score	8.36±2.20 (2-14)	8.32±2.65 (1-15)
Expressive language scale score	7.57±1.99 (1-13)	7.76±2.03 (2-13)
Motor scale score	16.69±3.22 (2-23)	17.81±4.07 (2-28)
Fine motor scale score	9.04±1.85 (1-13)	9.54±2.14 (1-13)
Gross motor scale score	7.62±1.76 (1-10)	8.24±2.26 (1-16)

In order to accurately interpret the differences in neurodevelopment scores between premature infants following the pre-pandemic period and those born during the pandemic, covariance analysis was performed by controlling group differences (mean birth weight, age at assessment, gestational age, maternal employment status). The first model included the statistically significant factors described in Table I. As one of the strongest predictors of development, the perinatal risk status was also incorporated into the model. The perinatal risk level x group interaction effect was also added to the model to examine its significance. Finally, Model 1 (Supplementary Table IIa) included the following variables: group (pre-post pandemic), mean birth weight, age at assessment, gestational age, maternal employment status, perinatal risk level, and perinatal risk level x group interaction effect; and it revealed that, regardless of the pandemic, the mother's employment status had a positive impact on the cognitive development of premature infants (p=0.002, Supplementary Table IIa, IIb). Since the mother's employment status could be related to her education level and its protective effect on the development of the children was already known, Model 2 was then created by including maternal educational level (Supplementary Table IIIa). According to the analysis's Model 2, which was similar to Model 1 except for maternal employment status substituted with maternal education Bayley scores in the cognitive, language, and motor domains were found to be significantly higher in infants born to mothers with a high school or higher education level (respectively; p=0.000, p=0.000, p=0.000, Supplementary Table IIIa, IIIb). In the final model, birth weight and gestational age (Supplementary Table I), which have previously been used to assess perinatal risk status, were excluded. The final model's findings, presented in Table III, indicate that maternal education level has a positive impact on the neurodevelopmental

outcome of infants (Table III, Supplementary Table IVa). The perinatal risk status was only associated with motor outcome (p = 0.043) (Table III, Supplementary Table IVb), and motor area scores of infants with moderate perinatal risk were significantly higher than those of infants with high perinatal risk (p = 0.037) (Supplementary Table IVc).

Discussion

The fact that the majority of studies on the early developmental effects of the COVID-19 pandemic have mostly been based on parent reporting has commonly drawn criticism.[7,11,15]

Shuffrey et al. revealed that they had more delays in gross motor, fine motor, and personal social development in the Ages and Stages Questionnaire (ASQ) filled out by parents compared to the pre-pandemic period.[11] According to Huang et al., there was no difference in the development of 6-month-old term-born infants who were assessed by clinic staff using the ASQ compared to the pre-pandemic period. Besides that, delays in fine motor and communication areas were found in children at one year of age in the study's follow up.[13] A recent meta-analysis investigating the neurodevelopmental effects of COVID-19 in infancy reported that overall neurodevelopment in the first year of life was not changed by either being born or raised during the SARS-CoV-2 pandemic or by gestational exposure to SARS-CoV-2. The limitations of the research, as stated by the authors, include the use of the ASQ for developmental evaluation, which was mainly filled out with parental reports, and the focus on the pandemic's impacts exclusively in the first year of life.[23] This study, using an objective tool, Bayley III, for the developmental assessment of children aged 18-24 months and constituting a pure group of premature infants, will provide an important contribution to a yet not much studied area. No significant difference in neurodevelopment was detected compared with the pre-pandemic period. The neurodevelopmental results of two-year-old

Table III. Covariance analysis of the factors effecting Bayley III composite scores.

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	cognitive scores	3282.866a	7	468.981	4.779	0.000
	language scores	3032.084b	7	433.155	3.472	0.002
	motor scores	2388,413c	7	341.202	3.478	0.002
Groups (pre-post pandemic)	cognitive scores	22.372	1	22.372	0.228	0.634
	language scores	35.921	1	35.921	0.288	0.592
	motor scores	217.144	1	217.144	2.214	0.138
Perinatal risk level	cognitive scores	348.693	2	174.346	1.777	0.172
	language scores	124.664	2	62.332	0.500	0.608
	motor scores	626.219	2	313.110	3.192	**0.043**
Age at assessment	cognitive scores	179.222	1	179.222	1.826	0.178
	language scores	16.990	1	16.990	0.136	0.712
	motor scores	129.942	1	129.942	1.325	0.251
Perinatal risk level x group interaction effect	cognitive scores	282.811	2	141.406	1.441	0.239
	language scores	247.281	2	123.640	0.991	0.373
	motor scores	93.506	2	46.753	0.477	0.622
Maternal education level	cognitive scores	2684.902	1	2684.902	27.360	**0.000**
	language scores	2701.255	1	2701.255	21.650	**0.000**
	motor scores	1212.617	1	1212.617	12.362	**0.001**

a: R Squared = 0.140 (Adjusted R Squared = 0.110), b: R Squared = 0.106 (Adjusted R Squared = 0.075), c: R Squared = 0.106 (Adjusted R Squared = 0.075), $p<0.05$ is significant

infants born before and after the pandemic weren't distinct, according to a current investigation that only examined preterm babies.[14]

The relationship between modifications in the neurodevelopment of premature babies and environmental factors, including maternal education, the number of children living at home, parents' stable union, the knowledge and experience of parents, parent-child interaction, and parental mental health, has been demonstrated in recent research.[16,24,25] The pandemic raised stress levels among parents, and especially in women who were pregnant during the pandemic, stress, anxiety, and depression symptoms were more prevalent in both the prenatal and postpartum periods.[7,8] In a study conducted following a previous disaster, it was found that these effects, which were associated with parental stress in children's development at 6 months of age in problem solving and personal social skills, vanished with responsive parental care at 30 months.[26] The maternal Edinburgh postpartum depressive symptoms scores in this study did not significantly differ between the groups. This could be attributable to the mothers in the study not having COVID-19 during pregnancy, the fact that they gave birth in a tertiary hospital and were monitored, or other protective factors. On the other hand, research conducted throughout the pandemic period has indicated an increase in the amount of time parents spend with their kids, which may have given rise to opportunities to improve parent-child interactions.[9] Despite the enormous difficulties the pandemic brought, social changes like having older siblings at home, parents working from home, and the opportunity to spend more time with the family may have lessened the effects of pandemic-induced stressors on young children.[7,27]

Another issue is that the pandemic reduced access to healthcare services and interrupted well-child follow-up. This precludes the diagnosis of developmental delays and referral to early intervention programs for children.[28] However at Hacettepe University Divison of Developmental Pediatrics where the study was conducted developmental pediatricians continued developmental evaluations of the premature babies and gave recommendations based on those assessments. Although early intervention services were unavailable during closures and strict social restrictions, families were informed of developmentally urgent situations throughout the visits and home based development promotion activities. Follow-up care for premature infants in a developmental pediatric outpatient clinic may have been a protective factor that could have had a positive impact on the infants' development. The detrimental effects of this process on children can be mitigated by improving health care services that were interrupted during the pandemic.

The protective effect of maternal education level on the neurodevelopment of premature infants at 18 to 24 months, regardless of the pandemic, is one of the study's key findings. Children of highly educated mothers tend to benefit from greater exposure to stimulating learning opportunities; education can enhance mothers' ability to be sensitive and nurturing with their children as well as increase the likelihood that mothers enroll their young children in early childhood education programs.[29] The high biological risks associated with preterm birth, however, may mitigate the beneficial effects of environmental factors on developmental outcomes. It is now widely known that brain injury and neurodevelopmental problems are related, but less is known about how experiences and the environment affect these relationships.[30,31] In the study by Joseph et al., it was demonstrated that, regardless of the gestational age of extremely preterm infants, a high maternal education level is significantly correlated with neurocognitive skills at the age of 10 years.[30] Another comprehensive study found that preschool-aged premature children with higher maternal education had better cognitive and motor skills. Furthermore, the link between brain injury and poor cognitive

outcomes in children born preterm was attenuated in children born to mothers of higher education level.[31] In contrast, Doyle et al. found that among extremely preterm survivors, perinatal biological risks persisted with negative associations with cognitive and academic outcomes until adolescence, and some social variables, like maternal education, assumed increasing importance in later years but mostly did not diminish or exceed the significant biological associations.[18] Despite these variations in studies, it is widely accepted that social and biological factors interact to influence how premature infants develop.

The long-term neurodevelopmental outcomes of preterm infants are known to be adversely impacted by postnatal comorbidities like infections, low arterial pH of umbilical cord blood, prolonged mechanical ventilation, ROP, BPD, severe IVH, PVL, and brain injury. As the gestational week and birth weight decrease, these risks rise.[16,18,31,32] The majority of the comorbidities mentioned in the literature are included in the high-risk group of the perinatal risk classification used in this study, and as a result, the motor development scores of high-risk premature infants were significantly lower than those of moderate-risk infants. Furthermore, the cognitive and language developmental scores fell as the perinatal risk level increased, though this trend was not statistically significant. In a current study that was similar to our study, the perinatal risks of premature babies born at 25–35 weeks of gestation and the results of the Bayley III evaluation at 36 months were assessed, and it was found that high-risk perinatal circumstances were associated with lower motor scale scores.[33] In the study by Lean et al., it was demonstrated that among very preterm children, medical risk was related to motor outcome at 5 years, and neonatal white matter abnormalities predicted worsening cognitive and motor development. The neural networks that support the development of motor skills mature in infancy, making them more susceptible to biological insults during the neonatal period compared to later developing cognitive and language networks. This may explain how medical risks of infants affect motor skills.[25] The motor scores of the low-risk infant group, on the other hand, were not significantly higher than those of the moderate and high perinatal risk groups in the study. The small number of infants at mild risk may be responsible for this. It could also be because mild motor delays in these infants go unnoticed or are not referred to services for early intervention. It has been emphasized in the literature that the rate of referral of late-term and low-risk preterm infants to early intervention services is lower than that of low gestational weeks and that these infants' developmental risks and delays should be closely monitored.[34,35]

One of our study's strength is that, unlike previous research, we focused on the pandemic's impact exclusively on the development of premature infants. Furthermore the study addressed significant risk and protective factors that may influence the developmental evaluation results of babies, such as perinatal risks, sociodemographic characteristics, and maternal postpartum depression. A confounding factor was also removed as the babies were not exposed to intrauterine COVID-19. Another strength is that we assessed children between the ages of 18 and 24 months, which will produce more reliable results in terms of developmental outcomes than the studies in the literature that look at the effects of the pandemic on younger children's development. Additionally, this study is valuable in that it eliminates biased results based on parental reports as the developmental assessments were conducted by skilled specialists using the Bayley III, a dependable and objective tool.

The most significant limitation of our study is the lack of data on other family dynamics, such as parental stress and anxiety levels, self-efficacy, effective stress-coping techniques, time spent with the child at home, and financial hardships, aside from maternal postpartum depression. The study included all premature infants (except for premature infants with visual and hearing impairments and infants with an autism

spectrum disorder diagnosis or suspicion) born between March 2020 and December 2020 and followed up in our developmental pediatrics clinic. However the study's single-center design and inclusion of premature babies born during the pandemic limited the number of cases included in the study. Given these limitations, it is not appropriate to generalize the research findings to all premature infants, but this study contributes to the lack of literature on this topic and highlights the need for multicenter or cohort studies.

Conclusion

Although children's developmental surveillance is always important, it becomes crucial during pandemics. Premature infants should be handled separately throughout this process, and their long-term follow-up should be maintained, as they are one of the most vulnerable groups in terms of developmental delay due to their biological and environmental risks. Additionally, it can be hypothesized that severe postnatal comorbidities, perinatal risks, and social factors, such as maternal education level, interact to affect the long-term neurodevelopmental outcomes of preterm infants.

Supplementary materials

Supplementary materials for this article are available online at https://doi.org/10.24953/turkjpediatr.2024.4551

Ethical approval

This study was approved by the Ethics Committee of Hacettepe University Faculty of Medicine (GO 22/828).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: EO, ENMK , GÖ, BSK, SK, HCİ, ECC, AMY, HTÇ, SK, ENÖ; data collection: EO, ENMK , GÖ, BSK, SK, HCİ, ECC, AMY ; analysis and interpretation of results: EO, SK; draft manuscript preparation: EO, ENMK , GÖ, BSK, SK, HCİ, ECC, AMY, ENÖ, HTÇ, SK. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

The role of certain perinatal features in the early motor repertoire of infants

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ABSTRACT

Background. Lower gestational age negatively affects the neurodevelopmental outcomes of infants. Early motor repertoire is a reliable way to predict neurodevelopmental outcomes. This study aimed to determine the correlation between gestational age and early motor repertoire in infants and also the roles of multiple pregnancies, gender, cranial utrasonography (USG) results, and birth weight in this relationship.

Methods. This study included 139 infants, who were video recorded 9-17 weeks post-term. The recordings were evaluated using the Motor Optimality Score-Revised (MOS-R). Structural equation modeling tool was used for the path analysis of the models.

Results. There was a weak positive correlation between gestational age and the MOS-R. In the relationship between gestational age and the MOS-R, multiple pregnancies, gender, and USG outcomes had a moderating effect. While abnormal USG, male gender, and singleton pregnancy increased this correlation to a moderate level, normal USG reduced the strength of the correlation. Female and twin pregnancies were non-significant in the model. Birth weight had a full mediating effect on the relationship between gestational age and the MOS-R.

Conclusions. Infants with younger gestational age or lower birth weight, male infants, and infants with problems on cranial USG may have poorer early motor repertoire.

Key words: birth weight, gestational age, motor repertoire, gender, cranial ultrasonography.

Factors like gestational age, birth weight, multiple pregnancy, and gender are associated with the neurodevelopmental outcomes of infants.[1,2] Lower gestational age and birth weight cause increases in the prevalence of cerebral palsy (CP).[3] Infants surviving very low/extremely low birth weight face increased risk in terms of death, growth retardation, and delayed neurodevelopment.[4] Additionally, multiple-pregnancy infants are four times more likely to have CP compared to singletons.[5] Triplet and quadruplet infants have higher CP prevalence than twins.[6] When examined in terms of gender, CP is observed more frequently in boys compared to girls and boys are at a disadvantage in terms of the risk of a more severe motor disorder.[7,8]

Damages occurring in the central nervous system (CNS) structures of infants due to problems such as intraventricular hemorrhage, hypoxic ischemic encephalopathy, and epilepsy and the severity of this damage may provide information about the developmental outcome of infants.[9] With the aim of determining injury to CNS structures, cranial ultrasonography (USG) is a common and predictive tool used for infants at risk for adverse outcomes.[10]

Detailed General Movements Assessment (GMA) is one of the most rapid and effective

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methods to assess CNS functions of an infant by examining the early motor repertoire of the infant.[11] Additionally it is one of the tools that can most accurately predict later neurological deficits.[11,12] It is possible to define the motor repertoire and posture of an infant with detailed GMA. Higher scores in the Motor Optimality Score-Revised (MOS-R) obtained as a result of detailed GMA show optimal neurodevelopmental outcomes, while lower scores indicate adverse neurodevelopmental outcomes.[13] Due to all these features, the MOS-R may guide early intervention practices.

If the MOS-R can accurately predict the neurodevelopmental outcome of an infant, it is expected that it will be affected by other variables impacting neurodevelopmental status. Many studies in the literature have shown that many perinatal characteristics are associated with the long-term outcome of infants.[4-8] However, the relationship between these variables and the MOS-R has not been determined. With the establishment of this relationship, the variables that may affect the motor repertoire of an infant will be clarified, and the data can be interpreted accordingly. Thus, we expect that by observing the infant's motor repertoire and predicting the developmental outcome, we can contribute to obtaining more accurate results in starting early intervention. For this reason, the aim of the current study was to provide answers to the following questions:

Is there a correlation between MOS-R and the gestational age of infants?

If there is, what are the roles of multiple pregnancy, gender, cranial USG results, and birth weight in this relationship?

Materials and Methods

Study design

This prospective cohort study was approved by the local non-interventional clinical research ethics committee (GO 21/895). Informed voluntary consent forms were signed by the families of infants included in the study.

Participants

The study included all infants at risk for neurodevelopmental problems with post-term age of 3-5 months who were referred to our outpatient clinic and applied to the Pediatric Neurology Unit of Ondokuz Mayıs University Children's Hospital between September 2021 to September 2022. Infants with major brain malformations, genetic disorders, musculo-skeletal problems (brachial plexus lesion, torticollis etc.), epilepsy, sepsis, or hypoxic ischemic encephalopathy were excluded from the study (Fig. 1). The sample size was determined as 100-150 participants to reach the minimum satisfactory size for the structural equation model.[14] As a result, the study was completed with 139 infants.

Outcome measures

Detailed General Movement Assessment (GMA): The detailed GMA evaluates motor repertoire via 3-5 minute videos of infants aged 9-17

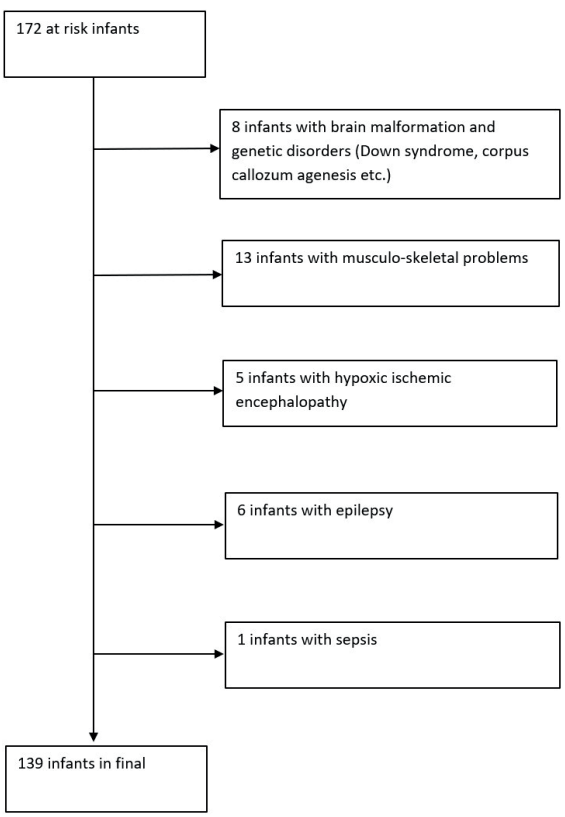

Fig. 1. Flow chart.

weeks. In detailed GMA, videos are assessed in 5 subcategories: The subcategories are fidgety movements, observed movement patterns, age-adequate movement repertoire, observed postural patterns, and movement character. Fidgety movements are scored as normal (12 points), abnormally exaggerated (4 points), and absent (1 point). Observed movement patterns are scored as normal patterns dominant (4 points), normal and atypical patterns equal (2 points), and atypical patterns dominant (1 point). Age-adequate movement is scored as present (4 points), reduced (2 points), and absent (1 point). Observed postural patterns are scored as normal patterns dominant (4 points), normal and atypical patterns equal (2 points), and atypical patterns dominant (1 point). Movement character is scored as smooth and fluent (4 points), abnormal but not cramped-synchronized (2 points), and cramped-synchronized (1 point). The MOS-R is obtained by adding the points in these subcategories. As a result, the MOS-R may be a maximum of 28 and minimum 5 points.[13] According to MOS-R classifications, 25-28 points are optimal.[13]

Clinical Characteristics: Clinical characteristics of the infants were obtained from the infant files (Table I).

Procedures

Videos recorded at the Pediatric Neurology Unit, Faculty of Medicine, Ondokuz Mayıs University were evaluated by researchers AK and AL at the Faculty of Physical Therapy and Rehabilitation, Hacettepe University. Early motor repertoires of the infants were evaluated via videos by detailed GMA according to the score sheet revised in 2019, and the MOS-R was calculated.[13] For this, a single video including 3-5 minutes of spontaneous motor movements that was taken while the infant was post-term age of 9-17 weeks in which they were active

Table I. Characteristics of infants.

		Infants (n= 139)
Gestational age, week: median (min max) (IQR)		33 (24-40) (30-37)
	Gestational age ≤ 29 weeks, n (%)	27 (19.4)
	Gestational age between 30-36 weeks, n (%)	76 (54.7)
	Gestational age ≥ 37 weeks, n (%)	36 (25.9)
Birth weight, gram: median (min-max) (IQR)		1856 (620-4470) (1420-2660)
Gender, female, n (%)		53 (38.1)
Multiple pregnancy, n (%)		35 (25.2)
Hospitalization duration, day: median (min-max)		20 (0-270)
Abnormal ultrasonography, n (%)		30 (21.6)
Respiratory distress syndrome, n (%)		39 (28)
Hyperbilirubinemia (TSB value < 25mg/dL), n (%)		17 (12.2)
Congenital hypothyroidism, n (%)		5 (3.6)
Preeclampsia, n (%)		12 (8.6)
Video recording age, week: median (min-max)		12 (9-17)
Weight for gestational age, n (%)	-3 SD	4 (2.9)
	-2 SD	8 (5.7)
	-1 SD	52 (37.5)
	0	7 (5.0)
	1 SD	53 (38.1)
	2 SD	13 (9.4)
	3 SD	2 (1.4)

IQR, interquartile range (25th-75th percentiles); SD, standard deviation; TSB, total serum bilirubin.

and awake, partly dressed, without stimulation in supine position. This was assessed by two raters who were blind to the infants' medical histories, and certified and experienced in detailed GMA.[11] In case of any disagreement, the videos were re-evaluated until a consensus was reached.

Two categories were included in the model as with or without a problem on cranial USG, being female or male, and multiple pregnancy of twin or singleton. Birth weight and gestational age were included as continuous variables in the model.

To identify the correlation between gestational age and the MOS-R and additionally, the role of birth weight, gender, being singleton/twin, and cranial USG results in this correlation, the model in Fig. 2 was created.

Statistical analysis

Statistical analyses were performed using the IBM SPSS v25 software. The fit of numerical variables to normal distribution was determined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov). Number and percentage values were calculated for descriptive statistics. The Kruskal-Wallis test was used to compare three numerical data groups that were not normally distributed (MOS-R of infants were divided into three groups according to gestational age). Post hoc analyses of 3 nonnormally distributed groups were performed using the Mann-Whitney U test after Bonferroni correction. For comparison of two numerical data groups without normal distribution, the Mann-Whitney U test was used, the Chi square test was used for comparison of categorical data groups. The relationship between numerical variables were calculated using the Spearman correlation coefficient. Statistical significance level was accepted as $p<0.05$ (except for moderating variable analysis in normal USG that considers $p<0.1$). To test mediation and moderation effects, the "IBM AMOS Graphics 25.0" software was used. Path analysis was performed using the SPSS Amos Graphics Structural Equation Modeling tool.

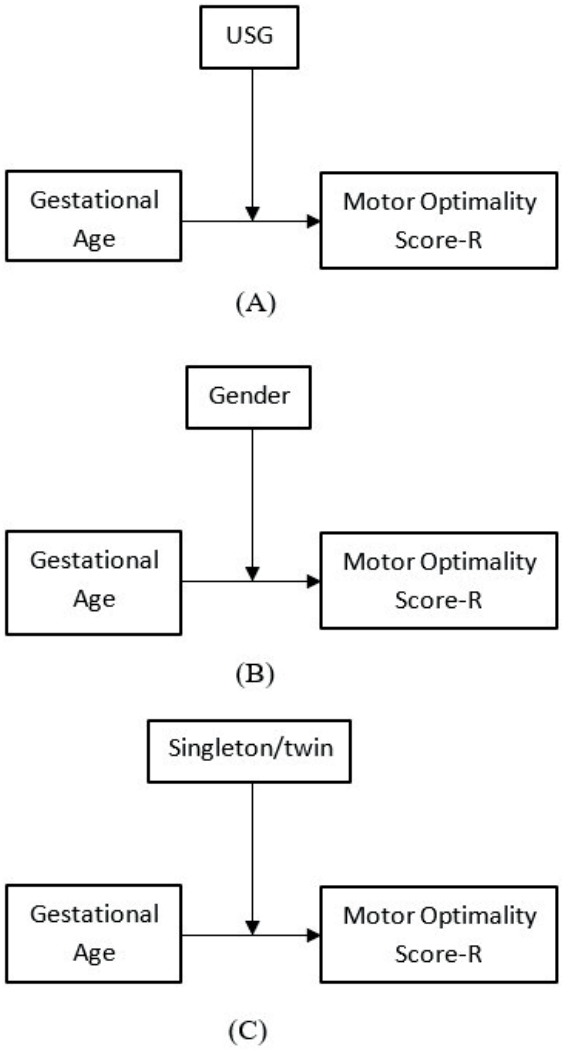

Fig. 2. Testing various moderator variables.

Results

A total of 139 infants, 53 girls (38.1%) and 86 boys (61.9%), were included in the study. The median gestational age of the infants was 33 weeks (min 24 weeks, max 40 weeks). Median birth weight was 1856 g (min 620 g, max 4470 g). According to Fenton growth charts, there were 4 infants within -3 standard deviations (SD), 8 infants in -2 SD, and 52 infants in -1 SD between gestational age and birth weight.[15] There were 104 singleton infants and 35 twin infants (Table I).

Comparison of perinatal characteristics of the infants is given in Table II.

Table II. Comparison of perinatal characteristics of infants (n= 139).

		Birth weight		P value
		<2500 gram	≥2500 gram	
Gestational age, week: median (IQR)		31 (29-34)	38 (37-39)	**<0.001**[a]
		Gender		
		Girl	Boy	
Gestational age, week: median (IQR)		34 (30-38)	33 (30-36)	0.95[a]
Birth weight, gram: median (IQR)		1840 (1290-2830)	1863 (1430-2520)	0.83[a]
		Multiple pregnancies		
		Single	Twin	
Gestational age, week: median (IQR)		33 (29.5-38)	33 (31-34)	0.65[a]
Birth weight, gram: median (IQR)		1960 (1340-2980)	1800 (1440-2000)	0.21[a]
Gender, n (%)	Girl	40 (28.8)	13 (9.4)	0.89[b]
	Boy	64 (46)	22 (15.8)	
		Ultrasonography		
		Normal	Abnormal	
Gestational age, week: median (IQR)		34 (30-37)	32 (29-35)	0.08[a]
Birth weight, gram: median (IQR)		1980 (1540-2780)	1430 (1200-1855)	**0.003**[a]
Gender, n (%)	Girl	44 (31.6)	9 (6.5)	0.30[b]
	Boy	65 (46.8)	21 (15.1)	
Multiple pregnancie, n (%)	Single	79 (56.8)	25 (18)	0.22[b]
	Twin	30 (21.6)	5 (3.6)	

[a]Mann-Whitney U test; [b]Chi-Square Test; IQR, interquartile range (25th-75th percentiles)

The median MOS-R was 24 (min 6, max 28). Forty-nine of the infants (35.2%) had the optimal MOS-R. While 21 infants (15.1%) had absent fidgety movements (n=18 preterm, n=3 term; n=9 female, n=12 male), 2 infants (1.4%) had abnormal fidgety movements (n=2 preterm, n=2 male). None of the infants had cramped synchronized movements. The details of the MOS-R and subcategory scores are presented in Table III.

When infants were divided into three groups in terms of gestational age as very preterm (29 weeks and younger), preterm (30-36 weeks), and term (37 weeks and older), there was a statistically significant difference between the MOS-R of these three groups (p=0.004). The MOS-R of the very preterm infant group was lower than those of the other two groups (very preterm-term p=0.004 and very preterm-preterm p=0.002).

A weak positive correlation existed between gestational age and the MOS-R (p<0.01, r=0.26).[16] Of the variability in the MOS-R, 6.8% could be explained by gestational age. According to the model, multiple pregnancy, gender, and USG results had a moderator effect on the correlation between gestational age and the MOS-R. Abnormal USG increased this correlation to a moderate level (p<0.05, r=0.39), and 15.1% of the variability in the MOS-R was explained. Being a male increased this correlation to a moderate level (p<0.01, r=0.3), and 8.8% of the variability in the MOS-R was explained. Being singleton similarly increased the level of the correlation to moderate (p<0.01, r=0.32) and 10.1% of the variability in the MOS-R was explained. Normal USG findings weakened the level of this correlation (p=0.08<0.1, r=0.165). Being a female or a twin was non-significant in the model. Birth weight fully mediated the relationship between gestational age and the MOS-R (p<0.001, r=0.235) (Fig. 3 and Table IV).

Table III. Detailed general movement assessment of infants.

		Premature (≤37 week) n=111		Term (>37 week) n=28	
		Female n (%)	Male n (%)	Female n (%)	Male n (%)
MOS-R	25-28 is optimal	14 (35.9)	23 (31.9)	7 (50)	5 (35.7)
	20-24 is mildly reduced	18 (46.2)	34 (47.2)	5 (35.7)	8 (57.2)
	9–19 is moderately reduced	7 (17.9)	14 (19.4)	2 (14.3)	1 (7.1)
	5–8 is severely reduced	-	1 (1.4)		
Fidgety score	Normal	32 (82.1)	59 (81.9)	12 (85.7)	13 (92.9)
	Exaggerated	-	2 (2.8)	-	-
	Absent	7 (17.9)	11 (15.3)	2 (14.3)	1 (7.1)
Observed movement patterns	Normal > Abnormal	38 (97.4)	67 (93)	13 (92.9)	12 (85.7)
	Normal = Abnormal	1 (2.6)	4 (5.6)	1 (7.1)	2 (14.3)
	Normal < Abnormal	-	1 (1.4)	-	-
Age-adequate movement repertoire	Age-adequate	21 (53.9)	38 (52.8)	11 (78.6)	8 (57.2)
	Reduced	11 (28.2)	17 (23.6)	3 (21.4)	3 (21.4)
	Absent	7 (17.9)	17 (23.6)	-	3 (21.4)
Observed postural patterns	Normal > Abnormal	21 (53.9)	35 (48.6)	8 (57.2)	10 (71.4)
	Normal = Abnormal	12 (30.7)	22 (30.6)	5 (35.7)	2 (14.3)
	Normal < Abnormal	6 (15.4)	15 (20.8)	1 (7.1)	2 (14.3)
Movement character	Smooth and fluent	7 (17.9)	10 (13.9)	3 (21.4)	3 (21.4)
	Abnormal, not CS	32 (82.1)	62 (86.1)	11 (78.6)	11 (78.6)
	CS	-	-	-	-

CS, Cramped synchronized; MOS-R, Motor Optimality Score-Revised.

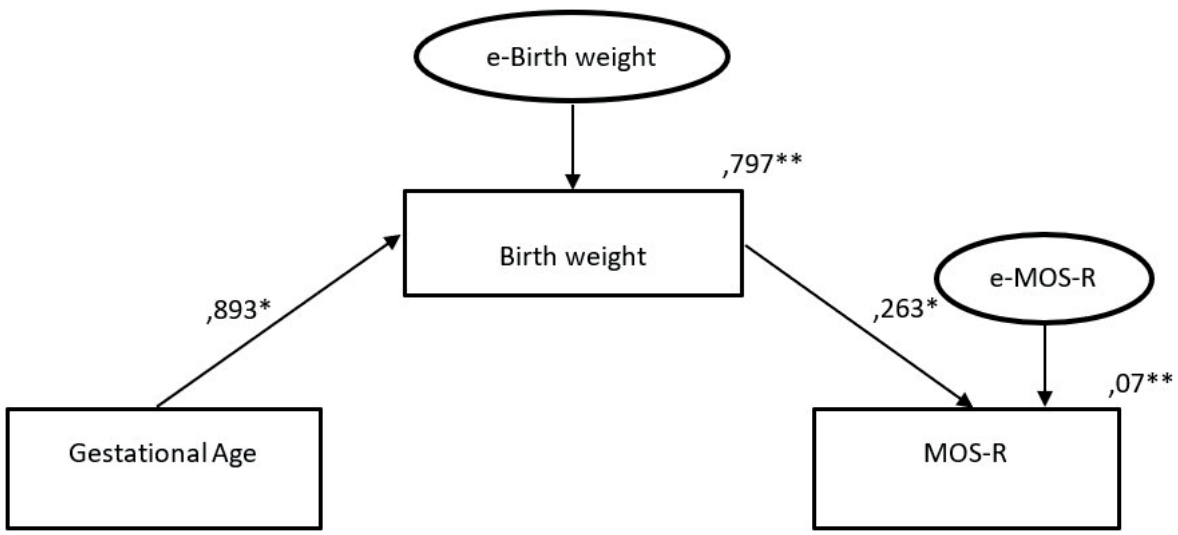

Fig. 3. Demonstration of mediation role of birth weight between gestational age and MOS-R.
(*standardized path coefficients, **coefficient of determination (i.e. R square))

Table IV. Path model and analysis.

	Standardized effects	
	Gestational age (independent variable)	Birth weight (mediator variable)
Birth weight (mediator variable)	0.893	0.000
MOS-R (dependent variable)	0.235	0.263

Mediator variable analysis results

Independent variable	Moderator variable	Dependent variable	N	P value	r
Gestational age →	Abnormal USG	MOS-R	30	**0.022**	0.39
	Normal USG		109	0.084	0.16
Gestational age →	Male	MOS-R	86	**0.004**	0.30
	Female		53	0.12	insignificant
Gestational age →	Singleton	MOS-R	104	**0.03**	0.34
	Twin		35	0.2	insignificant

Moderator variables analysis results

MOS-R: Motor Optimality Score-Revised

Discussion

We aimed to determine the correlation between gestational age and early motor repertoire of infants and additionally the roles of multiple pregnancy, gender, cranial USG results, and birth weight in this relationship. There was a weak positive relationship between gestational age and the MOS-R. Multiple pregnancy, gender, and USG findings were moderator variables of this relationship, whereas birth weight was a mediator variable.

Not all of the variables researched in this study are fully independent. For example, infants with young gestational age have proportionally low birth weights. The birth weight and gestational age of infants born as twins are generally lower than singleton infants. This situation shows that the researched variables affect each other. To remove this effect and to be able to determine the mediating and moderating effects of the variables on each other, structural equation modeling was used as the main statistical method in our research.

Herrero et al.[17] found no correlation between gestational age and birth weight with MOS in a study researching the motor repertoire of infants with Down syndrome (gestational age 29-41 weeks). Fjørtoft et al.[18] reached the same conclusion in a study of extremely preterm (EPT) infants (gestational age mean 26.6 SD 1.8 weeks). Our study includes a larger range of gestational ages (from 24 to 40 weeks). Additionally, as genetic problems have the potential to impact the MOS-R, infants with genetic problems were excluded from the study to remove this effect.[17,19] For this reason, our results may be different from these two previous studies.

Örtqvist et al.[20] in their study comparing EPT infants with term infants, and Salavati et al.[21] comparing very preterm infants with term infants with regards to MOS have found that preterm infants have a poorer motor repertoire. The findings of the current study support the results of these two studies. The findings of these three studies are consistent with the existing knowledge that prematurity increases the risk of poor neurodevelopment.

Dostanic et al.[22] found that GMA quality was only associated with preterm birth, while perinatal factors like being small for gestational age and gender were not associated with GMA quality in a study performed with 89 twin pairs of infants with abnormal neurological signals and/or perinatal risk factors in at least

one of the twins. In the current study, infants with pronounced risk factors were excluded (infants with hypoxic ischemic encephalopathy, sepsis, etc.). Thus, we tried to eliminate other problems that may affect the MOS-R. There is a methodological difference between the two studies as one used detailed GMA and the other used global GMA. Lower MOS-R means an increased risk of adverse outcomes.[13] The finding that very preterm infants had lower MOS-R than preterm and term infants in the current study support the knowledge that reduced gestational age and birth weight increase the risk of adverse neurodevelopmental outcomes.[3,21]

In the current study, a weak positive correlation between gestational age and the MOS-R may be attributed to the fact that the number of infants (n=76) in the preterm group (gestational age between 30-36 weeks) was much higher than in the very preterm and term groups. We suggest that the large correlation may further increase if the groups formed in terms of gestational age include equal numbers of infants. However, our results are important in terms of showing that the expected relationship between motor repertoire and research variables exists.

In studies, male gender was associated with poor neurodevelopmental outcomes, while in the cohort with gestational age younger than 32 weeks, male gender and gestational age were found to be of limited use as prognostic factors.[1] In a study comparing MOS of EPT infants with term infants, Örtqvist et al.[20] stated that gender did not cause a difference in MOS for EPT infants. In the current study, there was no statistically significant difference between the numbers of male and female infants (p=0.5). Being male affected the relationship between gestational age and MOS-R while being female was not. This result may support the correlation of male gender with poor neurodevelopmental outcomes. However, again, there is a need for studies with more participants to further clarify this topic.

Multiple pregnancy is thought to cause increased risk of neonatal morbidity and mortality.[23] The reason for this is generally linked to low birth weight and prematurity.[5] Bonellie et al.[24] stated that being a twin increased the risk of CP rather than preterm birth and low birth weight in their study researching the effect of different risk factors on cerebral palsy in twins. A systematic review in 2018 found no differences between twin-singletons in the research measuring neurodevelopmental outcomes from 1-5 years of age, while some differences were observed in studies measuring neurodevelopmental outcomes at later ages.[25] In light of all these studies, if neurodevelopment is affected by multiple pregnancy, it is expected that MOS-R will be affected. In our study, there was no statistically significant difference between the gestational age and birth weights of singleton and twin infants. Being singleton affected the relationship between gestational age and MOS-R while being twin was not. The number of EPT infants (gestational age <31 weeks) was much higher among singletons in our study which might be the reason for this finding. Additionally, 24% of singletons and 14% of twins had problems on cranial USG. The different number of infants in these two groups (singleton 104, twin 35) may be another reason for the emergence of these results.

Fjørtoft et al.[18] found EPT (<28 weeks) and/or extremely low birth weight (<1000 g) infants had poorer quality of motor repertoire compared to term infants. The authors stated that findings could not be explained by severe abnormalities on neonatal USG scans. In our study, as gestational age increased, the MOS-R increased. Infants with problems on USG had lower MOS-R compared to infants without problems. The gestational age range in our study encompasses a large group. Analyses were not performed according to severe USG findings, and the recently revised MOS-R was used. Therefore, according to the results of the current study, infants with young gestational age and a problem on USG may have lower MOS-R and thus, may have higher risk of poor

neurodevelopmental outcomes.

In very preterm infants, neurodevelopmental outcomes may be associated with diverse variables such as gender and gestational age; however, these variables alone cannot explain poorer motor or cognitive function.[1] The MOS-R is a predictive tool. Additionally, developments in technology and care conditions as well as all medical and rehabilitation applications within the scope of early intervention have positive effects on the neurodevelopment of infants. The fact that all these interventions are associated with mortality and morbidity rates may have resulted in the lower-than-expected effect of the perinatal factors on MOS-R in the study.

The lack of equal numbers of infants included in the groups during analysis (twin-singleton, etc.) is a limitation of the study. Additionally, it may be important to follow up long term, and to reach higher numbers of infants to be able to clarify the results.

In conclusion, the weak positive relationship between gestational age and early motor repertoire is affected by birth weight, which is a mediator variable, and multiple pregnancy, gender, and USG findings, which are moderator variables. Infants with younger gestational age or lower birth weight, male infants, and infants with problems on cranial USG may have poorer early motor repertoire. The potential of these perinatal characteristics to impact the infant's neurodevelopmental outcome may be determined by evaluating the infant's early motor repertoire. Subsequently, it is possible to start early intervention at a very young age.

Ethical approval

This study was approved by Hacettepe University, non-interventional clinical research ethics committee (GO 21/895). Informed voluntary consent forms were signed by the families of infants included in the study.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: AK, AA, GÖT, AL; data collection: AA, GÖT; analysis and interpretation of results: AK, AA, SE, AL; draft manuscript preparation: AK, AA, GÖT, AL. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

The predictive role of lung clearance index on FEV_1 decline in cystic fibrosis

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ABSTRACT

Background. The lung clearance index (LCI) is a sensitive lung function index that is used to detect early lung disease changes in children with cystic fibrosis (CF). This study aimed to define the predictive role of baseline LCI, along with other potential factors on the change in forced expiratory volume in one second (FEV_1) during one-year follow-up in CF patients who had a percent predicted (pp) FEV_1 ≥80.

Methods. LCI was concurrently performed on 57 CF patients who had $ppFEV_1$ ≥80 at month zero. The $ppFEV_1$ decline was evaluated prospectively during the one year follow up. The primary outcome of $ppFEV_1$ decline in the study group in one year was dichotomized according to the median value for the decline in $ppFEV_1$, which was 3.7. The LCI value predicting $ppFEV_1$ decline at the end of one year was calculated with receiver operating characteristic curve analysis. Regression analysis was performed. Furthermore, a decision tree was constructed using classification and regression tree methods to better define the potential effect of confounders on the ppFEV1 decline.

Results. The LCI value for predicting $ppFEV_1$ decline >3.7% at the end of one year was 8.2 (area under the curve: 0.80) Multivariable regression analysis showed that the absence of the F508del mutation in at least one allele, LCI >8.2 and initial FEV_1 z-score were predictors of a $ppFEV_1$ decline >3.7 ($p<0.001$). Factors altering $ppFEV_1$ decline>3.7% at the end of one-year evaluated by decision trees were as follows: initial FEV_1 z-score, type of *CFTR* mutation, LCI value and initial weight-for-age z-score.

Conclusions. LCI is sensitive for predicting $ppFEV_1$ decline in patients with $ppFEV_1$ ≥80 along with the initial FEV_1-z-score and type of *CFTR* mutation.

Key words: cystic fibrosis, multiple breath wash-out, lung clearance index, spirometry, FEV_1 decline.

Cystic fibrosis (CF) is one of the most common life-limiting genetic diseases that mainly affects the respiratory system. In recent years, the early diagnosis of the disease, close monitoring of lung health and on-site therapy interventions have prolonged the lives of patients with CF (pwCF). Pulmonary involvement is of early onset and progresses insidiously.[1]

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Conventional spirometry has been the standard test used for evaluating lung function in patients with CF. Failure to perform spirometry effectively in young children and the failure to capture changes in spirometry in the early stages of the disease have led to a search for new tests. The lung clearance index (LCI) derived from the multiple breath washout (MBW) test, is the most commonly used index for measuring ventilation distribution inhomogeneity.[2,3]

The rate of forced expiratory volume in one second (FEV_1) decline is related to disease progression and has been shown to predict

mortality. To date risk factors for FEV_1 decline have been identified as non-modifiable factors such as sex, age, CF transmembrane regulator (*CFTR*) genotype, history of meconium ileus, pancreatic insufficiency, and modifiable factors such as pulmonary exacerbations, airway colonization high initial FEV_1 and CF-related diabetes.[4] However, the predictive role of LCI along with these parameters on FEV_1 decline has not been fully established.

The primary aim of this study was to define the predictive role of baseline LCI derived from the MBW technique, along with other potential factors by decision trees on FEV_1 change in a one year follow up in pwCF who had a percent predicted (pp) FEV_1 ≥80 when LCI was performed. Our hypothesis in this study was that a higher baseline LCI would be related to a higher FEV_1 decline in patients with accompanying factors and we also aimed to investigate these factors.

Materials and Methods

Study design

Children between 5-18 years with a confirmed diagnosis of CF, attending a tertiary pediatric CF clinic, who were able to cooperate to spirometry and LCI and had $ppFEV_1$ ≥80 were enrolled.[5] This was a single-center, prospective cohort study. The study was approved by Hacettepe University Ethics Committee for Non-Interventional Studies (GO 20-637). Patients and caregivers gave written consent to participate in the study. The study was conducted between April 2018- April 2019.

The sample size was calculated using the formula below:

$$n = \frac{Z^2_{1-\alpha/2} \times S_P \times (1 - S_p)}{L^2 \times (1 - Prevalans)}$$

(S_P = anticipated specificity, α = size of the critical region [1 − α is the confidence level], $Z_{1-\alpha/2}$ = standard normal deviation corresponding to the specified size of the critical region [α] L = absolute precision desired on either side [half-width of the confidence interval, CI] of sensitivity or specificity)[6]

According to this formula, when $Z_{1-\alpha/2}$=1.96, SP=0.85, L=0.15 and prevalence=0.39 (based on the Turkish cystic fibrosis registry data, where 39% of the patients have low FEV_1% predicted[7]), the minimum sample size was calculated as 56.

The MBW test was performed at the initial visit at the time of inclusion, along with spirometry. The spirometry was then performed at 3, 6 and 12 months during routine outpatient visits. The study was terminated by performing the last spirometry at the twelfth month after the MBW was performed. The patients' demographic data including weight, height, and body mass index (BMI), transcutaneous oxygen saturation, physical examination findings, microorganism growth and colonization status in sputum culture, were recorded. The radiological examinations findings which were performed according to the decision of the clinician, considering the clinical condition of the patients were recorded. At each visit, patients were questioned for acute pulmonary exacerbation (aPEx) signs and compliance with their standard therapies (medications and chest physiotherapy). All aPEx events and intravenous / oral antibiotic therapies that occurred between visits were recorded.

aPEx was defined according to the study conducted by Fuchs et al.[8] Chronic *P. aeruginosa* infection was defined according to the study by Lee et al.[9] Mucus samples for microbiologic analysis were collected at all test occasions.

Measurements

Patients performed the MBW test using a Nitrogen Analyzer connected to a Sensormedics Vmax Spectra 22 Device. Nitrogen (N_2) gas was used as the inert gas. The MBW tests were performed in alliance with the segregation rules according to the ATS/ERS consensus statement.[10-13] MBW measurements were performed by the same staff using the same equipment. MBW test was performed with

the patient in the sitting position, breathing through a mouthpiece, wearing a nose clip. After a relaxed tidal breath, the patient was switched to 100% oxygen breathing until the end-tidal N_2 concentration declined below $1/40^{th}$ of the starting end-tidal concentration for at least three consecutive breaths. The LCI was calculated as the cumulative expired volume divided by the functional residual capacity (FRC) at 1/40 of the initial N_2 concentration. MBW test completion was established when three technically acceptable tests were achieved. All MBW traces were controlled for technical quality and convenient breathing pattern. Calibration was performed prior to testing on each test day. Quality control of MBW trials were conducted according to the 2013 ATS/ERS MBW consensus guideline.[10-12]

Spirometry was performed according to the ATS/ERS statement.[14] Spirometry completion was established when three technically acceptable tests were achieved. The percent predicted values and z-scores were calculated using all age prediction equations for spirometry from the Global Lung Function Initiative.[15] The decline in $ppFEV_1$ at the 12th month was calculated according to the initial $ppFEV_1$.

Statistical analyses were performed using the SPSS version 25.0 software package (IBM, SPSS, Chicago, IL, USA). Normal distribution of data was tested analytically (Kolmogorov-Smirnov/ShapiroWilk tests) and visually (histogram, probability plots). Categorial variables were described as relative and absolute frequencies. Continuous variables which are normally distributed were summarized as mean ± standard deviation (SD) and analyzed using Student's t-test. Repeated measure ANOVA was used for dependent variables for repeated measures that are normally distributed. For significant ANOVA results, Bonferroni test was used for binary comparisons between groups.

Correlations between parameters were assessed using Pearson correlation coefficient (r). The primary outcome $ppFEV_1$ decline in one year was dichotomized according to the median value for the decline in $ppFEV_1$ in one-year follow-up which was 3.7. To define LCI value to predict $ppFEV_1$ decline at the end of one year the patients were grouped into two: patients who had a decline in $ppFEV_1$ ≤3.7 and patients who had a decline in $ppFEV_1$ >3.7 and it was calculated using receiver operating characteristic (ROC) curve analysis. The cut-off point was determined based on Youden index. Regression analysis was performed to adjust the effect of potential confounders on the $ppFEV_1$ decline. The SMOTE approach was used to rebalance the data. Independent variables that had a relation with dependent variables with a p-value of ≤0.25 in univariable regression analysis were further analyzed in a multivariable regression model. We used backward logistic regression analysis using $ppFEV_1$ decline >3.7 (dichotomous variable) as the dependent variable and presence/absence of F508del mutation in at least one allele, baseline LCI, initial FEV_1 z-score, initial weight for age (WFA) as independent variables.

A decision tree was constructed to better define the potential effect of confounders on the $ppFEV_1$ decline. In the decision tree patients were divided into two groups according to the median $ppFEV_1$ decline >3.7. The decision trees were created using the R programming language version 4.0.0. "Rpart" library was used to construct decision trees. The data was divided into training and test data. During the learning phase, a training dataset was used to develop the classification model. In the second step, the test set was used to evaluate the classification model's accuracy after it had been trained using the training set. Accuracy rate, sensitivity and specificity were measures used to assess the model's performance. The "Performance Estimation" library was used to rebalance data using the SMOTE technique.[16-18]

Results

Over the one-year recruitment period among 360 pwCF aged 0-18 years, 57 subjects with $ppFEV_1$ ≥80 who were able to perform the MBW and

spirometry were enrolled. The demographic, microbiologic, radiologic, treatment data and the latest chest X-rays and thorax CT of the patients are summarized in Table I. During the one-year follow-up, 23 patients (40.3%) had aPEx; 14 (24.6%) patients had one, 8 (14%) patients had two, and one (1.8%) patient had 4 exacerbations. The median pulmonary exacerbation number was 1 (interquartile range [IQR]: 1-2) per patient per year. A total of 54 courses of non-prophylactic antibiotics (oral 84.4%, intravenous 15.6%) were used during the study.

The initial, 3, 6, and 12-month spirometry values and BMI-z-score are summarized in Table II. A significant decline in FEV_1 (pp-z-score) and FEF_{25-75} (pp-z-score) in the third, sixth, and twelfth months was shown by using repeated measure ANOVA. There was no significant decline in BMI z-score at the end of one year.

The mean LCI value was 7.39 (± 2.00). The mean LCI was higher in girls, patients without F508del mutation in at least one allele, patients with pancreatic insufficiency, and patients with bronchiectasis/atelectasis. However, they were not statistically significant (p=0.7, p=0.6, p=0.6, p=0.1 respectively) (Table III). According to the Pearson correlation test, there was no correlation between LCI and initial, and twelfth month $ppFEV_1$ and z-scores (r=-0.1 p=0.46, r=-0.08 p=0.53 for initial $ppFEV_1$ and z-scores; r=-0.18 p=0.20, r=-0.13 p=0.3 for twelfth month $ppFEV_1$ and z-scores). No correlation was found between BMI-z-score and FEV_1, FEF_{25-75} z-scores and LCI.

The median $ppFEV_1$ decline for the study group was 3.7 (IQR: 0.5-6.5). The LCI value for predicting $ppFEV_1$ decline >3.7 at the end of one year was calculated using the ROC curve analysis and was found to be 8.2 (area under the ROC curve: 0.80, sensitivity 46.2% [95% CI: 24.1-68.3], specificity 86.4% [95% CI: 75.7-96.3], p<0.001) (Fig. 1).

Regression analysis was performed to evaluate the effect of covariates on $ppFEV_1$ decline. Age, gender, age at diagnosis, presence/absence of F508del mutation in at least one allele, baseline LCI, initial FEV_1 z-score, total acute pulmonary exacerbations, *Pseudomonas aeruginosa* and *Staphlyococcous aureus* colonization, presence of bronchiectasis ± atelectasis, initial WFA and BMI z-score were selected as covariates for predicting a $ppFEV_1$ decline >3.7 in univariable analysis. Multivariable backward logistic regression analysis with presence/absence of F508del mutation in at least one allele, baseline LCI, initial FEV_1 z-score, initial WFA z-score showed that absence of F508del mutation in at least one allele, LCI >8.2 and initial FEV_1 z-score were predictors of $ppFEV_1$ decline >3.7 (p<0.001, Table IV, accuracy: 0.84, sensitivity: 0.81, specificity: 0.88).

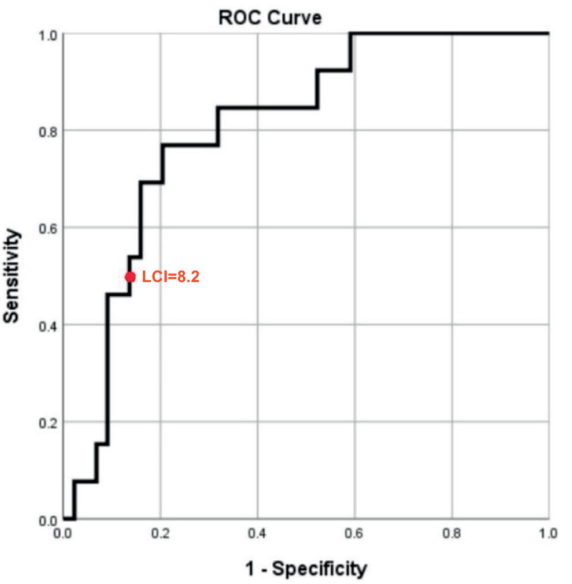

Fig. 1. Receiver operating characteristic (ROC) curve of lung clearance index for predicting ability of FEV_1 decline by > 3.7% at the end of one year. The red dot represents the cut of value lung clearance index=8.2 which is defined by the ROC curve analysis [area under the ROC curve: 0.80, sensitivity 46.2% (95% CI: 24.1-68.3), specificity 86.4% (95% CI: 75.7-96.3), p<0.001]

Table I. Demographic, microbiologic, radiologic, and treatment data of subjects at time of the initial visit (N=57).

Male/female	31/26
Age, yr, mean (SD)	11.6 (3.5)
Age at diagnosis, yr, median (IQR)	0.3 (0.2-1.5)
Genotype, n (%)	
F508del/F508del	10 (17.5)
F508del/other	13 (22.8)
Other/other	34 (59.7)
Exocrine pancreatic insufficiency	50 (87.7)
Chronic liver disease, n (%)	15 (26.3)
Cystic fibrosis related diabetes, n (%)	4 (7)
Weight for age z-score, mean (SD)	-0.31 (1.10)
Height for age z-score, mean (SD)	-0.47 (1.08)
BMI z-score, mean (SD)	0.01 (1.09)
Transcutaneous oxygen saturation (%), mean (SD)	96.9 (1.5)
Microbiological growth (sputum or deep oropharyngeal), n (%)	
Methicillin sensitive *Staphylococcus aureus*	32 (56.1)
Methicillin resistant *Staphylococcus aureus*	9 (15.8)
Pseudomonas aeruginosa	16 (28.1)
Haemophilus influenzae	2 (3.5)
Burkholderia cepacia	2 (3.5)
Stenotrophomonas maltophilia	2 (3.5)
Achromobacter	1 (1.8)
Candida species	9 (15.8)
Aspergillus fumigatus	2 (3.5)
Microbiological colonization, n (%)	
Staphylococcus aureus	42 (71.9)
Pseudomonas aeruginosa	15 (26.3)
Chest X-ray, n (%)	57 (100)
Normal	3 (5.3)
Pulmonary infiltration	3 (5.3)
Chronic changes	51 (86.4)
(air trapping, mosaic pattern, bronchiectasis and/ or atelectasis)	
Thorax CT, n (%)	10 (17.5)
Atelectasis	6 (10.5)
Bronchiectasis	8 (14)
Mucus plugs	8 (14)
Lymphadenopathy	4 (7)
Medications	
Inhaled dornase alpha, n (%)	
Adherent to treatment	52 (91.2)
Not adherent to treatment	3 (5.3)
Not recommended by the physician	2 (3.5)
Inhaled mannitol or hypertonic saline, n (%)*	
At month zero	0 (0)
Chest physiotherapy, n(%)	
Regular	44 (77.2)
Irregular	13 (22.8)

BMI: body mass index, CT: computed tomography, IQR: interquartile range, SD: standard deviation, yr: year.
* Only one patient started inhaled mannitol treatment at the third month, and five patients started inhaled hypertonic saline treatment at the sixth month visit.

Table II. Percent predicted and z-scores of FEV_1 and FEF_{25-75} and BMI z-score at initial, third, sixth and twelfth month.

Spirometry parameters	Clinical visit time (month)				p value
	0	3	6	12	
FEV_1, mean (SD)					
% predicted	107.0 (15.7)	102.6 (17.7)	102.6 (17.7)	101.4 (18.9)	0.001*
z-score	0.55 (1.59)	0.12 (1.90)	0.12 (1.90)	-0.09 (1.98)	0.001**
FEF_{25-75}, mean (SD)					
% predicted	107.2 (35.9)	98.8 (37.4)	98.8 (37.4)	94.1 (37.3)	<0.001+
z-score	0.14 (1.94)	-0.29 (2.11)	-0.29 (2.11)	-0.53 (2.17)	<0.001++
BMI z-score, mean (SD)	0.01 (1.09)	-0.09 (1.06)	-0.09 (1.06)	-0.08 (1.03)	0.5

* FEV_1 %predicted month 0 is statistically significant with FEV_1 %predicted month 6 (sig: 0.01) and FEV_1 %predicted month 12 (sig: 0.01), but not with FEV_1 %predicted month 3 (sig: 0.06). FEV_1 %predicted month 3 is not significant with FEV_1 %predicted month 6 (sig: 0.9) and FEV_1 %predicted month 12 (sig: 0.9). FEV_1 %predicted month 6 is not significant with FEV_1 %predicted month 12 (sig: 0.9).
** FEV_1 z score month 0 is statistically significant with FEV_1 z score month 3 (sig: 0.03) FEV_1 z score month 6 (sig: 0.01), FEV_1 z score month 12 (sig: 0.005). FEV_1 z score month 3 is not significant with FEV_1 z score month 6 (sig: 0.9) and FEV_1 z score month 12 (sig: 0.9). FEV_1 z score month 6 is not significant with FEV_1 z score month 12 (sig: 0.9).
+ FEF_{25-75} %predicted month 0 is statistically significant with FEF_{25-75} %predicted month 3 (sig: 0.01), FEF_{25-75} %predicted month 6 (sig: 0.01) and FEF_{25-75} %predicted month 12 (sig: 0.001). FEF_{25-75} %predicted month 3 is not significant with FEF_{25-75} %predicted month 6 (sig: 0.9) and FEF_{25-75} %predicted month 12 (sig: 0.6). FEF_{25-75} %predicted month 6 is not significant with FEF_{25-75} %predicted month 12 (sig: 0.7).
++ FEF_{25-75} z score month 0 is statistically significant with FEF_{25-75} z score month 3 (sig: 0.02) FEF_{25-75} z score month 6 (sig: 0.01), FEF_{25-75} z score month 12 (sig: 0.001). FEF_{25-75} z score month 3 is not significant with FEF_{25-75} z score month 6 (sig: 0.9) and FEF_{25-75} z score month 12 (sig: 0.9). FEF_{25-75} z score month 6 is not significant with FEF_{25-75} z score month 12 (sig: 0.9).
BMI: body mass index, FEF_{25-75}: forced expiratory flow between 25% and 75% of forced vital capacity, FEV_1: forced expiratory volume in the first second, SD: standard deviation.

Table III. The mean lung clearance index value of patients according to different categories.

	Lung Clearance Index Mean (SD)	p value
Gender (n)		0.7
Female (26)	7.52 (1.40)	
Male (31)	7.28 (1.56)	
CFTR mutation (n)		0.6
F508del in at least one allele present (23)	7.21 (1.74)	
F508del absent (34)	7.51 (2.18)	
Pancreatic insufficiency (n)		0.6
Present (50)	7.46 (1.10)	
Absent (7)	6.88 (0.94)	
Bronchiectasis / atelectasis (n)		0.1
Present (33)	7.76 (2.10)	
Absent (24)	6.90 (1.57)	
Pulmonary exacerbation during one year interval (n)		0.3
Present (23)	7.10 (1.50)	
Absent (34)	7.60 (1.30)	

* *CFTR*: cystic fibrosis transmembrane conductance regulator, SD: standard deviation.

Table IV. Backward logistic regression analysis for variables predicting $ppFEV_1$ decline >3.7.

Model	Odds ratio	95% CI	Sig
Step 1			
Constant	1.34	0.65-2.75	0.4
Absence of F508del mutation	0.014	0.002-0.093	<0.001
LCI >8.2	7.15	2.1-24.0	0.001
Initial FEV1 z- score	0.19	0.09-0.41	<0.001
Initial WFA z -score	1.22	0.62-2.42	0.6
Step 2			
Constant	1.32	0.65-2.70	0.4
Absence of F508del mutation	0.013	0.002-0.082	<0.001
LCI >8.2	7.65	2.31-25.31	<0.001
Initial FEV_1 z- score	0.19	0.09-0.42	<0.001

CI: confidence interval, LCI: lung clearance index, $ppFEV_1$: percent predicted forced expiratory volume in one second, sig: significance, WFA: weight for age.

The independent variables that had a relation with >3.7 $ppFEV_1$ decline in univariate analysis were also analyzed by decision trees. Patients who had $ppFEV_1$ decline >3.7 were grouped as "high", whereas the second group consisted of patients who had $ppFEV_1$ decline ≤3.7 and were grouped as "low" in the decision trees. Only 22.8% of the patients (n:13) had $ppFEV_1$ decline >3.7. To overcome the class imbalance problem in the first step 10% of the dataset was reserved for validation. The SMOTE approach was used to resample and balance the remaining dataset. The data set which became balanced in terms of the class distributions of outcome then were then split into parts: 70% for train data set and 30% for test data set. Using the train data set, a decision tree was created. The first splitting variable is initial FEV_1 z-score followed by *CFTR* mutation analysis, LCI ≤8.2 defined by ROC curve, and initial WFA z-score. The predicted class is shown by colors, with pink representing a decrease of ≤3.7% in FEV_1 and blue representing a decrease of >3.7% in FEV_1.

The classification rules of the decision tree generated by the CART algorithm are given as follows:

1) If a patient's initial FEV_1-z-score is ≥0.62, a decline in $ppFEV_1$ in one year follow up will be ≤3.7 with a 100% probability.

2) If a patient's initial FEV_1-z-score is <0.62 and has a F508del mutation in at least one allele, a decline in $ppFEV_1$ in one year follow up will be ≤3.7 with a 91% probability.

3) If a patient's initial FEV_1-z-score is between -0.60 and 0.62, the patient does not have a F508del mutation, LCI is ≤8.2 and initial WFA-z-score is ≥0.27, a decline in $ppFEV_1$ in one year follow up will be ≤3.7 with an 80% probability.

4) If a patient's initial FEV_1-z-score is between -0.60 and 0.62, the patient doesn't have a F508del mutation, LCI is ≤8.2 and initial WFA-z-score is less than 0.27, a decline in $ppFEV_1$ in one year follow up will be >3.7 with an 88% probability.

5) If a patient's initial FEV_1-z-score is between -0.60 and 0.62, the patient doesn't have a F508del mutation and LCI >8.2, a decline in $ppFEV_1$ in one year follow up will be >3.7 with a 93% probability.

6) If a patient's initial FEV_1-z-score is less than -0.60, a decline in $ppFEV_1$ in one year follow up will be >3.7 (Fig. 2).

The results of the decision tree show that factors altering $ppFEV_1$ decline >3.7% at the end of one year are the initial FEV_1 z-score, type of CFTR mutation, LCI value and initial weight-for-age z-score. According to the results of performance

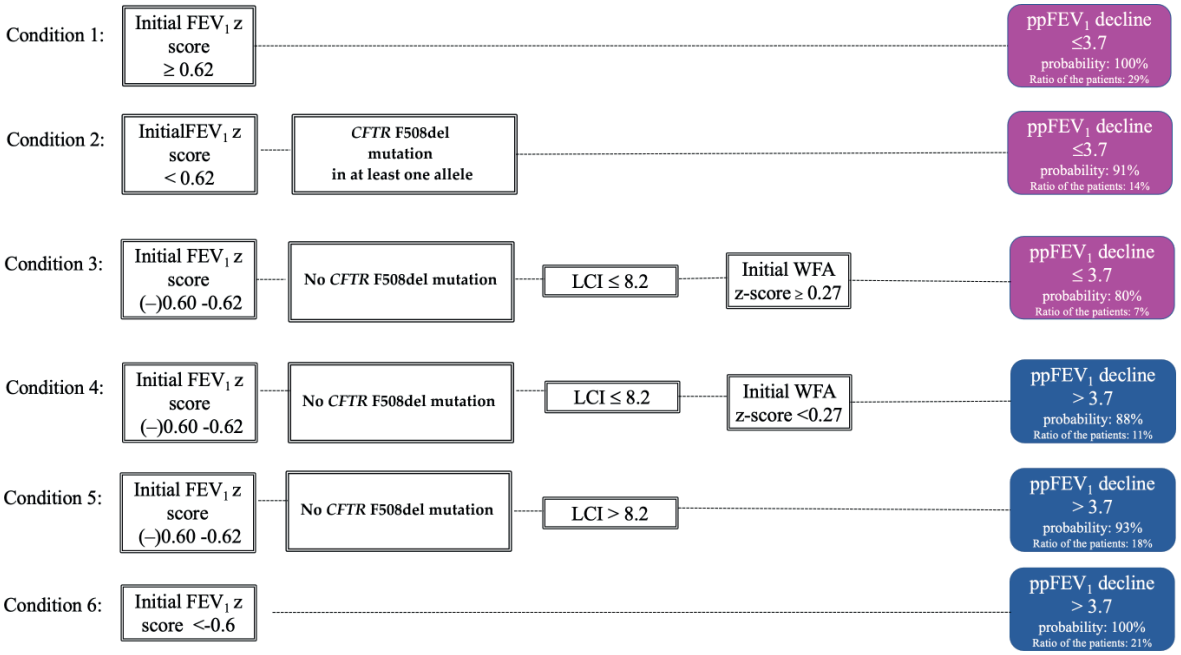

Fig. 2. Decision tree for determining FEV1 decline >3.7.

The first splitting variable is initial FEV_1 z-score followed by CFTR mutation analysis, LCI ≤8.2 defined by ROC curve, and initial WFA z-score. The predicted class is shown by colors, with pink representing a decrease of ≤3.7% in FEV_1 and blue representing a decrease of >3.7% in FEV_1.

The classification rules of the decision tree generated by the CART algorithm are given in the figure and in the text.

*CFTR: cystic fibrosis transmembrane regulator, LCI: lung clearance index, $ppFEV_1$: percent predicted forced expiratory volume in one second, WFA: weight for age.

metrics the model's ability to predict whether a decrease in $ppFEV_1$ in one-year follow-up was lower than or equal to greater than 3.7% which is quite strong (Train dataset accuracy: 94.7%, sensitivity: 95%, specificity 95%; Test dataset accuracy: 87.5%, sensitivity: 81%, specificity: 94%; validation dataset accuracy: 84.6%, sensitivity: 100%, specificity 80%). The detailed results of the decision tree model including the accuracy, sensitivity and specificity and confusion matrix for each dataset (train, test and validation) are shown in Table V and VI.

Discussion

In our tertiary pediatric CF clinic, spirometry was performed on 250 patients during 2019, among these patients 23% had $ppFEV_1$ ≥80. Therefore, this wide cohort of patients required a more sensitive method for monitoring lung health which would enable us to apply the right interventions when necessary. To achieve this goal, we aimed to determine an LCI value that could be a warning for a near-future $ppFEV_1$ decline along with other potential predictors. In this first report of LCI results in pwCF from Turkey designed in a mild CF population including school-age children and adolescents we found that $ppFEV_1$ significantly declined during a one-year follow-up in patients who initially had a $ppFEV_1$ ≥80. This decline in $ppFEV_1$ was >3.7 in almost one quarter of the patients. For this reason, LCI values were calculated using ROC curve analysis; the value that could predict FEV_1 decline >3.7% was found to be 8.2. The other predictors for $ppFEV_1$ decline along with LCI were the initial FEV_1-z-score, type of *CFTR* mutation and initial WFA z-score.

The annual $ppFEV_1$ decline in different studies ranges between 0.06-3.64%.[4] The $ppFEV_1$ decline in our study, which was 3.7%, is significantly higher compared to other studies. The higher

Table V. The accuracy, sensitivity and specificity of the decision tree model.

	Train dataset	Test dataset	Validation dataset
$ppFEV_1$ decline <3.7	38 (50%)	16 (50%)	10 (76.9%)
$ppFEV_1$ decline ≥ 3.7	38 (50%)	16 (50%)	3 (23.1%)
Accuracy	94.74 %	87.5 %	84.62 %
Sensitivity	0.947	0.812	1.000
Specificity	0.947	0.937	0.800
Positive predictive value	0.947	0.928	0.600
Negative predictive value	0.947	0.833	1.000

$ppFEV_1$: percent predicted forced expiratory volume in one second

Table VI. The confusion matrix for train, test and validation dataset for the decision tree model.

Prediction for train dataset, n	Reference for train dataset, n	
	Low	High
Low	36	2
High	2	36
Prediction for test dataset, n	Reference for test dataset, n	
	Low	High
Low	15	3
High	1	13
Prediction for validation dataset, n	Reference for validation dataset, n	
	Low	High
Low	8	0
High	2	3

$ppFEV_1$ decline in our cohort can be explained by the following: First of all, our cohort consisted of children with high baseline $ppFEV_1$ which has been reported as an independent risk factor for FEV_1 decline in several studies.[19-21] The reason for $ppFEV_1$ decline in patients with high baseline FEV_1 can be explained by several reasons. First of all, physicians may underestimate the early decline in FEV_1 which is still within normal limits and not intervene as quickly as possible in pwCF with moderate/severe disease. Secondly, patients might think that being in a state of wellness means there is no need for any treatment and they may not take their standard therapies/physiotherapy either involuntarily (simply forgetting their therapies) or voluntarily (nonadherence). In our study, a quarter of the patients were non-adherent to physiotherapy which we believe is related to the high number of adolescents (n=44) who are prone to being non-adherent to treatments. We believe the second reason for the higher FEV_1 decline when compared with the literature is associated with newborn screening (NBS). It's well known that patients diagnosed with NBS have improved respiratory, nutritional outcomes and survival.[22] NBS for CF was implemented in Türkiye on 01.01.2015 by the Ministry of Health, so none of the patients enrolled in the study were diagnosed through NBS. The third reason for higher FEV_1 decline can be explained by the low rate of inhaled hypertonic saline (HS) or inhaled mannitol which is mainly due to financial obstacles as the drugs were only reimbursed after 2018. All of the factors mentioned above put our mild CF patients at greater risk compared to pwCF with moderate/severe disease.

The mean LCI for healthy populations ranges between 6.2-7.2, and the upper normal limit for LCI, which is defined as mean LCI+2SD, is reported as 7.9-8.2.[23-25] Differences in normal values between studies can be explained by age differences, methods of analysis, software used, devices and set-up, and the tracer gas used. The upper limit of normal (ULN) of LCI for healthy school-age children and adolescents was defined as 7.91.[25] When this upper limit was taken into consideration, almost one quarter of the patients had an elevated LCI. In the study of Ellemunter et al.[26], they found an elevated LCI in almost 80% of the mild pwCF. Similarly, in the 2014 study of Fuchs et al.[24], they showed that 83% had an increased LCI. Also, Fuchs et al.[24] reported a mean baseline LCI of 8. One of the reasons for the lower LCI in the current study may be the difference in FEV_1-z-scores of patients who were enrolled. In our study, the mean FEV_1-z-score was 0.55, whereas it was -0.26 in the study of Fuchs et al. In addition, in the current study, a more homogeneous group by age was included, whereas adults were also involved in Fuchs et al. study.

With the understanding that early lung disease arises in the peripheral airways, LCI has become a tool that can predict future respiratory functions when the patient has preserved spirometry values.[27,28] In our study, the LCI value, predicting near future FEV_1 decline was 8.2 which is slightly higher than the ULN in published reference equations.[25] LCI measurement can be performed in functional lung tissue, therefore it is mostly preferred in mild CF patients in order to detect early lung changes and monitor disease progression. LCI can also be used to detect pulmonary exacerbations and first PA growth.[29,30] Besides, there are several studies evaluating medical treatment (dornase alpha, hypertonic saline, CFTR modulators) responses by LCI measurements.[31,32] Recently, Kurz et al. showed that increased LCI is associated with a greater risk of death or lung transplantation.[33] Future studies are needed to define how to implement LCI monitoring in CF patients in daily practices in terms of LCI monitorization frequency and the change in LCI value. It is also necessary to clearly state whether follow-up with LCI improves management and survival in patients with CF.

Our study has some limitations. This was a single-center study designed without a control group. Compliance with medical therapies was evaluated according to the patients' declaration which may cause information/recall bias. The reported compliance with medical therapies has been shown to be less sensitive and correct by overestimating the real number of performed treatments compared to electronic measures such as inhalers counting the inhalation cycles. Besides the low sensitivity of the LCI cut off defined by the ROC curve to predict FEV_1 decline can be related to the sample size which is within the acceptable limits but still within the lower limit of normal. Also, due to low sensitivity, the false negative rate was high and negative diagnoses were not very reliable. Because of this limitation, our results cannot predict the FEV_1 decline by only LCI, but can predict the FEV_1 decline along with initial FEV_1-z-score, initial WFA z-score and type of *CFTR* mutation. To overcome this limitation larger prospective, longitudinal, multicenter studies are needed. In addition, the relatively small sample size is a problem in terms of applying logistic regression and decision tree models. This problem affects the validity of the results derived from regression and classification models. In addition, since the class distributions are imbalanced, the use of the SMOTE method and the low number of observations in the validation set can reduce the reliability of the results. Last of all, the variability in LCI ranging between 15-25%, which has been shown to be highest in pwCF with more severe lung disease could not be interpreted because we only measured LCI values at the beginning of the study.[34] However, the study conducted by Oude Engberink et al.[35] also showed that the variability is lower in LCI measurements taken 24 hours apart, which suggests that our findings can reflect close to normal LCI values.

Conclusions

Our study confirms that LCI is a helpful tool for predicting FEV_1 decline in patients who have $ppFEV_1 \geq 80$ along with several parameters such as the initial FEV_1 z-score, type of *CFTR* mutation. Given the feasibility of LCI in infants and preschool children, we should encourage its use in children with mild CF, alongside spirometry, to enhance medical treatment strategies and improve survival.

Ethical approval

Informed consent was obtained for participation in the study and the study was approved by Hacettepe University Ethics Committee for Non-Interventional Studies (GO 20-637 Date: February 2018).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: BÖ, EY, NE, HKÜ, DD, UÖ, NK; data collection: BÖ, DAT, BS, CC; analysis and interpretation of results: BÖ, HKÜ, EY, DD, UÖ, NK; draft manuscript preparation: BÖ, EY, HKÜ, NE. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

The relationship between lung function, exercise capacity, oxidant and antioxidant response in primary ciliary dyskinesia and cystic fibrosis

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ABSTRACT

Background. There is a need to identify the complex interplay between various physiological mechanisms in primary ciliary dyskinesia (PCD) and cystic fibrosis (CF). The study investigated the interaction between respiratory function, exercise capacity, muscle strength, and inflammatory and oxidant/antioxidant responses in patients with PCD and CF.

Methods. The study included 30 PCD patients, 30 CF patients, and 29 age and sex-matched healthy subjects. Exercise capacity was assessed using the modified shuttle walk test (MSWT). Handgrip strength (HGS) was used to evaluate general muscle strength. Oxidative stress-inflammatory parameters were also assessed. Pulmonary function test was performed by spirometry. Regarding the forced expiratory volume in 1 second (FEV_1) z-score, patients with PCD and CF were subdivided into normal, mild, and severe/moderate groups.

Results. Forced vital capacity (FVC) z-scores were lower in PCD and CF patients than controls. FEV_1, FEV_1/FVC, peak expiratory flow (PEF), and forced mid expiratory flow ($FEF_{25-75\%}$) z-scores were lower in PCD than in the other groups. HGS was lower in both mild PCD and normal CF patients relative to the controls. MSWT distance was lower in severe/moderate PCD patients than controls. Catalase (CAT), glutathione S-transferase (GST), glutathione peroxidase (GPx), and malondialdehyde (MDA) levels did not differ significantly among the study groups, but superoxide dismutase (SOD) level in severe/moderate PCD, and glutathione (GSH) level in normal CF were higher than in controls. Interleukin-6 (IL-6) level was higher in patients with normal PCD and CF compared to the controls. IL-1β level was higher in PCD compared to controls. Additionally, correlations among these parameters were also determined in some patient groups.

Conclusion. Homeostasis related to respiratory function, aerobic performance, muscle strength, inflammatory response, and oxidant/antioxidant balance were affected in PCD and CF. Evaluating these mechanisms together may contribute to elucidating the pathophysiology of these rare diseases.

Key words: aerobic performance, handgrip strength, primary ciliary dyskinesia, cystic fibrosis, oxidative stress-inflammatory parameters.

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Primary ciliary dyskinesia (PCD) (ORPHA: 244) is an autosomal inherited recessive disorder characterized by structural and functional defects of motile cilia.[1,2] Ciliary dysfunction disrupts mucociliary transport and results in recurrent infections occurring in the upper and lower respiratory tract.[3]

Cystic fibrosis (CF) (ORPHA: 586) is an inherited, multisystemic disease caused by a defect in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. CFTR is mainly a chloride ion channel, but it also regulates other membrane channels and facilitates mucociliary clearance. Patients with CF cannot adequately clear this thickened mucus which causes chronic inflammation, airway damage, infections, and eventually respiratory failure.[4,5] Therefore, management of the respiratory tract is critical in patients with CF as well as in patients with PCD. Previous comparisons of PCD and CF have revealed that exercise capacity, which provides important information about global health, morbidity, and mortality, is consistently reduced in children with PCD and CF.[6–8] Limited information is available on the mechanisms of decreased exercise capacity in PCD and CF.

In the literature, the effect of the oxidant-antioxidant balance on the pathogenesis and progression of many diseases has been evaluated.[9–11] This balance and inflammation are vital for cell viability, proliferation, and function in PCD and CF.[12,13] Tucker et al.[14] stated that oxidative stress caused a decrease in respiratory function in patients with CF. In addition, there is a link between oxidative stress and exercise capacity in various patient groups.[15] We aimed to elucidate the relationship between respiratory function, exercise capacity, muscle strength, inflammatory response, and oxidant-antioxidant balance in patients with PCD and CF to comprehensively investigate the pathophysiological mechanisms underlying respiratory disease in these patients. We hypothesized that PCD and CF patients would exhibit poorer pulmonary function, exercise capacity, and muscle strength than healthy subjects, and this alteration is associated with an augmented inflammatory response and an imbalance in the oxidant-antioxidant equilibrium in these patients. Establishing these relationships would enable us to take adequate steps towards advancing the multifactorial nature of these diseases and facilitating the development of effective therapeutic interventions.

Methods

Study design and subjects

The study was conducted at Pediatric Pulmonology Department of Hacettepe University Hospital between March 2018 and February 2020. In addition, it was approved by Hacettepe University Noninterventional Clinical Research Ethics Committee with approval no: GO 18/194 on 13 February 2018.

This study included a total of 89 volunteers aged 6-18 years and was divided into three groups: PCD (n=30), CF (n=30), and healthy subjects (n=29). The sample size was calculated using sample size software (G*Power version 3.1.9.2, Germany) with parameters set at 90% power, $\alpha = 0.05$, $\beta = 0.1$. In addition, patients with PCD and CF were subdivided into normal, mild, and severe/moderate groups according to their the FEV_1 z-score. Patients, healthy subjects, and their parents signed an informed consent form. The control group consisted of 30 subjects, but one healthy subject was excluded due to withdrawing family consent to participate.

The diagnosis of PCD was made according to the recent guidelines,[16] and a combined approach of complementary methods was applied. The PCD group considered clinical and radiological findings, genotyping, nasal nitric oxide level, transmission electron microscopy, ciliary beat pattern, and frequency criteria.[17] The diagnosis of CF was established upon typical clinical findings, with at least two positive sweat chloride tests and/or two CF-causing *CFTR* mutations.[18] Exclusion criteria were being clinically unstable (respiratory, cardiovascular, neurological, etc.), taking systemic steroids, having a recent history

of pulmonary exacerbations (the previous 30 days), having a FEV_1 of ≤40%, and not being able to perform exercise tests for the PCD and CF patients. Patients who met the inclusion criteria during the study were recruited according to age and sex similarity. In addition, the control group included participants who had no systemic or acute illness, physical health problems and were matched for age and sex.

All patients' and healthy subjects' socio-demographic and clinical characteristics were recorded, and body mass index (BMI) was calculated. BMI-for-age z-scores were calculated using the World Health Organization (WHO) anthropometric calculator (AnthroPlus v.1.0.4) based on WHO Child Growth Standards and Growth Reference data. Physical examination, lung function test, and blood sample collection were performed in all patients with PCD, CF, and healthy subjects. Exocrine pancreatic insufficiency status, fat-soluble vitamin values, and usage of modulator therapy were also recorded. Additionally, pulse oxygen saturation (SpO_2) evaluated in room air was recorded when the participants were recruited into the study.

Spirometry

A spirometer (Vyntus™ SPIRO PC Spirometer, Mettawa, US) was used to perform the pulmonary function tests. The FEV_1, forced vital capacity (FVC), FEV_1/FVC, forced midexpiratory flow 25–75% ($FEF_{25–75}$%), and peak expiratory flow (PEF) were measured according to European Respiratory Society (ERS) standards.[16] Airflow limitation classification was based on the z-score of FEV_1 according to American Thoracic Society (ATS)/ERS recommendations (z-score >-1.645: Normal, between -1.645 and -2.5: Mild, between -2.51 and -4: Moderate, and <-4: Severe.[19] In this study, patients with PCD and CF were classified as normal, mild, moderate, and severe in terms of FEV_1 z-score and intra-group statistical comparisons were performed between those classified as normal, mild, and severe/moderate.

Standard microbiological assessment

The sputum samples were obtained when the patients were recruited into the study. Sputum samples were inoculated on BD Columbia agar with 5% sheep blood; at the same time, sputum samples were inoculated with BD Mac Conkey II agar BD chocolate agar. Sheep blood agar and chocolate agar were incubated at 37 °C with a 5% CO_2 incubator, but Mac Conkey agar at 37 °C incubator. The isolates were identified based on colony morphology, Gram staining, conventional methods, and matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI Biotyper C System [Bruker Daltonics, Germany]). Intracellular and pathogenic bacteria in sputum were evaluated.

Additionally, the bacterial colonization was considered chronic when more than 50% of the preceding 12 months were culture-positive.[20]

Physical activity

Physical activity level (PAL) was determined using the Bouchard Three-Day Physical Activity Record. Physical activities were recorded at 15 minute intervals for three days (two consecutive weekdays and one day for the weekend). A scale from 1 (sedentary activity) to 9 (intense manual work or high-intensity sports) was used to qualify energy expenditure as the approximate median energy cost in kcal/kg/15 min. The mean value from the three days was considered for the analysis.[21]

Aerobic performance

A modified shuttle walk test (MSWT) was used to evaluate exercise capacity. Both before and after the test, heart rate was measured using telemetry (Polar S 610i, Lake Success, New York, USA), blood pressure by using a manual sphygmomanometer (Erka Perfect Aneroid Sphygmomanometer, Germany), and SpO_2 by using a portable pulse oximeter (Finger Pulse Oximeter, Germany). In addition, dyspnea and general fatigue were evaluated in all groups.[22]

Handgrip strength

A baseline hand dynamometer (Baseline Standard Hydraulic Hand Dynamometer, 90 kg, Baseline, New York, USA) was used to determine the handgrip strength (HGS). The HGS was measured in a sitting position, with the elbow in 90 degrees of flexion, and the forearm and wrist in a neutral position. In order to reduce the effects of muscle fatigue, a one-minute break was given between measurements.[23] The hand dynamometer was squeezed with maximum force throughout the test and held for three seconds.[24] In addition, each muscle group was tested bilaterally and recorded in Newtons (N), with an average value of three reproducible attempts.

Oxidant-antioxidant and inflammatory parameters

Blood samples were drawn via forearm venous puncture and collected into heparinized vacutainer tubes, and samples were collected and kept in sterile containers. Plasma samples were obtained through 10 minutes of centrifugation at 2000 rpm. All plasma samples were aliquoted into 2 mL eppendorf tubes and stored at −80°C until analysis. In these samples, glutathione (GSH), catalase (CAT), superoxide dismutase (SOD), glutathione S-transferase (GST), and glutathione peroxidase (GPx) levels were investigated to evaluate antioxidant status. On the other hand, malondialdehyde (MDA) level as a lipid peroxidation marker was measured to assess oxidant status. In addition, interleukin (IL-1β, IL-6, IL-8) levels were detected in plasma through a sandwich enzyme immunoassay to determine leukocyte activation.

All experiments were carried out using an ELISA kit (Cloud-Clone Corp., USA), following the protocol provided by the manufacturer and absorbance was read at 450 nm using a microplate reader (SpectraMax® M5 Microplate Reader, Molecular Devices LLC, USA).

All experiments based on oxidant-antioxidant balance and inflammation parameters were carried out with technical duplicates.

Statistical analysis

Statistical analysis was conducted using IBM SPSS 23.0. (SPSS Inc., Chicago, USA). Numerical variables were summarized by mean±standard deviation or median [25-75th percentile] as appropriate. Categorical variables were shown as frequencies and percentages. The differences in numerical variables between independent groups were analyzed using the one-way ANOVA when variables were normally distributed and group variances were homogeneous. Welch ANOVA compared groups when variables were normally distributed, and group variances were heterogeneous. Posthoc comparisons were performed by Tukey HSD or Games Howell test, respectively. Kruskal Wallis test was used when the distribution of the variables was not normal. The Dunn test made pairwise comparisons. Mann Whitney U test was used to show differences between two independent groups in terms of continuous variables those not normally distributed. Relations between categorical variables were determined by using the chi-square test. The Spearman correlation coefficient (r) was used to determine the association between continuous variables. The values of $p<0.05$; $p<0.01$; $p<0.001$ were considered statistically significant.

Results

Demographic characteristics and clinical laboratory values for study groups are presented in Table I. The groups were similar in age and sex ($p>0.05$). Median FVC z-scores were lower in the PCD and CF patients than in the healthy subjects ($p<0.001$). In addition, median FEV_1, FEV_1/FVC, PEF , and $FEF_{25-75\%}$ z-scores were lower in the PCD patients compared to the other groups ($p<0.001$). In addition, *Haemophilus influenzae* was the predominant microorganism detected in 60% of the PCD patients, and 3.3% of patients exhibited chronic colonization by both *H. influenzae* and *Pseudomonas aeruginosa*. The results obtained from CF patients showed that methicillin-susceptible *Staphylococcus aureus*

Table I. Characteristics of PCD and CF patients and healthy subjects.

Characteristic	Healthy (n=29) (Mean ± SD)	PCD (n=30) (Mean ± SD)	CF (n=30) (Mean ± SD)	p value
Age (years)	13.8±3.2	13.6±3.5	13.4±3.4	0.920
Gender (F/M)	17/12	17/13	17/13	0.985
Weight (kg)	54.45±17.30	47.71±18.97	44.01±13.33	0.057
Height, z-score	0.14±0.96	-0.10±1.26	-0.55±1.21	0.073
BMI, z-score	0.15±2.05	-0.06±1.31	-0.36±1.05	0.425
O_2 saturation (%)	97±2	96.2±1.6	96.4±1.5	0.563
FVC, z-score	0.3±1.2[a]	-1.9±1.7[b]	-1.1±1.8[b]	<0.001*
FEV_1, z-score	1.1±1.0[a]	-2.4±1.7[b]	-0.8±2.1[c]	<0.001*
FEV_1/FVC, z-score	1.6±1.2[a]	-1.3±2.1[b]	0.4±1.7[c]	<0.001*
PEF, z-score	-0.02±1[a]	-1.8±1.3[b]	-0.7±1.1[a]	<0.001*
$FEF_{25-75\%}$, z-score	0.8±1.2[a]	-2.8±1.4[b]	-1.1±2[c]	<0.001*

Same parameters carrying different letters (a,b,c) are statistically different at *p<0.001.
BMI: body mass index, CF: cystic fibrosis, F/M: Female/Male, $FEF_{25-75\%}$: forced expiratory flow 25–75%, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, PCD: primary ciliary dyskinesia, PEF: peak expiratory flow, SpO_2: oxygen saturation, SD: standard deviation.

(MSSA), *P. aeruginosa*, and methicillin-resistant *S. aureus* (MRSA) were detected in 66.6%, 20%, and 6.6% of cases, respectively. Additionally, 6.6% of these patients displayed chronic colonization by both MSSA and *P. aeruginosa*. All patients had been diagnosed with exocrine pancreatic insufficiency and were prescribed pancreatic enzyme replacement therapy alongside vitamin supplements. Notably, none of the patients were undergoing modulator therapy during the study period. Among the CF patients, three exhibited vitamin A deficiency, two had vitamin E deficiency, and an additional two presented with vitamin D deficiency.

There was no significant difference among study groups in terms of PAL (p>0.05). Median MSWT distance was lower in severe/moderate PCD patients compared to healthy subjects (p=0.005, Table II). Median HGS level was lower in both mild PCD and normal CF patients than in healthy subjects (p=0.013, Table II and III).

According to the results of oxidant-antioxidant parameters, CAT, MDA, GPx, and GST levels did not differ between study groups (p>0.05). In addition, the SOD level was higher in the severe/moderate PCD patients than in the healthy subjects (p=0.037, Table II) while the GSH level was higher in normal CF compared to healthy subjects (p=0.027, Table III). Regarding inflammation parameters, IL-6 level was higher in patients with normal PCD and CF relative to healthy subjects (p=0.002, Table II; p=0.015, Table III, respectively). Additionally, IL-1β level was higher in PCD patients than in healthy subjects (p<0.001, Table II) while the IL-8 of PCD patients tended to be higher compared to healthy subjects (p=0.052, Table II).

In this study, the correlation coefficients were calculated for each study variable of PCD patients and their significant relationships are demonstrated in Table IV. Findings can be listed as follows: GSH significantly correlated with MDA (r =0.404, *p=0.027). GPx significantly correlated with CAT, IL-6, IL-8, IL-1β, and HGS levels (r=-0.376, *p=0.044; r=0.394, *p=0.034; r=0.387, *p=0.035; r=0.560, **p=0.002; r=-0.362, *p=0.049, respectively). IL-6 significantly correlated with IL-8 and IL-1β levels (r=0.430, *p=0.020; r=0.684, **p<0.001, respectively). In addition, there was a positive correlation between IL-8 and IL-1β levels (r=0.422, *p=0.023). PAL significantly correlated with HGS levels (r=0.392, *p=0.035).

Table II. Comparison of physical activity level, handgrip strength, aerobic performance, oxidant-antioxidant, and inflammatory parameters in healthy subjects and PCD patient groups based on FEV_1 z-score.

Study Parameters	Healthy Subjects (n=29)	Severe/Moderate PCD Patients (n=10)	Mild PCD Patients (n=9)	Normal PCD Patients (n=11)	p value
PAL	2.33 [2 – 2.61]	1.73 [1.53 – 2.46]	2.09 [1.58 – 2.27]	2.35 [1.88 – 2.63]	0.193
HGS (kg)	24 [16.51 – 29.07]^{a}	16.88 [10.62 – 25.26]^{ab}	13.5 [8.82 – 18.64]^{b}	24.75 [16.88 – 40.13]^{ab}	0.013
MSWT distance (m)	810 [680 - 990]^{a}	530 [425 - 700]^{b}	590 [495 - 785]^{ab}	700 [580 - 840]^{ab}	0.005
GSH (μg/mL)	2196.06 [390.89 – 7878.13]	8439.46 [101.3 – 17561.28]	7725.65 [3739.18 – 9850.45]	6322.46 [605.94 – 7871.02]	0.354
CAT (ng/mL)	0.23 [0.15 – 0.39]	0.26 [0.15 – 0.35]	0.51 [0.3 – 0.66]	0.24 [0.13 – 0.43]	0.096
SOD (pg/mL)	948.8 [774.67 – 1036.42]^{a}	1123.25 [1007.84 – 1359.74]^{b}	968.93 [847.11 – 1732.58]^{ab}	897.87 [845.08 – 1087.75]^{ab}	0.037
GPx (ng/mL)	3.33 [2.14 – 5.76]	3.88 [3.21 – 9.47]	3.83 [3.11 – 5.95]	4.91 [3.11 - 8]	0.500
MDA (ng/mL)	8599.44 [6660.51 – 10252.38]	9663.4 [7081.17 – 11144.64]	8110.34 [6898.31 – 12307.18]	9693.82 [8271.97 – 12593.26]	0.272
GST (ng/mL)	7.94 [3.41 – 14.15]	4.49 [2.55 – 7.58]	6.55 [4.12 – 13.58]	11.15 [4.54 – 61.57]	0.186
IL-6 (pg/mL)	39.89 [17.78 – 81.44]^{a}	160.39 [116.58 – 236.27]^{ab}	180.92 [146.37 – 226.63]^{ab}	171.51 [136.99 – 413.28]^{b}	0.002
IL-8 (pg/mL)	77.46 [49.69 – 112.79]	111.42 [86.77 – 129.55]	110.45 [81.09 – 129.52]	124.98 [100.17 – 177.64]	0.052
IL-1β (pg/mL)	92.73 [37.81 – 271.11]^{a}	657.39 [328.83 – 1795.2]^{b}	788.24 [389.03 – 1243.36]^{b}	602.45 [329.87 – 1132.69]^{b}	<0.001

Data are presented as median [1st-3rd quartile]. Same parameters carrying different letters (a,b,c) are statistically different at p<0.05.

CAT: catalase, GPx: glutathione peroxidase, GSH: glutathione, GST: glutathione S-transferase, HGS: handgrip strength, IL: interleukin, MDA: malondialdehyde, MSWT: modified shuttle walk test, PAL: physical activity level, PCD: primary ciliary dyskinesia, SOD: superoxide dismutase.

In addition to the above findings, the correlations between the study variables were also evaluated in CF patients and the results are demonstrated in Table V. Based on the statistical analyses, GPx significantly correlated with IL-6, IL-8, and IL-1β levels (r=0.373, *p=0.046; r=0.473, *p=0.011; r=0.615, **p<0.001, respectively). There was a positive correlation between MDA and IL-6 levels (r=0.375, *p=0.045). On the other hand, a negative correlation was present between GST and IL-1β levels (r=-0.421, *p=0.026). IL-6 levels significantly correlated with IL-8 and IL-1β levels (r=0.788, **p<0.001; r=0.450, *p=0.014, respectively), while there was also a positive correlation between IL-8 and IL-1β levels (r=0.605, **p=0.001). Additionally, PAL was significantly correlated with HGS and MSWT levels (r=0.607, **p<0.001; r=0.472, **p=0.008, respectively). Furthermore, a significant positive correlation was present between HGS and MSWT levels (r=0.502, **p=0.005).

Table III. Comparison of physical activity level, handgrip strength, aerobic performance, oxidant-antioxidant, and inflammatory parameters in healthy subjects and CF patient groups based on FEV_1 z-score.

Study Parameters	Healthy Subjects (n=29)	Severe/Moderate CF Patients (n=8)	Normal CF Patients (n=20)	p value
PAL	2.33 [2 – 2.61]	1.96 [1.76 – 2.42]	2.05 [1.83 – 2.31]	0.087
HGS (kg)	24 [16.51 – 29.07]^{a}	15 [8.95 – 24.38]^{ab}	15.19 [9.62 – 22.88]^{b}	0.013
MSWT distance (m)	810 [680 - 990]	625 [522.5 - 815]	710 [642.5 – 907.5]	0.064
GSH (μg/mL)	2196.06 [390.89 – 7878.13]^{a}	6424.09 [1402.93 – 9300.86]^{ab}	7536.66 [3206.89 – 11261.22]^{b}	0.027
CAT (ng/mL)	0.23 [0.15 – 0.39]	0.35 [0.3 – 0.38]	0.27 [0.16 – 0.4]	0.324
SOD (pg/mL)	948.8 [774.67 – 1036.42]	936.27 [771.97 – 1102.12]	1042.79 [824.49 – 1160.44]	0.128
GPx (ng/mL)	3.33 [2.14 – 5.76]	2.88 [2.63 – 3.99]	2.98 [1.99 – 4.18]	0.728
MDA (ng/mL)	8599.44 [6660.51 – 10252.38]	8456.05 [6838.28 – 11178.7]	9959.45 [8165.06 – 11698.89]	0.135
GST (ng/mL)	7.94 [3.41 – 14.15]	14.03 [3.21 – 68.66]	7.68 [4.88 – 42.09]	0.503
IL-6 (pg/mL)	39.89 [17.78 – 81.44]^{a}	107.75 [11 – 198.75]^{ab}	111.45 [52.12 – 177.32]^{b}	0.015
IL-8 (pg/mL)	77.46 [49.69 – 112.79]	105.58 [27.43 – 189.63]	93.91 [41.83 – 127.29]	0.762
IL-1β (pg/mL)	92.73 [37.81 – 271.11]	88.39 [20.25 – 1131.3]	122.22 [59.56 – 820.02]	0.498

Data are presented as median [1st-3rd quartile]. Same parameters carrying different letters (a,b,c) are statistically different at $p<0.05$.

CAT: catalase, CF: cystic fibrosis, GPx: glutathione peroxidase, GSH: glutathione, GST: glutathione S-transferase, HGS: handgrip strength, IL: interleukin, MDA: malondialdehyde, MSWT: modified shuttle walk test, PAL: physical activity level, SOD: superoxide dismutase.

Note: There were two mild CF patients according to the FEV1 z-score. Therefore, this CF patient subgroup was not included in these comparisons because the number of patients needed to be increased to draw robust results.

Discussion

The study highlighted substantial alterations in homeostasis related to lung function, aerobic performance, muscle strength, inflammatory processes, and oxidant-antioxidant balance in patients with PCD and CF compared to healthy controls. The most important findings of the current study are that our results revealed an interrelated alteration between these mechanisms, potentially impacting the quality of life of patients with these rare diseases.

The involvement of the respiratory system plays a crucial role in determining the survival and quality of life of patients with PCD and CF.[25] In the present study, we determined a decrease in lung function in patients with PCD and CF relative to healthy subjects, which could be associated with limitations in

Table IV. Correlation assessment of patients with PCD in terms of physical activity level, handgrip strength, aerobic performance, oxidant-antioxidant, and inflammatory parameters.

	CAT (ng/mL)	SOD (pg/mL)	GPx (ng/mL)	MDA (ng/mL)	GST (ng/mL)	IL-6 (pg/mL)	IL-8 (pg/mL)	IL-1β (pg/mL)	PAL	HGS (kg)	MSWT distance (m)
GSH (μg/mL)	r=-0.127	r=0.261	r=0.061	r=0.404	r=-0.113	r=-0.134	r=0.003	r=-0.151	r=-0.056	r=-0.174	r=-0.357
	p=0.513	p=0.164	p=0.750	*p=0.027	p=0.551	p=0.488	p=0.988	p=0.434	p=0.772	p=0.358	p=0.053
CAT (ng/mL)		r=-0.010	r=-0.376	r=-0.223	r=-0.170	r=-0.119	r=-0.120	r=-0.323	r=-0.118	r=-0.224	r=0.273
		p=0.958	*p=0.044	p=0.246	p=0.377	p=0.545	p=0.535	p=0.093	p=0.550	p=0.242	p=0.152
SOD (pg/mL)			r=-0.069	r=0.251	r=-0.122	r=-0.081	r=-0.143	r=0.020	r=0.101	r=0.187	r=0.242
			p=0.716	p=0.181	p=0.522	p=0.677	p=0.449	p=0.919	p=0.603	p=0.323	p=0.197
GPx (ng/mL)				r=0.329	r=0.146	r=0.394	r=0.387	r=0.560	r=-0.053	r=-0.362	r=-0.308
				p=0.076	p=0.442	*p=0.034	*p=0.035	**p=0.002	p=0.783	*p=0.049	p=0.098
MDA (ng/mL)					r=0.282	r=-0.144	r=0.046	r=-0.012	r=0.015	r=-0.111	r=-0.080
					p=0.131	p=0.457	p=0.811	p=0.949	p=0.939	p=0.560	p=0.675
GST (ng/mL)						r=-0.052	r=0.292	r=-0.050	r=0.071	r=0.006	r=0.248
						p=0.787	p=0.118	p=0.796	p=0.715	p=0.974	p=0.186
IL-6 (pg/mL)							r=0.430	r=0.684	r=0.079	r=-0.123	r=0.078
							*p=0.020	**p<0.001	p=0.688	p=0.526	p=0.686
IL-8 (pg/mL)								r=0.422	r=0.145	r=0.011	r=0.083
								*p=0.023	p=0.453	p=0.954	p=0.661
IL-1β (pg/mL)									r=0.327	r=-0.095	r=0.046
									p=0.089	p=0.623	p=0.811
PAL										r=0.392	r=0.238
										*p=0.035	p=0.214
HGS (kg)											r=0.318
											p=0.087

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).
CAT: catalase, GPx: glutathione peroxidase, GSH: glutathione, GST: glutathione S-transferase, HGS: handgrip strength, IL: interleukin, MDA: malondialdehyde, MSWT: modified shuttle walk test, PAL: physical activity level, PCD: primary ciliary dyskinesia, SOD: superoxide dismutase.

Table V. Correlation assessment of patients with CF in terms of physical activity level, handgrip strength, aerobic performance, oxidant-antioxidant, and inflammatory parameters.

	CAT (ng/mL)	SOD (pg/mL)	GPx (ng/mL)	MDA (ng/mL)	GST (ng/mL)	IL-6 (pg/mL)	IL-8 (pg/mL)	IL-1β (pg/mL)	PAL	HGS (kg)	MSWT distance (m)
GSH (μg/mL)	r=-0.211	r=0.032	r=-0.252	r=0.194	r=-0.065	r=0.044	r=-0.185	r=-0.176	r=-0.101	r=0.169	r=0.164
	p=0.263	p=0.866	p=0.187	p=0.304	p=0.739	p=0.821	p=0.337	p= 0.360	p=0.594	p=0.372	p=0.387
CAT (ng/mL)		r=-0.009	r=0.233	r=-0.247	r=0.026	r=-0.143	r=0.036	r=-0.183	r=0.196	r=0.122	r=0.231
		p=0.962	p=0.225	p=0.188	p=0.895	p=0.458	p=0.853	p=0.341	p=0.300	p=0.521	p=0.220
SOD (pg/mL)			r=-0.181	r=-0.266	r=0.358	r=-0.308	r=-0.259	r=-0.215	r=0.264	r=0.267	r=0.102
			p=0.5348	p=0.156	p=0.056	p=0.104	p=0.176	p=0.263	p=0.158	p=0.154	p=0.592
GPx (ng/mL)				r=-0.090	r=0.336	r=0.373	r=0.473	r=0.615	r=0.075	r=-0.058	r=0.064
				p=0.644	p=0.081	*p=0.046	*p=0.011	**p<0.001	p=0.698	p=0.763	p=0.743
MDA (ng/mL)					r=-0.087	r=0.375	r=0.351	r=0.167	r=-0.319	r=-0.239	r=-0.109
					p=0.653	*p=0.045	p=0.062	p=0.388	p=0.086	p=0.204	p=0.567
GST (ng/mL)						r=-0.189	r=-0.317	r=-0.421	r=0.231	r=-0.105	r=0.076
						p=0.336	p=0.100	*p=0.026	p=0.228	p=0.588	p=0.695
IL-6 (pg/mL)							r=0.788	r=0.450	r=-0.086	r=0.070	r=0.040
							**p<0.001	*p=0.014	p=0.657	p=0.719	p=0.838
IL-8 (pg/mL)								r=0.605	r=0.1027	r=0.150	r=0.101
								**p=0.001	p=0.889	p=0.436	p=0.602
IL-1β (pg/mL)									r=0.012	r=0.051	r=-0.159
									p=0.952	p=0.794	p=0.410
PAL										r=0.607	r=0.472
										**p<0.001	**p=0.008
HGS (kg)											r=0.502
											**p=0.005

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).
CAT: catalase, CF: cystic fibrosis, GPx: glutathione peroxidase, GSH: glutathione, GST: glutathione S-transferase, HGS: handgrip strength, IL: interleukin, MDA: malondialdehyde, MSWT: modified shuttle walk test, PAL: physical activity level, SOD: superoxide dismutase.

exercise capacity, muscle strength, increased inflammatory responses, and imbalances in oxidant-antioxidant mechanisms.

The current investigation evidenced a reduction in the MSWT distance in patients with severe/moderate PCD compared to their healthy peers despite similar PAL levels. Similarly, Madsen et al.[7] reported that the aerobic fitness of PCD patients was lower than that of healthy subjects. This impaired aerobic capacity in PCD patients is probably due to reduced respiratory functions and increased inflammation. In addition, the MSWT level of CF patients was lower compared to healthy subjects, although this difference was insignificant. In literature, Leite et al.[26] demonstrated that children with CF had functional limitations in the MSWT distance.

Additionally, HGS levels were lower in both mild PCD and normal CF patients compared to the healthy subjects. Similar to our results, Sahlberg et al.[27] found that muscle strength and function decreased in CF patients compared to control subjects. Another study in the literature showed that PCD patients had lower handgrip strength than control subjects.[28] Muscle weakness in these patients could be related to a combination of factors, including nutritional status, airway obstruction, impaired aerobic capacity, inactivity, systemic inflammation, and oxidative stress. Importantly, MSWT distance was positively related to HGS level in CF patients in the current study. Similarly, Wells et al.[29] stated that there was a positive correlation between HGS and peak aerobic power (VO_2 peak) in children with CF. However, Cardoso et al.[30] reported no significant relationship between HGS and MSWT in children and adolescents with CF. This difference may be due to the body composition, including growth, weight, and height, which are related to muscle strength and MSWT performance in CF. In addition, previous investigations involving PCD patients have not yet explored this specific correlation.

Although PCD and CF have different genetic and functional origins, patients suffer from recurrent infections due to impaired cilia functions and mucus accumulation.[4,5] In addition, cystic fibrosis is included in the subgroup of immunodeficiency motility disorders, in which monocytes are affected, and chemotaxis is impaired.[31–33] In the literature, it has been reported that cytokines have a crucial role in inflammatory responses during infection.[34] Monocytes of PCD patients produced significantly more IL-1β than healthy individuals when stimulated with bacterial products (i.e., lipopolysaccharide and peptidoglycan).[12] Shoemark et al.[35] reported that IL-6, IL-8, and TNF-α levels were significantly higher in nasal samples of PCD patients than in controls. However, to the best of our knowledge, only one study has considered blood biomarkers of inflammation in PCD patients. In that study, Marino et al.[36] showed that the mean plasma concentrations of IL-1β, IL-2, IL-6, IL-8, and TNF-α in PCD patients and these cytokines were not increased in their cohort compared to available normative data.[37,38] On the other hand, it was stated that the serum levels of IL-6 and IL-1β were higher in patients with CF compared to controls.[39,40] According to our plasma results, IL-6 levels were higher in normal PCD and CF patients than in healthy subjects. On the other hand, IL-1β levels were higher in PCD patients than in healthy subjects, while IL-8 levels in PCD patients tended to be higher compared to healthy subjects. Moreover, there was a positive relationship between IL-8 and IL-1β in PCD and CF patients. Furthermore, IL-6 was significantly related to IL- 8 and IL-1β in the patient groups.

Many biomarkers of the oxidant-antioxidant system that may be useful in better understanding and managing these patients were evaluated in the current study. As a result, SOD levels were higher in severe/moderate PCD patients compared to healthy subjects while GSH levels were higher in normal CF patients than in healthy subjects. The other antioxidant parameters, such as CAT, GSH,

and GPx levels were also increased in patients with PCD compared to healthy controls, although these differences were not statistically significant. Given these results, we could speculate that increased chronic inflammation may trigger antioxidant mechanisms in the PCD patients. Oxidative stress is characterized as an imbalance between the antioxidant and oxidant systems, and it has rarely been studied in PCD. Zihlif et al.[41] stated that oxidative stress, as shown by 8-isoprostane, increased in the exhaled breath condensate of PCD children compared to healthy subjects. Additionally, Reula et al.[42] investigated the oxidative stress status in ciliated nasal epithelial cells (CNEC) from patients with PCD. As a result of the study, reduced GSH and total superoxide (O2-) were higher, and nitric oxide (NO) levels were lower in PCD patients than in PCD-like and the control group. Nevertheless, no significant alteration was observed in the oxidative damage in lipids and proteins of PCD and PCD-like patients compared to the control group. On the contrary, oxidative stress has been widely investigated in CF disease.[43–45] Olveira et al.[43] evaluated various oxidation biomarkers in plasma samples of 36 CF and 41 controls. Accordingly, CF patients' CAT, 8-isoprostanes, and thiobarbituric acid reactive substances [TBARS] levels were higher, but SOD levels were lower than controls. Another study determined that the plasma GPx levels were higher in 76 CF patients than in 40 control subjects. On the other hand, SOD activity in red blood cells was not different among study groups.[44] Galiniak et al.[45] reported that 42 CF patients' serum MDA levels were higher than 16 controls. In another study, GST activity was not different in 36 CF patients compared to 9 healthy subjects.[46] Another marker they studied was GSH, which is one of the main reactive oxygen species neutralization mechanisms. According to the results, in the presence of *P. aeruginosa* infection (n=12), the GSH level was similar to that of the healthy subjects (n=9). On the other hand, uninfected CF children's (n=24) GSH content was significantly decreased compared to controls (n=9).[46] From this perspective, it should not be overlooked that findings related to the antioxidant activities of CF patients could be affected by many factors, including accompanying diseases and clinical conditions such as disease severity and bacterial infections.

Another feature of our study was determining the correlation between the study groups' oxidative stress and inflammation parameters. The literature shows strong evidence that oxidative stress and inflammation are tightly related processes.[47] Similarly, our correlation findings support the interdependence between these pathophysiological processes. For instance, GPx was significantly related to IL-8, IL-6, and IL-1β levels in PCD and CF patients.

Our study has several limitations. Firstly, it was a single-center study, which limits the generalization of the results. Secondly, larger sample sizes may be needed to evaluate the statistical differences further. Thirdly, participants were selected by the study team, which may have led to selection bias. Finally, radiological findings could not be included in the study because not all patients had a thorax computed tomography. Despite these limitations, the study's strength is that these mechanisms have been considered together in pediatric patients with PCD and CF for the first time.

Conclusion

The processes including clinical findings, functional exercise capacity, muscle strength, oxidant-antioxidant balance, and inflammation were affected in PCD and CF patients. These alterations could be linked to each other through cause-and-effect relationships. It is crucial to know the cause-and-effect relationships in disease to improve treatment outcomes and develop a comprehensive perspective on the pathogenesis of the disease. In this study, impaired lung function could result in decreased physical capacity and muscle strength, as well as changes in the inflammatory and oxidant-antioxidant systems. On the other hand, the imbalance in the oxidant-antioxidant

equilibrium and inflammatory response, which are closely related, may potentially affect muscle weakness and physical performance. Hopefully, our multifactorial findings may provide a new perspective for future studies of these rare diseases to understand the underlying mechanisms of diseases and contribute to finding new therapeutic approaches. In addition, our findings have to be confirmed by larger-scale, multicenter studies.

Ethical approval

The present study was approved by Hacettepe University Noninterventional Clinical Research Ethics Committee with approval no: GO 18/194 on 13 February 2018.

Author contribution

Study conception and design: YK, CBO, HSU, DII, UO, MTB, HA, GG, SS; data collection: YK, CBO, HSU, AC, DAT, SEP, MH, UO; analysis and interpretation of results: YK, SS, GG, MTB, UO, DII, SK; draft manuscript preparation: YK, DAT. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Pulmonary involvement in children with Langerhans cell histiocytosis

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ABSTRACT

Background. Pulmonary Langerhans cell histiocytosis (pLCH) is a rare disease, mostly a component of multisystemic LCH. We aimed to investigate the clinical features and treatment results in children with pLCH.

Methods. We retrospectively reviewed the clinical, radiological, and treatment data of 37 patients with pLCH, diagnosed from 1974 to 2022.

Results. 10% (n=37) of 367 patients with LCH had lung involvement. The median age was 1.8 years (range: 0.4 & 17.7) with a male-to-female ratio of 2.3. At admission 29.7% (n=11) presented with respiratory symptoms. Imaging showed a spectrum from nodular opacities to multiple cysts. All but one patient had multisystem disease. Twenty-nine received vinblastine-containing therapy. Ten-year event-free (EFS) and overall survival (OS) rates were 47.8% and 63.3%, respectively. In children younger and older than two years of age, the 10-year EFS was 53.3% vs. 40.2% and the 10-year OS was 58.7% vs. 68.8%, respectively. In children with and without risk organ involvement, 10-year EFS was 51.9% vs. 46.3% and 10-year OS was 51.9% vs. 73.7%.

Conclusions. Lung and multisystem involvement are significant concerns in LCH, highlighting the need for careful management to reduce morbidity and mortality.

Key words: Langerhans cell histiocytosis, children, pulmonary involvement.

Pulmonary Langerhans cell histiocytosis (pLCH) is a distinct form of interstitial lung disease driven by the proliferation of Langerhans cells.[1] Accounting for 7-16% of Langerhans cell histiocytosis (LCH) cases[2], its pathogenesis remains elusive but has been increasingly described as 'inflammatory myeloid neoplasia'.[1,2] Clinical manifestations of LCH are diverse, and the clinical course of the multisystem LCH (MS-LCH) can range from spontaneous remission to fatality. Conversely, cases confined to a single organ or system generally predict a favorable outcome.[2,3] Although most pLCH instances occur within the context of multisystem disease[2], recent insights suggest that pulmonary involvement does not independently predict the prognosis in MS-LCH. Patients with concomitant liver, spleen, or bone marrow afflictions are identified as having 'high-risk disease', correlating with increased mortality.[2,3] In this study, we aimed to investigate the clinical features and treatment results in children with pLCH.

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Patients and Methods

This retrospective study examined the clinical records of 37 patients diagnosed and treated with pLCH at Hacettepe University İhsan Doğramacı Children's Hospital, Department of Pediatric Oncology from 1974 to 2022. Approved by the Cumhuriyet University Ethical Committee (21.09.2023, no: 2023-09/21) we collated demographic, clinical and survival data for these children. LCH was classified as single-system LCH when only one organ was involved, and as multisystem when two or more organs/systems were affected. Risk organ involvement included the hematopoietic system, liver, and spleen.[3]

Pulmonary involvement was initially identified via chest radiograph including interstitial infiltrates, reticulonodular change, cystic or honeycomb appearance in all patients, and/or evidence of disease by lung biopsy, and supplemented by computed tomography (CT) in 14 cases due to the non-availability of CT in the early years.[2,4–6] Patients for whom chest tomography could not be obtained were diagnosed based on clinical findings and chest X-ray findings. We retrieved reports of chest radiographs and CT scans from the patients' medical records to pinpoint diagnostic characteristics.

According to the Histiocyte Association criteria, the diagnosis of LCH was defined as definite (demonstration of Birbeck granules on electron microscopy or CD1a expression on lesion cells by immunohistochemistry) or probable (morphology compatible with LCH and staining of S-100 protein by immunohistochemistry).[2]

Patients with LCH who are younger than 2 years of age at diagnosis have a higher risk of organ involvement and a poor prognosis.[7–10] Therefore, patients were grouped as younger than 2 years old and aged 2 years and older. Event-free survival (EFS) and overall survival (OS) rates were compared between the two groups. Patients were evaluated from diagnosis to the latest uneventful follow-up, disease progression, relapse or death due to any cause for EFS, and from diagnosis to death for OS. EFS and OS rates were calculated for 5 years and 10 years. Continuous variables, median values, and ranges are presented. Median follow-up time was calculated for surviving patients. The Kaplan-Meier method for cumulative survival and the log-rank test were used for statistical analysis. A value of $p<0.05$ was considered statistically significant. The statistical analysis was performed with IBM SPSS Statistics for Windows (v21; Armonk, NY).

Results

From 1974 to 2022, among 367 children with LCH under 18 years who were treated at our hospital, 37 (10%) exhibited lung involvement, with a male-to-female ratio of 26:11 (2.3). Lung biopsies were performed on five patients,three by thoracotomy and two by thoracoscopy. In the remaining cases, the diagnosis of LCH was confirmed by skin biopsy (n=10), bone biopsy (n=7), lymph node biopsy (n=6), liver (2), palatal biopsy (n=2), bone marrow biopsy (n=1) and gingival biopsy (n=1). Both skin and bone biopsy, bone and bone marrow biopsy, bone marrow and lymph node biopsy were also performed on three patients.

Ages at diagnosis ranged from 0.4 to 17.7 years (median 1.8 and mean 4.3 years). Twenty patients (54%) were under two years of age. Multisystem involvement was present in all but one patient, who at 11.7 years old, was confirmed to have isolated lung involvement via biopsy. Additional organ involvement was as follows: bone, skin, liver, bone marrow, spleen, palate, and thyroid involvement were identified in 21, 20, 13, 6, 5, 2 and 1 patients, respectively. Risk organ involvement was noted in 18 patients, (liver 13, bone marrow 6, spleen 5 patients) (Table I).

At the time of diagnosing pulmonary involvement, clinical respiratory findings were reported in 30% (11 out of 37) of the patients characterized by dyspnea in 5 patients, cough

Table I. The characteristics of 37 patients with pulmonary LCH.

Characteristics	n	%
Multisystem disease with risk organ involvement	18	49
Organ involvement*		
Lung	37	100
Bone	21	57
Skin	20	54
Liver	13	35
Hematologic	6	16
Spleen	5	14
Thyroid	1	3

* Individual patients might have one or more involved sites.
LCH: Langerhans cell histiocytosis.

in 4, wheezing in 1, and chest pain in 1. Physical examination findings in patients with pulmonary involvement included rales, decreased breath sounds, tachypnea, rhonchi, nasal flaring, hypoxia, prolonged expiration, retraction, and bronchial sound in 15, 9, 5, 3, 3, 3, 2, 2 and 1 patient, respectively. Venous blood gas analysis was performed in ten patients, and only three of them had respiratory acidosis. Laboratory findings of these patients with respiratory failure were as follows (mean ± SD): venous pH, 7.32±0.01; venous HCO_3^-, 21.3±6.48 mmol/L; serum CO_2, 48.7±2.54 mmol/L. Transcutaneous oxygen saturation values of these three patients at room air were 78%, 85%, and 88%. Due to the retrospective nature of the study, the data for the other cases were not available. There were 7 patients with acute respiratory failure, 6 of whom were accompanied by sepsis. Three patients were admitted to the intensive care unit and required mechanical ventilation. One of these 3 patients required extracorporeal membrane oxygenation (ECMO). Three of the remaining 4 patients developed acute respiratory failure during their follow-up in the pediatric oncology unit and one patient died during the operation due to acute respiratory failure.

From the chest X-ray of all patients, the following were observed: interstitial infiltration (65%, n=24), cystic lesions (14%, n=5), pneumothorax (14%, n=5) (Fig. 1), nodular opacities (11%, n=4), and honeycomb appearance, ground-glass appearance, and left lower lobe atelectasis in one patient each (3%). Pulmonary involvement was defined by chest CT in 14 patients, revealing air cysts (Fig. 2), nodular opacity, and pneumothorax in 10 (27%), 6 (16%), and 5 (14%) patients, respectively. Additional chest CT findings included a honeycomb appearance, ground glass opacities, emphysematous appearance, pleural effusion, and left lower lobe atelectasis in one patient each.

Due to the young age of the patients and the retrospective nature of the study, pulmonary function tests (PFTs) were conducted in only four children. Three children had restrictive ventilation dysfunction, while the PFT results for the fourth child were normal. The FEV1/FVC ratios of these patients were 80%, 83.1%, and 114%, consistent with the restrictive pattern. Besides, predicted vital capacity

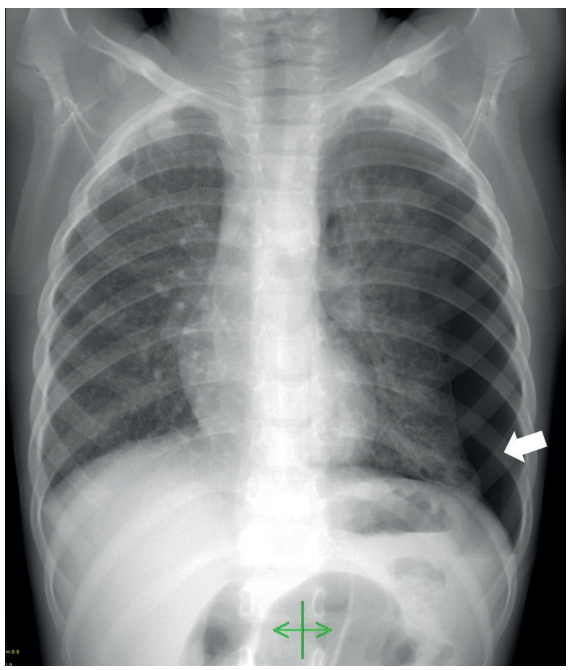

Fig. 1. 4-year-old boy with Langerhans cell histiocytosis. Posteroanterior chest radiograph shows left sided pneumothorax (arrow). There are widespread cystic changes and diffuse reticulonodular opacities in both lungs.

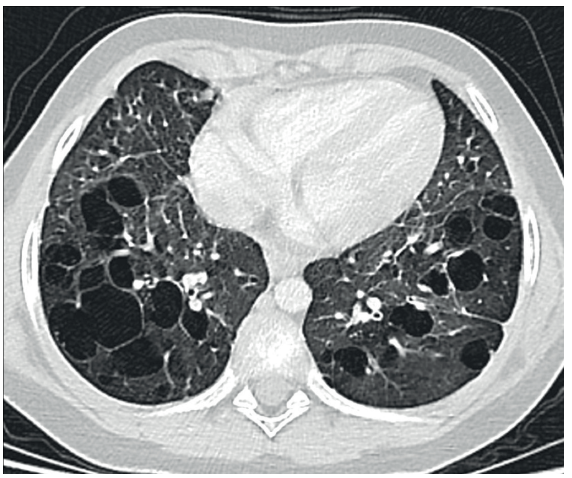

Fig. 2. 6-year-old boy with Langerhans cell histiocytosis. Axial computed tomography of the chest through lower lobes demonstrates numerous thin-walled lung cysts.

percentage values were low at 21%, 68%, and 74%. These tests were performed 1.5 and 12 months after the diagnosis in two patients and one year before the diagnosis of LCH in another patient. Due to the retrospective nature of the study, PFT findings during the follow-up were not available in the records of these patients. Additionally, bronchoalveolar lavage (BAL) was not utilized for diagnostic purposes in any of the cases.

Lung biopsy was performed on five patients. Wedge biopsies by thoracotomy in three patients and biopsies by video-assisted thoracoscopic surgery in two patients revealed prominent eosinophils and lymphoplasmacytic cell infiltration consisting of grooved or infolded nuclei histiocytic giant cells in the lung parenchyma. Histiocytic cells were positive for S-100 and CD1a by immunohistochemical staining. In addition, lung biopsies of two patients showed an appearance consistent with fibrosis in some areas.

Treatment primarily consisted of chemotherapy and targeted management for respiratory complications. Since 1974, the institution has utilized a variety of chemotherapy protocols. Vinblastine was the mainstay treatment for 26 patients, used either as a monotherapy or in combination with other drugs. Single-agent vinblastine was used in 8 patients (22%), while a vinblastine and prednisone combination was given to 18 patients. Treatment could not be given to one patient due to pneumonia. The remaining 10 patients were treated with vinblastine / prednisone / etoposide (n=2), vinblastine/prednisone/6-mercaptopurine (n=1), vinblastine / cyclophosphamide (n=1), prednisolone/etoposide (n=1), prednisolone only (n=1), 6-mercaptopurine / methotrexate (n=1) and cyclophosphamide / prednisone / vincristine (n=3) regimens.

During the study period, five children experienced pneumothorax incidents, with one patient having four recurrences, two patients with three recurrences each, and two others with two recurrences each. Of the pneumothorax episodes, six were on the left side and eight on the right. Notably, all three episodes in a single patient occurred on the right side, whereas in the other patients, the episodes were bilateral. Each of the five initial pneumothorax episodes was managed with chest tube drainage, followed by pleurodesis due to the recurrent nature of the condition. Pleurodesis was conducted an average of 59 days post-initial pneumothorax, 25 days after the second, and 8 days subsequent to any further occurrences. This procedure was carried out nine times in total, using talc in four instances, bleomycin in three, and tetracycline in two.

One patient died without treatment on the first day of hospitalization due to pneumonia. Six patients received radiotherapy, only one was given pulmonary radiotherapy.

Eleven children died. The causes of death for four could not be determined as they missed their regular check-ups. The average time from the date of admission to the date of death of the 11 patients was 7.6 months. The median follow-up for surviving children was 202.4 months (95% confidence interval: 168.6-236.1 months). One 11.7-year-old patient with isolated pulmonary

involvement is alive and well 12 years post-treatment. 5-year event-free survival (EFS) and OS were 54.7% and 63.3%, while 10-year event-free survival and OS were 47.8% and 63.3% in 37 patients with pLCH (Fig. 3). According to the comparison of survival rates of children <2 years old and ≥2 years old, the 10-year EFS rate was 53.3% vs. 40.2% (p= 0.79) and the 10-year OS rate was 58.7% vs. 68.8%, respectively (p=0.65) (Table II, Fig. 4). We also compared 10-year EFS and OS between pLCH children with (RO^+) or without (RO^-) risk organ involvement.

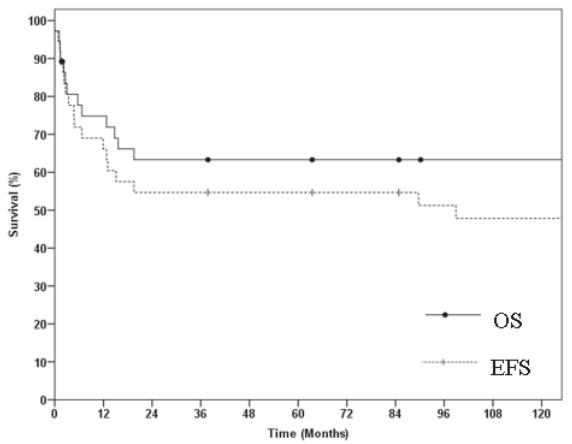

Fig. 3. Overall (OS) and event free survival (EFS) in 37 patients with pulmonary Langerhans cell histiocytosis.

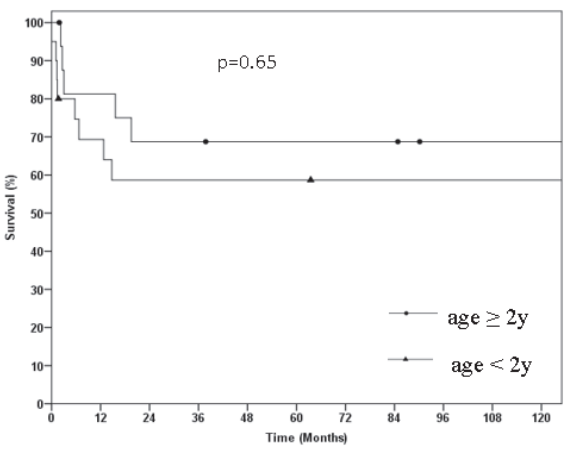

Fig. 4. Overall survival in 37 patients with pulmonary Langerhans cell histiocytosis according to age group.

In terms of the presence or absence of risk organ involvement, the 10-year EFS rates for patients were EFS (RO^+) 51.9% and EFS (RO^-) 46.3%, (p=0.83). The 10-year OS rates for patients with or without risk organ involvement were also OS (RO^+) 51.9% and OS (RO^-) 73.7% (p=0.17) (Table II, Fig. 5). The long-term pulmonary functions were not routinely monitored in the follow-up of the patients. The outcome of the patients are presented as overall and event-free survival based on the clinical follow-up.

Table II. The 5-year and 10-year EFS and OS rates of children with pLCH.

	Survival		p
	5 years (%)	10 years (%)	
Age <2 years OS	58.7	58.7	0.651
Age ≥2 years OS	68.8	68.8	
Age <2 years EFS	53.3	53.3	0.786
Age ≥2 years EFS	56.3	40.2	
RO+ OS	51.9	51.9	0.171
RO- OS	73.7	73.7	
RO+ EFS	51.9	51.9	0.838
RO- EFS	57.9	46.3	
All OS	63.3	63.3	
All EFS	54.7	47.8	

EFS: Event-free survival, OS: Overall survival, pLCH: pulmonary Langerhans cell histiocytosis, RO-: Without "risk organ" involvement, RO+: With "risk organ" involvement.

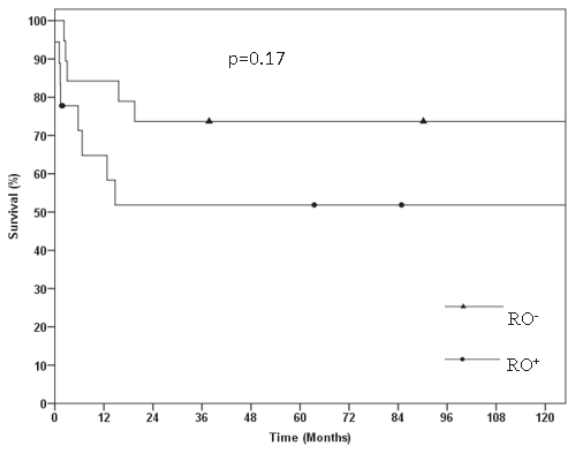

Fig. 5. Overall survival in 37 patients with pulmonary Langerhans cell histiocytosis, with or without risk organ (RO) involvement.

Discussion

Our work indicated a pLCH prevalence rate of 10%, which is consistent with the findings of Le Louet et al.[11] (7.4%) in a similar cohort. In children, pLCH usually part of broader multisystem LCH, with 10-30% displaying lung lesions. Isolated pLCH in children is rare, with unclear etiology. Our study includes a noteworthy case of an 11.7-year-old with isolated pulmonary involvement who, 12 years post-treatment is alive and well. pLCH presents with a range of symptoms, from chronic cough and dyspnea to no symptoms. The symptoms may begin insidiously.[8,12] Despite extensive lung involvement on imaging, only 30% of our patients exhibited respiratory symptoms. This underscores the need for routine lung radiological exams in all new LCH diagnoses, including chest X-ray and CT.[5,13]

Common radiological findings for pLCH include bilateral interstitial infiltrates, cysts, nodular opacities, and pneumothorax.[14] These findings could be isolated or mixed.[5] Chest radiography often reveals bilateral interstitial changes. Nodular changes, cystic changes, pneumothorax may also be seen.[2,6,15] However, its diagnostic utility is limited. Chest CT is more sensitive, showing detailed lung lesions, making it the preferred method for diagnosing pLCH. Chest CT frequently identifies a reticulonodular pattern early in the disease, with cystic changes becoming more prominent as the disease advances.[2,5,6,15] Chest CT is routinely used for the differential diagnosis of pLCH.[13] In our study, chest X-rays indicated bilateral interstitial changes in most patients as seen in literature, but chest CT was more likely to reveal cystic and nodular changes.

PFTs in pLCH can be normal or show restrictive or obstructive patterns. Initially, about 20% of patients may have normal PFT results, but as the disease progresses, a restrictive pattern due to limited ventilation can develop, potentially leading to obstructive dysfunction later.[1,15–18] In our study, PFTs indicated that three patients had a restrictive pattern, while one had normal pulmonary function. Young age population and retrospective nature of our work limits our further analysis of PFTs in this group.

If isolated pLCH is suspected, a lung biopsy is important in confirming the diagnosis and guiding treatment.[2] CD1a, S-100 positivity in immunohistochemical staining and detection of cytoplasmic Birbeck granules by electron microscopy are characteristics of LCH.[2,19] However, if clinical and radiological findings suggest pulmonary involvement and a biopsy from extra-pulmonary sites confirms LCH, the need for lung biopsy may be eliminated to avoid morbidity.[2] The diagnosis was confirmed with a biopsy in all cases. The lung biopsy was performed in 5 cases, the rest had biopsy from other involved sites.

Transbronchial biopsies and BAL might be useful in patients undergoing bronchoscopy, with >5% CD1a and CD207 positive cells in BAL fluid being significant.[2,13,20–22] However, a positive result is seen in only up to 25% of cases, and less than 5% CD1a positive cells do not rule out pLCH.[15,22,23] Challenges in transbronchial biopsy include sampling errors and the risk of pneumothorax due to the irregular distribution of diseased tissue.[21] Additionally, the infrequent staining of BAL cells with CD1a in labs, cost, and quality control issues are noted.[21,24] Studies show a low diagnostic sensitivity for BAL.[15,17,24] In our series, no patients required bronchoscopy and BAL for diagnostic purposes.

LCH treatment follows the Histiocyte Society's LCH-IV protocol, which doesn't specify a lung involvement treatment arm. Standard initial therapy includes prednisone and vinblastine.[15,25] In our study, 29 patients received vinblastine-based treatments, while others received varying regimens. Clofarabine and targeted mitogen-activated protein kinase (MAPK) pathway therapies like BRAF and MEK inhibitors show promise for refractory LCH.[15,25]

The best approach to prevent recurrent pneumothorax in childhood LCH is not fully established.[11,26] Tube thoracotomy and

pleurodesis are common treatments, with pleurodesis recommended after the first recurrence.[15,27] Although chemotherapy protocols for LCH can slow disease progression, they don't prevent pneumothorax. In our study, all patients with pneumothorax underwent pleurodesis after being treated with chest tube drainage, using agents like talc, bleomycin, and tetracycline, in line with literature findings.[26,28,29] Patients with severe cases may require intensive care, and strategies to prevent air leak recurrences are crucial. ECMO can provide support during intensive care or bridge to lung transplantation.[2,12,15] Le Louet et al.[11] showed that 17 (15%) of 111 children diagnosed with pLCH required intensive care, and 10 of 17 children required mechanical ventilation.

In pediatric LCH, organ involvement significantly impacts prognosis. Single-system LCH boasts nearly 100% survival, but multisystem disease increases mortality risks, with a higher rate of recurrence and complications. Multisystemic LCH without risk organ involvement has a 5-year survival of 98%, dropping to 77% with such involvement.[30] Ronceray et al.[3] reported that 52% of pLCH patients had risk organ involvement, which didn't affect survival at diagnosis. Similarly, our study found 49% with risk organ involvement, with no impact on 10-year survival outcomes. Pulmonary LCH, often part of multisystemic LCH, contributes to morbidity but isn't a standalone prognostic factor. Studies report a 5-year OS of about 93.6% and event-free survival of about 55.7% for children with pulmonary LCH, with intensive care cases showing a 62.7% survival rate.[1,11] In our study, the 10-year OS rate was 63.3%. This rate is considered low and is likely due to most patients being diagnosed and treated before the 1990s, which implies that recent advancements in treatment and supportive care have improved outcomes. Even with severe lung involvement, early diagnosis and treatment lead to a good prognosis for pLCH. Early management can mitigate complications like pneumothorax and respiratory failure, reducing the risk of chronic conditions like fibrosis and restrictive lung disease.[12,19]

Our study on pLCH in children faces limitations due to its retrospective nature, limited patient data, and being a single-center study with a small sample size. Additionally, not all patients had lung biopsies, and early cases lacked a chest CT. Despite these constraints, our study contributes valuable insights into pLCH, an area lacking comprehensive data in Türkiye.

In summary, children with pLCH have high survival rates, yet pulmonary involvement, while not independently impacting survival, can cause serious long-term effects if untreated. Prompt and effective treatment is essential for managing pulmonary symptoms and preventing irreversible damage. As Türkiye lacks specific data on pLCH in children, aligning local findings with global research is critical to establishing national guidelines.

Ethical approval

Approval was obtained from the Non-Interventional Clinical Researches Ethics Board of Cumhuriyet University (dated 21.09.2023, no: 2023-09/21). The study was conducted according to the principles of the Declaration of Helsinki.

Author contribution

The authors confirm their contribution to the paper as follows: study conception and design: ÇC, TK; data collection: ÇC, TK; analysis and interpretation of results: ÇC, TK, BY, BO, DO, EY, EM, İYB, UÖ, BA, NK, AV, MH; draft manuscript preparation: ÇC, TK. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Gastroenteropancreatic neuroendocrine tumors in children and adolescents

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ABSTRACT

Background. Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are rare in children and adolescents. Standard management of these tumors has not been well established due to their rarity in this age group. We aimed to report the clinical and pathological characteristics of patients with this rare disease followed and treated between the years 1993-2022.

Materials and methods. The medical records of patients with GEP-NETs were reviewed.

Results. Fourteen patients (11 girls, 3 boys) were diagnosed with GEP-NET. The median age was 13 (9-18) years. Tumor localization was the appendix in 12, stomach in one and pancreas in one patient. Mesoappendix invasion was detected in four patients two of whom underwent right hemicolectomy (RHC) and lymph node dissection (LND). Of those, one patient had lymph node involvement. The other two had not further operations. Somatostatin was used in one with pancreatic metastatic disease and the other with gastric disease after surgery. No additional treatment was given in other patients. All patients are under follow-up without evidence of disease at a median follow-up of 85 months (7-226 months).

Conclusion. GEP-NETs should be considered in the differential diagnosis of acute appendicitis and in cases with persistent abdominal pain. In children, there is invariably a favorable prognosis, and additional surgical interventions other than simple appendectomies generally do not provide benefits. Mesoappendix invasion may not necessitate RHC and LND.

Key words: gastroenteropancreatic neuroendocrine tumors, appendiceal neuroendocrine tumors, appendix, children and adolescents.

Neuroendocrine tumors (NETs), originating from neuroendocrine cells, are heterogeneous tumors representing distinct clinical and biological features. Neuroendocrine cells are widely distributed in many organ systems in the body and thus neuroendocrine tumors (NETs) can arise in almost any part of the body.[1] NETs are rare in children. The incidence is approximately 6 cases per 100,000 in adults and 2.8 cases per million in children.[2,3]

Tumors arising from neuroendocrine cells occurring anywhere along the gastrointestinal tract are called gastroenteropancreatic neuroendocrine tumors (GEP-NETs).[4] Pediatric neuroendocrine tumors are most commonly located in the appendix. Although liver is a rare primary tumor localization, it is the most common site for metastatic disease.[5-8]

In this study, we aimed to evaluate the demographic, clinical characteristics, treatment and outcomes of children and adolescents diagnosed with GEP-NET.

Materials and Methods

The medical files of children and adolescents under the age of 18 years with a diagnosis of GEP-NET between the years 1993 and 2022 at the Istanbul University Oncology Institute

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were retrospectively evaluated regarding demographic, clinical characteristics, treatment and outcomes.

The histopathological characteristics of the specimens, stained with hematoxylin and eosin, were assessed. These characteristics included the size and location of the tumor, degree of differentiation, extent of appendix wall infiltration, perineural invasion, and lymphovascular invasion. Ki-67 proliferation index was used to determine the proliferative rate. Histologic grading was reported.[9]

This study was reviewed and approved by Institutional Ethics Committee of Istanbul University Oncology Institute (2023/1627403).

Results

Fourteen patients (11 girls, 3 boys) were diagnosed with GEP-NET. The median age at diagnosis was 13 (9-18) years. Tumor localization was the appendix in 12 patients, stomach and pancreas in one each. Characteristics of the patients are given in Table I.

Patients with appendiceal neuroendocrine tumors (aNETs) were all diagnosed after an appendectomy performed due to the preliminary diagnosis of acute appendicitis. The patients were reported to have at least one of the symptoms of abdominal pain, nausea, and vomiting at hospital admission. The patient with a tumor located in the stomach was diagnosed after endoscopic polypectomy due to prolonged dyspeptic complaints resistant to medical treatment. The patient with pancreatic NET (pNET) had been admitted to the hospital due to prolonged abdominal pain and MRI revealed a mass in the pancreas with metastasis in the liver. A trucut biopsy of the lesions in the pancreas and liver confirmed the diagnosis.

The size of the tumor was less than 2 cm in 13 patients (range 0.1 cm-1.4 cm) with primary tumors arising from appendix and stomach. One patient with pancreas primary had a tumor size of 10 cm. A total of seven patients had grade I and seven had grade II NET. Histopathological examination revealed mesoappendix invasion in four patients two of whom underwent right hemicolectomy and lymph node dissection (>20 lymph nodes removed). Of those two patients who underwent right hemicolectomy (RHC) and lymph node dissection (LND), one was found to have three lymph nodes positive for NET metastasis and the other was negative. The parents of the other two patients with mesoappendix invasion refused the recommendation for RHC and LND. Both patients are still under regular follow-up with no evidence of disease.

Of the 14 patients, at diagnosis one with aNET and lymph node metastasis had carcinoid syndrome. The patient described episodes of hot flushes with transient non-pruritic, macular erythematous rash, mostly localized on the face.

Serum chromogranin A (CgA) level was found to be high at diagnosis in the patient with pNET and liver metastasis. Urine 5-hydroxyindoleacetic acid (5-HIAA) levels investigated after surgery were within normal ranges in all the other patients.

Imaging studies with gallium-68 (Ga-68) dotatate positron emission tomography/computed tomography (PET/CT) were performed in all patients after histopathological diagnosis was established. There was no somatostatin receptor expression in any of the patients, except the patient with pNET whose study with Ga-68 dotatate PET/CT revealed significant increased somatostatin receptor expression in the pancreas and metastatic lesions in liver and spleen.

The patient with pNET was treated with resection of the tumor in pancreas tail and liver, splenectomy and cholecystectomy followed by somatostatin for one year and is under regular follow up without evidence of disease (NED).

The patient with gastric NET was treated with somatostatin for six months after surgery. She is followed with NED. None of the other patients received further treatment after surgery.

Table I. Patient characteristics, treatment and outcome

Patient number	Age at diagnosis (yr)	Gender	Complaint	Preliminary diagnosis	Tumor localization	Tumor diameter (cm)	LN involvement	Ki 67 (%)	Histology / grade	Invasion						Ga-68 DOTATATE uptake status	Carcinoid syndrome	Treatment	Duration of FU / event-free FU (months)	Outcome
										Mesoappendix	Serosa	Vascular	Lymphatic	Perineural	Surgical margin					
1	17	F	Abdominal pain, vomiting	Acute appendicitis (perforated)	Appendix	0.7	-	3	Well-diff. / II	+	+	-	+	+	-	-	-	Appendectomy. (RHC and LND recommended but not performed)	135 / 135	NED
2	10	F	Abdominal pain	Acute appendicitis (perforated)	Appendix	0.8	-	2	Well-diff. / II	-	+	+	-	-	-	-	-	Appendectomy	226 / 226	NED
3	10	F	Abdominal pain, vomiting	Acute appendicitis	Appendix	0.4	-	2	Well-diff. / I	-	-	-	-	-	-	-	-	Appendectomy	99 / 99	NED
4	11	F	Abdominal pain, vomiting	Acute appendicitis	Appendix	0.4	-	NA	Well-diff. / II	-	-	-	-	-	-	-	-	Appendectomy	217 / 217	NED
5	18	F	Dyspeptic complaints		Stomach	0.5	-	NA	Well-diff. / II	-	-	-	-	-	-	-	-	Polypectomy followed by somatostatin	82 / 82	NED
6	14	F	Abdominal pain, vomiting	Acute appendicitis	Appendix	1.1	+	1	Well-diff. / I	+	+	+	+	+	+	-	+	Appendectomy followed by RHC and LND	68 / 68	NED
7	16	F	Abdominal pain, vomiting	Acute appendicitis	Appendix	1.4	-	2	Well-diff. / I	+	+	+	+	-	+	-	-	Appendectomy followed by RHC and LND	7 / 7	NED
8	12	M	Abdominal pain, vomiting, fever	Acute appendicitis	Appendix	0.5	-	2	Well-diff. / I	-	-	-	-	-	-	-	-	Appendectomy	14 / 14	NED
9	10	F	Abdominal pain	Acute appendicitis	Appendix	0.7	-	NA	Well-diff. / I	-	+	+	+	-	-	-	-	Appendectomy	88 / 88	NED
10	15	M	Abdominal pain	Acute appendicitis	Appendix	0.1	-	0	Well-diff. / I	-	-	-	-	-	-	-	-	Appendectomy	59 / 59	NED
11	15	M	Abdominal pain	Acute appendicitis	Appendix	0.5	-	2	Well-diff. / I	-	-	-	-	-	-	-	-	Appendectomy	100 / 100	NED
12	9	F	Abdominal pain	Acute appendicitis	Appendix	0.9	-	3.5	Well-diff. / II	+	-	-	+	+	-	-	-	Appendectomy. (RHC and LND recommended but not performed)	41 / 41	NED
13	12	F	Abdominal pain	Acute appendicitis	Appendix	0.6	-	2	Well-diff. / II	-	-	-	-	-	-	-	-	Appendectomy	204 / 204	NED
14*	17	F	Abdominal pain		Pancreas*	10	-	7	Well-diff. / II							+	-	Mass resection in pancreas tail and liver, splenectomy and cholecystectomy followed by somatostatin	75 / 75	NED

*This is the only patient with metastasis (liver and spleen)

-: negative, +: positive, F: female, FU: follow-up, LN: lymph node, LND: lymph node dissection, M: male, NA: not available, NED: no evidence of disease, RHC: Right hemicolectomy, Well-diff.: well-differentiated

Patients were followed up by physical examination, laboratory tests for serum CgA and urine 5-HIAA and imaging studies with ultrasound every three months during treatment and for the first two years after treatment, every six months until five years after treatment and yearly thereafter. The median follow-up of the patients was 85 months (7-226 months). All patients are alive with no evidence of disease.

Discussion

Neuroendocrine tumors (NETs) are rare and slow growing tumors with various histological and clinical features constituting 2% of all malignant tumors of the gastrointestinal tract.

The incidence of GEP-NETs is reported to be 3.6/100,000 people annually by the National Cancer Institute Surveillance, Epidemiology, and End Results Program.[10] The epidemiological data of childhood NETs is limited due to their rarity among children. An incidence of 2.8 cases per million among children and adults under age of 30 constituting less than 1% of childhood malignancies has been reported.[2,3]

The World Health Organization (WHO) categorized NETs as grade I, grade II, or grade III considering mitotic number and Ki-67 proliferation index of tumors in 2010.[9] Through studies reporting the differences in survival statistics of patients with grade III tumors, WHO reported an updated classification of NETs in 2017 based on histologic features in which grade III tumors with well-differentiation were denominated as "neuroendocrine tumors" whereas those with poor differentiation as "neuroendocrine carcinomas''. All tissue samples in our study were re-classified histologically according to WHO classification.[11,12]

Neuroendocrine tumors originate from diffuse enterochromaffin (Kulchitsky) cells throughout the gastrointestinal (GI) tract and bronchopulmonary system.[13]

Though GEP-NETs can form in different parts of the GI tract, the most common site of origin in pediatric patients is the appendix representing almost 80% of cases.[14] In our series, 85.7% of the cases were located in the appendix.

GEP-NETs can cause various clinical signs and symptoms. Patients diagnosed with aNET often are admitted with the complaint of abdominal pain accompanied by nausea and/or vomiting, and they are diagnosed incidentally after being operated with a preliminary diagnosis of acute appendicitis. In a study reviewing related publications including more than 350000 appendectomy cases, the incidence of aNET was reported as 2-5 case per 1000 appendectomies, and the overall incidence in childhood was reported to be between 1:100,000 and 1.14:1 million per year.[13] Most aNETs are diagnosed postoperatively, often are hormonally inactive small tumors (<1.5-2 cm) and have a good prognosis.[15] Tumor diameters of >2 cm were frequently reported in patients with extra-aNET.[16] The size of the tumor in the patient with pNET and liver metastasis was 10 cm in our study.

Pancreatic NETs constitute approximately 30% of pancreatic tumors in children and adolescents and represent about a third of all GEP-NETs. Pancreatic NETs frequently tend to be multifocal. Approximately half of pNETs have metastasis at diagnosis, and the most common site of metastasis is the liver. Symptoms may occur due to the local effects of the pancreatic mass and/or the hepatic metastases.[17,18]

Unlike adults, carcinoid syndrome leading to symptoms such as diarrhea, flushing, and wheezing due to the release of vasoactive substances secreted by the tumor, has been reported less frequently in children.[19]

Neuroendocrine neoplasms can be sporadic or occur as part of inherited disorders. About 5% of NETs arise in the context of an inherited tumor syndrome. Hereditary syndromes shown to be associated with NETs include familial adenomatous polyposis (FAP),

multiple endocrine neoplasia type 1 (MEN-1), multiple endocrine neoplasia type 2 (MEN-2), multiple endocrine neoplasia type 4 (MEN-4); neurofibromatosis type 1 (NF-1), and von Hippel–Lindau syndrome (VHL).[20-23] Some NETs may also be associated with ectopic Cushing's syndrome due to adrenocorticotropic hormone (ACTH) hypersecretion. The most common ectopic ACTH producing NETs have been reported in pediatric cases with bronchial and pancreatic localizations.

Gastrin-secreting neuroendocrine neoplasms may cause Zollinger-Ellison syndrome which can present as severe peptic ulcer disease, gastroesophageal reflux disease (GERD), and chronic diarrhea caused by a recurrent epigastric pain and malabsorption from gastric and duodenal ulcers and diarrhea.[19,24] In our study, the patient with dyspeptic complaints resistant to medical treatment was diagnosed with gastric NET after endoscopic polypectomy. There was no patient with an inherited disorder in our series.

Various imaging modalities can be used in the detection and follow-up of NETs including ultrasound, computed tomography (CT), and magnetic resonance imaging. Some of these modalities have limitations such as low sensitivity of CT for tumors <2 cm and the low metabolic activity in PET/CT for well-differentiated tumors. Ga-68 dotatate PET/CT is a functional imaging modality used with somatostatin receptor (SSR) analogues. Studies suggest Ga-68 dotatate PET/CT should be considered a first-line diagnostic tool in adult and pediatric patient populations which surpasses conventional diagnostic imaging techniques with its high sensitivity in detecting well-differentiated NETs, identifying NETs in cases of unknown primary sites, and detecting metastases.[24,25] All of our patients had a postoperative Ga-68 dotatate PET/CT study, there was no uptake in any of our patients, except the one with the pancreatic origin with metastasis in the liver and spleen. After total resection of the tumor, Ga-68 dotatate PET/CT was negative in this patient also.

Tumor size and mesoappendix involvement have been considered the primary determinatives for aggressiveness of aNETs. More controversial prognostic factors include lymphovascular invasion, subserosal invasion, and infiltration of the base of the appendix. For patients with aNET, RHC has been recommended for tumors larger than 1.5-2 cm in diameter, with mesoappendiceal or vascular invasion or with high mitotic activity.[26-30] The guidelines from the European Neuroendocrine Tumor Society (ENETS) advocate for appendectomy alone in cases of appendiceal NETs ≤2 cm. For tumors <2 cm but with positive or unclear margins, or exhibiting deep mesoappendiceal invasion, ENETS recommends a right hemicolectomy. In cases of tumors >2 cm, ENETS also suggests a right hemicolectomy.[31] On the other hand, the North American Neuroendocrine Tumour Society (NANETS) guidelines propose a right hemicolectomy for tumors >2 cm, those that are incompletely resected, those showing invasion at the base of the appendix or mesoappendix, as well as those with lymphovascular invasion or positive lymph nodes.[32] These guidelines are intended for adults; therefore, they should be used cautiously in children and adolescents. The interdisciplinary GPOH-MET study group suggests RHC after complete resected tumors larger than 15 mm in children.[6] Dall'Igna et al.[33] recommend partial checectomy or ileocecal resection to perform more extensive surgery in cases where the tumor cannot be completely removed and/or when surgical margins are not tumor free. There are also reports of low percentage of lymphatic spread and distant metastases in aNETs larger than 2 cm in diameter in children who had not undergone secondary surgery.[34]

According to the publication by Njere et al.[35] where more than 900 pediatric cases were evaluated, it was reported that although the risk of positive lymph nodes is increased 28-fold when the tumor size was >2 cm compared to <2 cm, there was no difference in terms of recurrence or mortality between those who

were followed up after appendectomy and those who underwent second surgery. Similarly, Yalçın et al.[36] in their institutional experience with 33 appendiceal NETs, presented a good outcome with observed cases exhibiting tumors ≤2 cm regardless of local invasion after appendectomy alone which could have been deemed as indications for additional surgery, thus contradicting recommendations drawn from adult experiences.

In our series, two of the four patients with mesoappendix invasion underwent RHC and lymph node dissection; lymph node metastasis was observed in one of these. No recurrence was observed in the two other patients with mesoappendix invasion who did not have RHC and LND. Although, this is a very limited series, our findings are parallel with the recommendation of limiting additional surgery (RHC) in small tumors with mesoappendiceal invasion.[36,37]

Although surgical total resection is the preferred primary treatment for NETs, other treatment options such as somatostatin analogues, cytotoxic chemotherapy, molecular targeted therapies and peptide receptor radionuclide therapy (PRRT) are used in metastatic and locally advanced cases which are generally considered unresectable.

As increased somatostatin receptors may exist in NETs, targeted treatment with octreotide which is a somatostatin analogue, has been shown to have antitumor activity and a cytostatic effect.[38]

Traditionally, cytotoxic chemotherapy has been known to have limited effects on NETs, however it has been used in some cases. A combination of capecitabine and temozolomide has been reported to provide favorable survival outcomes in patients with metastatic NETs.[39] Pediatric and adult patients with NETs have been reported to respond to treatment with cyclophosphamide, vincristine and dacarbazine. Irinotecan and cisplatin may also be an alternative treatment modality.[40] Everolimus, an mTOR inhibitor, has been found to be effective in metastatic progressive NETs of gastrointestinal tract and bronchial origin and progression-free survival benefit was confirmed in the RADIANT 4 trial.[41]

In conclusion, NETs are rare in children and most are localized in the appendix. aNETs often cause sign and symptoms of acute appendicitis and have a good prognosis. Primary healthcare physicians, pediatricians and pediatric surgeons should be aware of NET in the differential diagnosis of acute appendicitis. Different from adults, children and adolescents typically have a consistently positive prognosis and additional surgical interventions beyond simple appendectomies generally do not provide benefits. According to recent data, in cases with mesoappendix invasion, RHC may be avoided. Specific pediatric guidelines are needed.

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Ethical approval

This study was reviewed and approved by Istanbul University, Oncology Institute Review Board (2023/1627403).

Author contribution

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

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Prevalence of premenstrual syndrome in adolescent girls

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ABSTRACT

Background. Premenstrual syndrome (PMS) is characterized by physical, cognitive, emotional, and behavioral symptoms that appear during the luteal phase of the menstrual cycle, disappear after menstruation, and are recurrent in every cycle. PMS significantly affects the social and academic lives of adolescents, and historically, it has been neglected by healthcare professionals. We aimed to evaluate the current point prevalence of PMS in Turkish adolescents presented to a tertiary adolescent medicine clinic.

Material and Method. Adolescent girls between the ages of 12 and 18 and who had regular menstrual cycles for at least three months without any mental or chronic illness were assessed. A clinic information form and the 'Premenstrual Syndrome Scale' (PMSS) questionnaire were completed. Those with a PMSS total score of more than 50% of the total score (>110 out of 220) were classified as PMS (+). Those classified as PMS were further classified as mild-moderate (score: 110-150) and severe (>150).

Results. The study included 417 adolescents. The point prevalence of PMS was found to be 61.2% (n:255). Of those with PMS, 49.4% had mild-moderate and 50.6% had severe PMS. The mean PMSS score was 154.56 ± 30.43 in the PMS group and 76.17 ± 20.65 in the non-PMS group ($p<0.001$). The mean age was 15.41 ± 1.3 years in the PMS group and 14.88 ± 1.35 years in the non-PMS group ($p=0.029$). None of the youth in our study applied to our clinic due to any premenstrual complaints.

Conclusion. PMS is frequently observed in youth, as indicated by our study. Adolescents have little awareness of PMS and their need for healthcare services. During the evaluation of adolescents, it is important for health care providers to acquire knowledge regarding the features of menstrual cycles and conduct a comprehensive psychosocial assessment.

Key words: adolescent health, adolescent girls, premenstrual syndrome, prevalence.

Premenstrual syndrome (PMS) is a cluster of physical, emotional, and behavioral symptoms triggered in the luteal phase starting with ovulation and regressing in the first few days of menstruation, leading to impairment in the academic, social, or individual functioning of the person and cannot be better explained by another diagnosis.[1,2] The etiology of PMS has not been fully clarified. It is stated that the current symptoms are related to increased sensitivity to changes in estrogen and progesterone hormone levels during the menstrual cycle.[3,4] Estrogen and progesterone have been shown to cause psychiatric symptoms via serotonin, dopamine, γ-aminobutyric acid (GABA) pathways, and physical symptoms via the renin-angiotensin-aldosterone system (RAAS). Commonly reported symptoms include headache, breast tenderness, depression, anxiety, social withdrawal, increased appetite, abdominal distension, fatigue, mood swings, irritability, and edema.[5] Although these symptoms start in

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adolescence, most women present to the clinic for treatment in their late 20s.[6]

Despite the fact that the exact prevalence of PMS is not known, it has been shown that up to 80% of women experience some physical and emotional changes before the onset of menses, 20 to 40% experience some degree of functional impairment and 2.5-5% have a significant effect on functionality.[6]

Studies evaluating the prevalence of PMS prospectively, are quite limited in the literature. In a meta-analysis conducted by Direkvand-Moghadam et al. the prevalence of PMS was found to be 47.8%.[7] The lowest prevalence was found to be 12.0% in France, and the highest prevalence was found to be 98.0% in Iran[8]. Similar results were obtained in PMS prevalence studies conducted in our country. Güvenç et al. included 250 nursing students with a mean age of 19.89 ± 1.43 in their study in 2012, and reported the prevalence of PMS as 36.4%.[9] In a 2004 study by Derman et al. on adolescent girls between the ages of 12-16, the rate of PMS was found to be 61.4%. PMS was mild in 49.5%, moderate in 37.1% and severe in 13.4% of the patients.[10]

Premenstrual symptoms are observed very frequently and at similar rates in the adolescent age group as in adults. However, PMS is among the most frequently missed and untreated diagnoses in this age group, which significantly affects the social and academic life.[7] We aimed to evaluate the current point prevalence of PMS in Turkish adolescents presented to a tertiary adolescent medicine clinic.

Methods

This study was conducted at the Division of Adolescent Medicine at Hacettepe University İhsan Doğramacı Children's Hospital, with female adolescents aged 12-18 years who had regularly menstruated for at least 3 months. Adolescents without chronic and/or psychiatric illness were included in the study. Study approval (GO20/838) was obtained from the Hacettepe University Non-Interventional Clinical Research Ethics Committee. Written assent was obtained from the adolescents and written consent was obtained from their care provider.

A clinic information form was filled out and age, anthropometric measurements (weight, height and body mass index (BMI), and menstrual characteristics such as age at menarche and menstrual cycle duration were recorded. We also recorded if the individual had sought medical care at our clinic for any premenstrual concerns. In addition, the 'Premenstrual Syndrome Scale' (PMSS) was filled out for each patient. This scale was developed by Gençdoğan in 2006 according to DSM III and DSM IV-R and aims to measure the severity of premenstrual symptoms.[11] The lowest score that can be obtained from the scale is 44 and the highest score is 220. Those with a PMSS total score of more than 50% of the total score are classified as PMS positive (>110). Those classified as PMS positive were further classified as mild-moderate if they scored between 110-150 and severe if they scored >150.

Statistical analyses

The statistical evaluation of results was performed using IBM SPSS 22 program (Chicago, IL). The distribution of variables was examined using the Kolmogorov-Smirnov test. Numerical data are presented as mean ± SD, and prevalence data are presented as n (%). To assess differences between numerical variables independent samples t-test was employed for normally distributed data and Mann-Whitney U test was used for non-normally distributed data. The level of significance was set at $p<0.05$.

Results

The study included 417 adolescent female patients. When the participants were classified according to the PMSS, 255 were determined to have PMS (61.2%) with a mean score of 154.56 ± 30.43. Of those with PMS, 126 (49.4%) had mild-moderate PMS with a mean score of 129.01 ± 11.74, and 129 (50.6%) had severe PMS with

a mean score of 179.91 ± 20.34. The mean age was slightly higher in the PMS group compared to the non-PMS group (p= 0.032). Other data were similar in both groups. Anthropometric measurements and menstrual information of the participants are given in Table I. None of the participants in our research sought medical attention at our clinic for any premenstrual issues.

Discussion

The aim of this cross-sectional, prospective evaluation, was to assess the point prevalence of PMS in a group of Turkish females. We found the point prevalence of PMS to be 61.2% in this population, and more importantly, of those PMS (+) individuals over 50% were classified as having severe PMS. Diagnosing PMS in adolescence is challenging due to several factors, including the lack of clear diagnostic criteria during this stage, the irregularity of adolescent menstrual cycles, the potential confusion between PMS symptoms and normal puberty symptoms, and the tendency of adolescents to withhold information about this issue unless specifically asked.[12]

The prevalence of adolescents meeting the diagnostic criteria for PMS ranges from 42% to 78% in the literature.[2,13] In 2023, the prevalence of PMS in adolescent girls in China was found to be 24.6%.[14] In the same year, a study conducted among university students in South Korea found that severe PMS findings were 72.7%.[15] In 2019, in a cross-sectional study conducted on high school students in Iran, the PMS rate was found to be 33.9%.[16] In a meta-analysis conducted in Turkey, the prevalence of PMS was analyzed in 6890 women of reproductive age. A total of 18 studies reporting the prevalence of premenstrual syndrome in Turkey were included in this meta-analysis and the prevalence of PMS was found to be 52.2%.[17] The subgroup prevalence was 59% in high school students, 50.3% in university students and 66% in women in the general population. Meta-regression analysis showed that there was no significant relationship between the mean age of the participants and the prevalence of premenstrual syndrome. The results of this study also showed that PMS is common among Turkish women of reproductive age. In a study conducted in our department in 2004, the prevalence was found to be 61.4% in 171 adolescent girls with a mean age of 13.9 years.[10] Our study builds upon the 2004 findings by Derman et al. by providing updated prevalence data and examining trends over time with a larger sample size. Given the potential changes in lifestyle, environmental factors, and healthcare practices over the past two decades, it is crucial to revisit and update these findings. These studies demonstrate the vast variation in the prevalence of this disorder. The absence of a definitive rate can be attributed to the variations in PMS diagnosis criteria employed in research studies and the limitations of community-based studies.[2] Additionally, cultural attitudes and perceptions towards menstruation and

Table I. Anthropometric measurements and menstrual information of the participants.

Anthropometric measurements and menstruation information	PMS N: 255	Non-PMS N:162	p value
PMSS scores	154.56 ± 30.43	76.17 ± 20.65	**<0.001**
Age (years)	15.41 ± 1.30	14.88 ± 1.35	**0.032**
Height (cm)	160 ± 5.48	161.48 ± 6.85	0.580
Body weight (kg)	58.16 ± 9.98	57.76 ± 15.59	0.856
BMI (kg/m^2)	22.47 ± 3.90	21.97 ± 4.79	0.512
Age at menarche (years)	11.80 ± 1.04	11.85 ± 1.19	0.777
Menstrual duration (days)	5.76 ± 1.00	5.87 ± 1.05	0.557

BMI: body mass index, PMS: premenstrual syndrome, PMSS: PMS Scale

women's health may influence the reporting and recognition of PMS symptoms, further complicating prevalence estimates. Another factor could be the age range of adolescents included in the studies. The increase in ovulatory cycles with age might lead to a higher PMS prevalence. The age difference between PMS and non-PMS adolescents in our study can be interpreted to suggest that PMS prevalence might be even higher in late adolescence.

According to the Royal College of Obstetricians and Gynecologists (RCOG) guidelines, the diagnosis of PMS depends on the prospective recording of symptoms for at least two cycles using a tool such as the daily recording of the severity of symptoms.[18] This recording system may not work in adolescents in whom irregular and anovulatory cycles are frequently observed and for this reason it is important that PMS be inquired as a routine part of the evaluation. In addition, adolescents have low health care seeking habits. Therefore, compliance with recording systems and follow-ups that require prospective responsibility and attention are health behaviours that are difficult for many adolescents. Even in adult women, studies have shown that although 80 percent of women experience mood and physical symptoms related to the menstrual cycle and 50 percent have a problem with functioning at work, only a quarter of them seek help.[19] Therefore, asking an adolescent to record her symptoms and come back may delay treatment or discourage the patient from giving feedback.

Psychosocial development throughout adolescence might create upheaval that complicates the diagnosis of PMS in youth. During middle adolescence, disagreements and mood variations between parents and adolescents occur more frequently and with greater intensity. If sudden shifts in mood occur during the luteal phase of the menstrual cycle, they may be seen as psychological symptoms of PMS, which are commonly considered typical psychological and behavioral patterns during this time.[20] Under such circumstances, it may be unwise to base one's actions solely on the symptoms observed during a limited number of cycles. Conversely, it is important to do thorough psychosocial questioning to avoid any delay in diagnosing PMS.

To address these issues, it is essential to gather a comprehensive and thorough medical history from an adolescent. This should include details such as the age of onset of menstruation, frequency of menstrual cycles, characteristics of menstrual bleeding, presence of dysmenorrhea, evaluation of premenstrual syndrome using a standardized scale, assessment of physical and mental distress, duration of symptoms, and any concurrent medical conditions or treatments. Obtaining this information will provide us with the necessary data for diagnosing PMS.[19]

A significant finding of the study was the lack of medical consultation for premenstrual issues among participants, despite the high prevalence of PMS symptoms. We hypothesize several factors contributing to this phenomenon. Firstly, the limited knowledge about PMS among adolescents and their parents can be attributed to insufficient education on menstrual health within school curricula and familial settings.[21] Secondly, cultural taboos surrounding menstruation perpetuate a lack of open discussion and awareness regarding PMS.[22] Lastly, the accessibility and availability of healthcare services, particularly adolescent-friendly clinics, play a crucial role in determining whether medical advice is sought for PMS symptoms.[23]

While there is debate about the use of diagnostic scales in adolescents, we maintain that they can serve as a valuable tool for screening for PMS. Subsequently, a comprehensive examination can be carried out for those who test positive. The PMSS scale utilized in this study has demonstrated its reliability in diagnosing PMS and determining its severity.[11]

Our study has some limiting features. The most important limitation is the small number of participants. In addition, detailed clinical interviews could not be performed to confirm

the diagnosis of our participants. The fact that our study was conducted among adolescents who applied to a tertiary adolescent medicine clinic may have caused the point prevalence to be higher. Additionally, the only available socio-demographic data pertained to the geographical location, with all patients originating from the same city. We recognize that more comprehensive socio-demographic and clinical data would have been valuable for a more detailed analysis. Despite these limitations, we believe that it is an important contribution to the literature in assessing the prevalence of PMS in adolescent girls in our country. Future longitudinal, cross-cultural studies with large and representative samples from diverse populations using standardized diagnostic criteria are needed.

Conclusions

PMS is a highly prevalent condition in the adolescent age group and severe cases are also prominent. However, it is also among the most frequently missed and untreated diagnoses in this age group. When left untreated, it can significantly interfere with their daily functioning, including school attendance.[24] Adolescents and adults exhibit variations in the diagnosis and monitoring of PMS. The level of awareness among adolescents regarding PMS and their need for healthcare services related to this issue is insufficient. Healthcare providers should familiarize themselves with the characteristics of the menstrual cycle and perform a comprehensive psychosocial assessment when examining youth, even if the presenting complaint is not PMS-related. By raising awareness, destigmatizing menstruation, and providing support services, PMS could be managed more effectively. This can be accomplished by implementing comprehensive menstrual health education programs in schools, launching public health campaigns, and raising awareness about PMS. Adolescent and adult women accept PMS symptoms as a natural part of their lives and do not complain about them. Encouraging open discussions, promoting positive media representation, and supporting advocacy for menstrual equity can help destigmatize menstruation. Additionally, establishing adolescent-friendly clinics, offering counseling services, and developing school-based support systems will provide the necessary support services for effective PMS management. These actions collectively aim to normalize menstruation, improve understanding, and ensure access to appropriate care for adolescents experiencing PMS.

Ethical approval

Study approval (GO20/838) was obtained from the Hacettepe University Non-Interventional Clinical Research Ethics Committee.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: SA, OA, LJ, MPK, data collection: OA, LJ, DAA; analysis and interpretation of results: OA, LJ, DAA, MPK, OD, SA; draft manuscript preparation: OA. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Subtle myocardial effects of rheumatic heart disease in children are revealed earlier with two-dimensional speckle tracking echocardiography

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ABSTRACT

Objective. Rheumatic heart disease (RHD) is the most common cause of acquired heart disease in developing countries and remains a serious public health problem. In the subclinical course of carditis, the absence of typical symptoms and the normal range of classical echocardiographic measurements used to evaluate cardiac functions have required new echocardiographic methods and parameters. Previous studies regarding rheumatic heart disease in children and adults have shown that strain patterns obtained by speckle tracking echocardiography, are in fact affected although left ventricular systolic functions are preserved, yet some studies have suggested otherwise. The aim of our study is to compare the use of speckle tracking echocardiography with conventional methods in the evaluation of cardiac functions and myocardial involvement in children with subclinical RHD.

Materials and Methods. The study group consisted of 24 patients with asymptomatic cardiovascular who had no history of acute rheumatic fever, but had definite or probable rheumatic valve disease. This study group was determined according to the World Heart Federation guidelines by an echocardiographic examination performed for different reasons, as well as the control group of 22 healthy children. In order to evaluate the left ventricular regional myocardial functions of the patients, tissue Doppler echocardiography (TDE) and speckle tracking echocardiographic parameters were compared with the control group.

Results. The mean ages of the patient and control groups were 14.1±2.7 years and 13.9±2.3 years, respectively. There was no statistically significant difference between the two groups in terms of conventional methods ($p>0.05$) but global longitudinal strain and strain rate values were found to be significantly lower in the patient group ($p<0.01$). These changes appeared to be relevant throughout the duration of the illness.

Conclusion. In patients with subclinical rheumatic heart disease, conventional echocardiographic evaluations are likely negative, whereas two-dimensional speckle tracking echocardiography reveal systolic and diastolic dysfunctions of the disease.

Key words: children, speckle tracking echocardiography, rheumatic heart disease

Rheumatic heart disease (RHD) is still one of the leading causes of morbidity and mortality in developing countries, which makes early diagnosis and management of the disease of prime importance.[1]

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Conventional echocardiography can yield valuable information on the morphology of the atrioventricular valves, degree of valvular involvement and functional evaluation. Unfortunately, these evaluations can fail because of their dependence on geometric assumptions.[2] Two-dimensional speckle tracking echocardiography (2D-STE) has been designed to detect cardiac deformation by tracking myocardial speckles throughout the cardiac cycle.

Primary advantages of this technique are being independent of geometric angles and translational movements of the heart.[3] Disadvantages of 2D-STE are noted as not being as accurate as three-dimensional speckle tracking echocardiography and having lower temporal resolution.[4]

The main objective of our study is to evaluate cardiac functions and find out whether subtle myocardial impaction in subclinical RHD can be detected by using 2D-STE and also compare our findings with conventional echocardiography.

Methods

The study was designed as a retrospective cross-sectional study. After the approval of the Health Sciences University Gulhane Training and Research Hospital Scientific Investigations Ethical Commitee (approval number: 46418926), 24 asymptomatic patients, admitted with a variety of symptoms and diagnosed with rheumatic valvular disease were reevaluated with speckle tracking echocardiography. Patients with a history of congenital heart disease, non-sinus rhythm, systemic disease state or medication were excluded. Patients were also classified as borderline and definite rheumatic heart disease according to the 2012 American Heart Association Criteria for echocardiographic evaluation of rheumatic heart diseases.[5] Their medical records were examined and compared to a control group of 22 healthy children.

The children in both groups were examined using a Philips Epiq 7C echocardiography system with a 5 μHz transducer (Philips, Andover, MA, USA). Left ventricular function analysis was done with conventional echocardiography, tissue Doppler and two-dimensional speckle tracking echocardiography. Using short-axis and apical views, real-time strain and strain rate values were obtained. The Philips Epiq 7C software was used for post-processing of the findings (Fig. 1). Obtained data were interpreted according to reference values for age, gender and body mass index.[6]

The data were statistically analyzed with IBM SPSS version 23.0. The Shapiro-Wilk test was used to detect normal distribution and chi-square test for comparing gender among groups. Variables with normal distribution

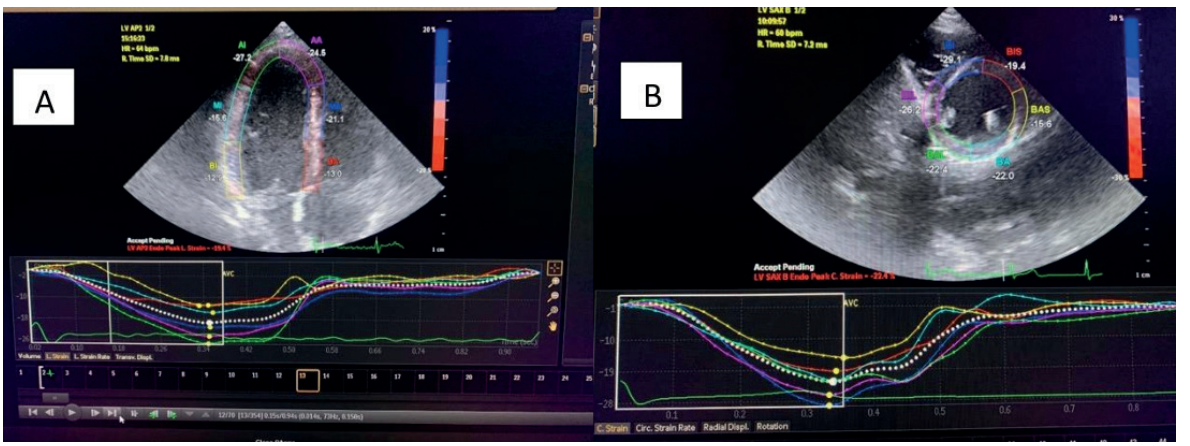

Fig. 1. A shows the evaluation of global longitudinal strain measurement. B shows radial and circumferential measurements.

were compared with independent samples t-test and variables without normal distribution were compared with Mann-Whitney U test. Quantitative data are presented as mean ± standard deviation or median (minimum - maximum). Categorical data are presented as frequency (percent). P value <0.05 is accepted statistically significant.

Results

The patient group consisted of 24 children aged 14.1 ± 2.7 years (range 8-18), 14 girls and 10 boys and the control group consisted of 22 healthy children, aged 13.7 ± 2.3 years (range 8-18), 14 girls and 8 boys. There were no statistically significant differences between the study and control groups in terms of age, weight, height, body mass index (BMI) and heart rate variables (p>0.05) as seen in Table I. Table II summarizes the major complaints, valvular dysfunction, RHD type and disease duration in the patient group.

There were no statistically significant differences between M-mode values and Doppler parameters calculated by conventional echocardiography, as outlined in Table III (p>0.05). However, 2D-STE measurements yielded significant differences; left ventricle apical 4-chamber, 3- chamber and 2-chamber (LVAP4, LVAP3, LVAP2, respectively) strain and strain rate values were significantly lower in the patient group as compared to the control group (p<0.001). Circumferential measurements showed the papillary muscle plane (SAXM) strain and strain rate did not differ significantly between the two groups (p>0.05), whereas that the parasternal short axis views at the mitral valve plane (SAXB) strain and strain were higher in the study group (p=0.01). Table IV summarizes the strain and strain rate measurements.

Table II. Clinical characteristics of our patient group

	Number and frequency (%)
Chief complaint at application	
Chest pain	3 (13.6)
Palpitation	2 (9.1)
Heart murmur	1 (4.5)
Sports participation	4 (18.2)
Other	13 (54.1)
Valvular dysfunction	
Mitral	20 (83.3)
Mitral+Aortic	4 (16.7)
Degree of valvular regurgitation	
Mild	20 (83.3)
Severe	4 (16.7)
Rheumatic heart disease type	
Borderline	12 (50.0)
Definite	12 (50.0)
Mean disease duration for patient group (month)	34.1 ± 28.6

Table I. Clinical properties of the patient and control groups

	Patient	Control	P
Age	14.1 ± 2.7	13.9 ± 2.3	0.726
Body weight (kg)	51.8 ± 14.8	49.9 ± 10.5	0.621
Height (cm)	159.5 ± 14.3	156.7 ± 10.0	0.461
Body mass index (kg/m^2)	19.9 ± 3.5	20.0 ± 2.7	0.967
Heart rate (beats per minute)	83.5 ± 14.2	81.8 ± 15.2	0.765

Table III. Comparison of conventional M-mode and Doppler echocardiographic parameters

	Patient	Control	P
LVEDS (mm)	25.4 ± 3.5	25.1 ± 4.7	0.830*
IVSS (mm)	11.2 ± 2.0	11.4 ± 1.2	0.696*
LVPWD (mm)	7.5 ± 1.1	7.7 ± 1.1	0.539*
LVEDD (mm)	42.3 (7.6- 50.8)	43.2 (31.1- 249.1)	0.185**
IVSDD (mm)	8.1 ± 1.6	8.2 ± 0.9	0.762*
LVMASS (gr)	107.6 ± 35.0	111.7 ± 27.4	0.666*
FS (%)	41.8 ± 4.3	44.3 ± 5.9	0.120*
EF (%)	72.8 ± 5.0	75.2 ± 6.6	0.186*
Mitral E (msn)	85.8 ± 15.3	87.5 ± 15.1	0.722*
Mitral A (msn)	59.3 ± 10.0	59.2 ± 10.0	0.994*
Mitral E/A	1.4 (1.2- 2.1)	1.5 (1.2- 1.8)	0.374**

2D-STE: two-dimensional speckle tracking echocardiography; A: peak velocity of late diastolic filling, E: peak velocity of early diastolic filling, EF: ejection fraction, FS: fractional shortening, IVSDD: interventricular septum end-diastolic thickness, IVSS: interventricular septum end-systolic thickness, LV mass: left ventricular mass, LVEDD: left-ventricular end-diastolic dimension, LVEDS: left ventricular end-systolic dimension, LVPWD: left ventricular posterior wall dimension.
*Independent samples t-test **Mann-Whitney U test. Data presented as median (minimum-maximum), or mean ± standard deviation

Table IV. Comparison of 2D-STE parameters between patient and control groups

	Patient group	Control group	P value
LVAP2	-16.9 (-27.3- -13.1)	-20.0 (-22.3- -17.2)	**<0.001****
LVAP2 Rate	-1.0 (-1.7- -0.7)	-1.4 (-2.6- 0.8)	**<0.001****
LVAP3	-17.4 ± 2.3	-19.4 ± 1.7	**0.002***
LVAP3 Rate	-1.1 ± 0.3	-1.5 ± 0.4	**<0.001***
LVAP4	-17.2 ± 2.9	-20.2 ± 1.2	**<0.001***
LVAP4 Rate	-1.0 (-2.1- -0.7)	-1.6 (-2.4- -0.8)	**0.003****
SAXM	-20.5 ± 2.9	-20.9 ± 2.0	0.638*
SAXM Rate	-1.2 (-1.8- -0.8)	-1.6 (-2.1- -0.9)	0.065**
SAXB	-20.8 ± 3.7	-21.6 ± 1.8	0.381*
SAXB Rate	-1.2 (-15.8- -0.7)	-1.8 (-2.5- -1.0)	**0.010****
LV Longitudinal Strain	-17.3 ± 2.2	-19.8 ± 1.1	**<0.001***
LV Longitudinal Strain Rate	-1.1 ± 0.2	-1.5 ± 0.5	**0.001***
Circumferential Global Strain	-20.6 ± 2.5	-21.2 ± 1.4	0.359*
Circumferential Global Strain Rate	-1.3 (-8.6- -0.8)	-1.5 (-2.3- -0.9)	**0.025****

2D-STE: two-dimensional speckle tracking echocardiography; LVAP2: Left ventricle apical 2-chamber; LVAP3: left ventricle apical 3- chamber; LVAP4: left ventricle apical 4-chamber; SAXM: circumferential measurements from papillary muscle plane; SAXB: parasternal short axis views at the mitral valve plane; Strain: % Strain rate: 1/Sec).
*Independent samples t-test **Mann-Whitney U test. Data presented as mean ± standard deviation, or median (minimum – maximum)

Four of our cases had severe valve insufficiency. Overall, speckle tracking measurements revealed minimally higher strain values of global measurements but not at all investigation plane distorted strain values were found.

Parameters between borderline and definite RHD did not show any significant difference either, as seen in Table V. 2D-STE values were also compared between definite, borderline and control groups. Table VI demonstrates

Table V. Comparison of 2D-STE parameters between the types of RHD

	Borderline RHD	Definite RHD	P
LVAP2	-17.61 ± 4.25	-17.05 ± 2.31	0.706*
LVAP2 Rate	-0.98 ± 0.23	-1.05 ± 0.30	0.517*
LVAP3	-17.79 ± 2.54	-16.96 ± 2.04	0.401*
LVAP3 Rate	-1.21 ± 0.33	-0.98 ± 0.29	0.103*
LVAP4	-17.10 (-22.90- -11.40)	-16.50 (-25.50- -14.70)	0.786**
LVAP4 Rate	-1.02 ± 0.29	-1.15 ± 0.42	0.415*
SAXM	-21.30 (-26.20- -16.00)	-18.65 (-25.20- -17.10)	0.203**
SAXM Rate	-1.34 ± 0.24	-1.07 ± 0.28	0.023*
SAXB	-21.50 ± 3.82	-19.88 ± 3.64	0.324*
SAXB Rate	-1.20 (-15.80- -0.70)	-1.31 (-1.80- -0.82)	0.771**
LV Long Strain	-17.42 ± 2.48	-17.21 ± 2.03	0.829*
LV Long Strain Rate	-1.07 ± 0.18	-1.06 ± 0.25	0.934*
Circumferential Global Strain	-21.31 ± 2.33	-19.82 ± 2.68	0.178*
Circumferential Global Strain Rate	-1.28 (-8.64- -0.89)	-1.19 (-1.75- -0.81)	0.314**

2D-STE: two-dimensional speckle tracking echocardiography; LVAP2: Left ventricle apical 2-chamber; LVAP3: left ventricle apical 3- chamber; LVAP4: left ventricle apical 4-chamber; RHD: rheumatic heart disease; SAXM: circumferential measurements from papillary muscle plane; SAXB: parasternal short axis views at the mitral valve plane.
*Independent samples t-test **Mann-Whitney U test. Data presented as mean ± standard deviation, or median (minimum – maximum)

Table VI. Adjusted significance values of comparison of 2D-STE parameters between the types of RHD and control group

	Borderline-Definite RHD	Borderline RHD-Control	Definite RHD-Control
LVAP2	1	**0.031**	**0.006**
LVAP2 Rate	1	**0.004**	**0.023**
LVAP3	1	0.289	**0.026**
LVAP3 Rate	0.624	0.092	**0.001**
LVAP4	1	**0.000**	**0.003**
LVAP4 Rate	1	**0.005**	0.075
SAXM	0.158	0.158	0.158
SAXM Rate	0.174	1	**0.007**
SAXB	0.412	0.412	0.412
SAXB Rate	1	0.087	0.114
LV Long Strain	1	**0.020**	**0.003**
LV Long Strain Rate	1	**0.008**	**0.008**
Circumferential Glob-al Strain	0.191	0.191	0.191
Circumferential Glob-al Strain Rate	0.912	0.375	**0.028**

2D-STE: two-dimensional speckle tracking echocardiography; LVAP2: Left ventricle apical 2-chamber; LVAP3: left ventricle apical 3- chamber; LVAP4: left ventricle apical 4-chamber; RHD: rheumatic heart disease; SAXB: parasternal short axis views at the mitral valve plane; SAXM: circumferential measurements from papillary muscle plane.
*The significance level is 0.05. Significance values were adjusted by Bonferroni correction for multiple tests.

global longitudinal strain and strain rate values, also circumferential strain rate values were significantly lower in borderline group compared to control group.

Disease duration and LVAP4 strain values were found to be negatively related as can be seen in Table VII (r=-0.521; p=0.038). Other strain parameters were non-related with disease duration (p>0.050).

Table VII. Correlations of 2D-STE measurements with disease duration

	Disease duration	
	r	P
LVAP2	-0.232	0.387
LVAP2 Rate	-0.223	0.406
LVAP3	-0.199	0.459
LVAP3 Rate	-0.193	0.473
LVAP4	-0.521	**0.038**
LVAP4 Rate	0.134	0.621
SAXM	0.014	0.960
SAXM Rate	-0.276	0.319
SAXB	-0.248	0.373
SAXB Rate	-0.201	0.472
LV Long Strain	-0.463	0.071
LV Long Strain Rate	-0.106	0.695
Circ. Global Strain	-0.118	0.675
Circ. Global Strain Rate	-0.248	0.374

2D-STE: two-dimensional speckle tracking echocardiography; LVAP2: Left ventricle apical 2-chamber; LVAP3: left ventricle apical 3- chamber; LVAP4: left ventricle apical 4-chamber; r: Spearman's rho correlation coefficient; RHD: rheumatic heart disease; SAXB: parasternal short axis views at the mitral valve plane; SAXM: circumferential measurements from papillary muscle plane.

Discussion

Widespread usage of conventional echocardiography has aided in the detection of subclinical RHD, which shows that RHD has been affecting more patients than previously predicted.[7] Clinical studies have revealed that 2D-STE could be beneficial for detecting diastolic dysfunction, postoperative mitral regurgitation and ischemia of myocardial tissue.[8-10] Dorobantu et al. have suggested that similar usage of 2D-STE can benefit children with acquired cardiomyopathy.[11] Also diminished radial strain values may reveal systolic dysfunctions earlier than conventional Doppler studies. Therefore, 2D-STE can facilitate early detection of RHD and institution of penicillin therapy to prevent valvular involvement. On the other hand, Sobhy et al. studied 30 children with RHD and preserved left ventricular systolic functions and 23 healthy controls with 3-dimensional speckle tracking echocardiography. They found 3D-derived left ventricular end-diastolic volume and sphericity index among patients were significantly increased when compared to controls. 3D-derived EF and longitudinal strain did not differ significantly. 3D-derived global circumferential strain was higher in patients when compared to controls. They also had cardiac magnetic resonance imaging of the patient group but none of the patients demonstrated late enhancement myocardial fibrosis.[12] In our study we only used 2D-STE, 3D-STE and magnetic resonance imaging, which may be more accurate yet hard to reach in daily clinical use. Pamuk et al. reported some significant changes in the strain measurements with 2D-STE in the acute phase of rheumatic fever and relieving with treatment.[13]

Acute rheumatic fever affects both genders equally but RHD tends to be more common in females; similarly, 58% of our study group was female.[14,15] Especially studies in developing countries have shown that subclinical rheumatic valvular disease or RHD without a known history of acute rheumatic fever could actually be a widespread form of the disease in endemic regions.[16] In our study, eighteen percent of our patient (n=4/24) group had been evaluated for sports participation.

Mitral valvulitis was observed in 83.3 % of our patient group; none of our patients had sole aortic valvulitis, which was always associated with mitral valvulitis (16.7%), similar to other reports.[17,18] Cantinotti et al. studied 544 healthy children to outline standardized Doppler values.[19] Our conventional Doppler studies showed that mitral and tricuspid E velocities, as well as E/A ratios, were normal in both study and control groups. We also observed longer E and A times and decreased A velocity as children got older.

In recent studies, speckle tracking echocardiography is seen to have a wide range of clinical uses. Harrington et al. evaluated 577 healthy children and composed normal left ventricular systolic and diastolic strain and strain rate values as well as Z scores.[6] Although we did not examine Z scores, our findings in both groups were within normal ranges according to

these values. Levy et al. evaluated 2325 healthy children and found GLS ranges between -16.7-23.6% (mean: -20.2; 95% CI, -19.5 to -20.8%).[20] We found average GLS values of -17.3% in the study group and -19.8% in the control group. Our findings support the observation that RHD causes decreased systolic functions. Also, Koopman et al. studied normal ranges of 2D-STE findings; the primary advantage of this study is the resemblance of average ages of participants to those of our study and approximately 10 percent of their participants being Turkish.[21] Their average values were -20.9 ± 2.7% for LPA2, -21.0 ± 2.7% for LPA3, -20.6 ± 2.6% for LPA4 and -24.2 ± 3.5% for SAXB. These figures show that our study group patients have decreased myocardial functions as compared to healthy children.

Beaton et al. first studied myocardial strain in a cohort of children with RHD in 2017.[22] They compared 14 definite and 13 borderline RHD patients with 112 healthy children and found no significant difference between left ventricle volumes and ejection fraction. However, GLS values were decreased in 57% of definite RHD and 44% of borderline RHD cases (p: 0.03, p: 0.002; respectively), similar to our results.

Limitations

Our study was conducted on a relatively small number of study patients. Another limitation might be omission of Z scores; however, the pediatric population is hard to standardize. These limitations may be overcome with further studies on larger cohorts that also include Z scores.

Conclusion

Routine conventional echocardiographic evaluations can benefit high-risk populations with rheumatic heart disease and we suggest that it is possible to determine myocardial dysfunction with 2D-STE earlier and more accurately than conventional echocardiography and the detection of subclinical myocardial dysfunction can help in risk stratification and also prognostic stratification of RHD. These patients might benefit from a change in heart failure treatment or of timing of surgery before irreversible myocardial damage occurs. Larger studies are needed for further investigation of this hypothesis.

Ethical approval

The study was approved by Health Sciences University, Gulhane Training and Research Hospital Scientific Investigations Ethical Commitee (date: 06.01.2022, number: 46418926).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: ŞK, AK; data collection: HIB; analysis and interpretation of results: İT, ŞK; draft manuscript preparation: İT, AK. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Prognostic significance of mean platelet volume to platelet count ratio in pediatric patients with acute kidney injury

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ABSTRACT

Background. Mean platelet volume (MPV), which is regarded as a marker of thrombocyte function and activation, is related to increased morbidity and mortality. In critically ill patients, the ratio of MPV to platelets can independently predict adverse outcomes. This study aimed to investigate the prognostic value of the mean platelet volume/platelet count ratio (MPR) for mortality in children with acute kidney injury (AKI).

Methods. In this retrospective study, patients hospitalized in the pediatric intensive care unit (PICU) between March 2020 and June 2022 were evaluated. Patients between 1 month and 18 years of age with AKI were enrolled. Clinical and laboratory data were compared between survivors and non-survivors. The MPR ratio was calculated on the first and third days of admission to the intensive care unit. A multiple logistic regression analysis was used to determine the association between MPR and mortality. ROC curves were used for the prediction performance of the logistic regression models and cut-off values of the thrombocyte indices.

Results. Sixty-three children with AKI were included in the study. The total mortality rate was 34.9% (n=22). MPR ratios were significantly higher in the non-survivors at admission (p=0.042) and at the 72nd hour (p=0.003). In the multiple logistic regression analysis, thrombocyte counts and MPR_{72h} ratio were found to be independent risk parameters for adverse outcomes in children with AKI.

Conclusions. MPR is an inexpensive and practical marker that may predict the outcome of children with AKI.

Key words: acute kidney injury, mortality, mean platelet volume, platelet count, mean platelet volume platelet count ratio, children.

Acute kidney injury (AKI) is a complex medical condition defined as a sudden deterioration of renal function, particularly in critically ill patients, such as sepsis, shock, trauma, major surgical operations, and the utilization of nephrotoxic medications.[1] The incidence of AKI varies from 1% to 82% in pediatric populations, while its incidence is 10% in patients admitted to the intensive care unit.[2] Despite improvements in the management of renal diseases, AKI has a high morbidity and mortality rate. It has been shown that AKI is related to 40-60% of mortality in the intensive care setting.[3,4] Nevertheless, mortality rates are considerably high, especially in dialysis-requiring AKI.[5] Therefore, early recognition of AKI or the factors indicating the highest risk of developing AKI is important in order to initiate appropriate treatment options. The development of AKI is the result of the activation of inflammation and coagulation following acute injury. Thrombocytes have a substantial role in the coagulation processes, and it has been indicated that activation of thrombocytes aggravates renal injury.[6] Although the adhesion molecule P-selectin is regarded as the "gold standard" marker of thrombocyte activation that is expressed from activated endothelium and thrombocytes cause the initial attachment of leukocytes to

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the inflamed vascular endothelium, it can't be broadly preferred in clinical practice because of the price and requirement of laboratory facilities.[7,8] In routine blood counts, mean platelet volume (MPV) is measured, which is accepted as a significant marker for the evaluation of thrombocyte function and activity.[9] Larger thrombocytes secrete more thromboxane-A2, β-thromboglobulin, and adhesion molecules to be more metabolically and enzymatically active.[10] A study showed that during renal ischemia-reperfusion injury, necrotic cell-derived DNA leads to the activation of thrombocytes, thrombocyte-granulocyte interaction, and following neutrophil extracellular trap formation, resulting in a further increase in kidney inflammation and tissue damage.[11] In recent years, many new studies investigating the understanding of the pathophysiology of AKI have led to the discovery of new biomarkers. However, the use of these biomarkers in clinical practice is quite limited. Thrombocyte activation and high inflammatory parameters in sepsis have important effects on the development of AKI.[12] Several studies have shown an inverse correlation between thrombocyte counts and MPV in seriously sick patients and suggested that the combination of thrombocyte counts and MPV may be clinically more important than thrombocyte counts or MPV alone.[13,14] Therefore, it is thought that the change in MPV/PLT count ratio (MPR) in pediatric patients may be related to AKI. The goal of this study was to determine the prognostic significance of the MPR for pediatric patients with AKI.

Material and Methods

Patient population

We conducted this retrospective, observational single-center research from March 2020 to May 2022 to analyze the association between MPR and AKI in patients at Afyonkarahisar Health Sciences University Faculty of Medicine Hospital Pediatric Intensive Care Unit (PICU). This study was approved by Ethical Committee of Afyonkarahisar Health Sciences University Faculty of Medicine (date: 01.07.2022, no: 2022/8). AKI was defined according to the Kidney Disease: Improving Global Outcomes 2012 (KDIGO) criteria as an increase in initial serum creatinine (SCr) of 0.3 mg/dl within 48 hours or a 1.5-fold increase in the initial SCr level within seven days or urine output (UOP) of < 0.5 ml/kg/hour for six hours.[15] Patients aged 1 month to 18 years old with AKI, length of hospital stay ≥ 72 h, and complete records were enrolled in the study. Mortality was defined as death prior to 28 days after admission.

Exclusion criteria

Children who received a platelet transfusion in the first 72 hours of their admission to the PICU, had chronic renal failure, diabetes mellitus, hematological or neoplastic disease, connective tissue disease, acute or chronic active inflammatory diseases, hospitalized for less than 72 hours, patients taking anticoagulant or antiaggregant drugs, and had missing data were excluded from the study.

Collection of blood samples

The patients' data were acquired from the electronic medical record system of the hospital. Blood specimens were gathered in tubes containing ethylene diamine tetraacetic acid (EDTA) and hemoglobin value, thrombocyte count, and MPV levels were analyzed within a maximum of 60 minutes after sampling. Demographic data, hemodynamic variables, laboratory values at the time of admission, and clinical outcomes on day 28 were recorded. Pediatric risk of mortality score III (PRISM III), Pediatric logistic organ dysfunction (PELOD, thrombocyte counts, and MPV levels were enrolled. In addition, for each patient MPR [(MPV value/platelet count/10^3) ×100] values were calculated separately for admission and at 72 hours.[16]

Statistical analysis

Statistical analysis was performed by SPSS Statistics 22 software (IBM, Armonk, NY, USA).[17] The patients were divided into two groups based on the outcome: survivors and non-survivors. The normality of the variables was assessed through a combination of visual methods, such as histograms and Q-Q plots, as well as analytical approaches including the Kolmogorov-Smirnov and Shapiro-Wilk tests. If the normal distribution assumption was satisfied mean ± SD was given; otherwise median (interquartile range - IQR) was given for continuous variables. Differentiations in continuous parameters were compared by the Mann-Whitney U test and independent samples t-test. Categorical variables were compared using the Pearson chi-square test, chi-square test with continuity correction, Fisher exact test, or Fisher-Freeman-Halton exact test, depending on the size of the cross-tables and the status of expected values less than 5.

Spearman's correlation analysis was used to determine the relationship among MPR_{adm}, MPR_{72h}, PLT_{adm}, PLT_{72h}, $MPV_{adm,}$ MPV_{72h}, PRISM III score, PELOD score, white blood cell (WBC), C-reactive protein (CRP), and serum albumin. As the MPR values were not normally distributed, the admission diagnosis and the MPR values were compared with the Kruskal-Wallis test.

Logistic regression analysis was performed to evaluate the association between the risk factors and mortality by calculating the odds ratios (OR), adjusted odds ratios (AOR), and 95% confidence intervals (CI). For multiple logistic regression, all possible factors identified with univariate analysis ($p<0.25$) were included in the model to detect independent predictors for outcome. Multicollinearity was assessed by calculating the variance inflation factor (VIF). Variables with values less than 5 were considered to have no significant similarity. Multiple logistic regression models with backward elimination were performed to analyze the association between thrombocyte indices and mortality. Hosmer Lemeshow statistics and Nagelkerke R square were used to check how well the logistic regression model fits the data. MedCalc for Windows, version 19.6 (MedCalc Software, Ostend, Belgium)[18] was used to plot receiver operating characteristic (ROC) curves, calculate the area under the ROC curve (AUC), and compare the prediction performance of the logistic regression models and cut-off values of the thrombocyte parameters. A cut-off value for the variables was calculated by the Youden Index. A p value < 0.05 was accepted as statistically significant.

Results

Eighty-seven AKI patients were admitted to the PICU during the research period. Twenty-four children who had connective tissue disease, diabetes mellitus, chronic renal failure, hematologic disease, or thrombocyte transfusion were excluded because they did not meet the study criteria. Hence, 63 children were finally enrolled. There were 33 male (52.4%) and 30 female (47.6%) cases. The children were allocated into two groups, survivors and non-survivors. Of these 63 patients with AKI, 41 were in the survivor group, while 22 were in the non-survivor group. The total mortality rate was 34.9%. Sepsis was the most common admission diagnosis (n=25, 39.6%), followed by cardiovascular disease (17.4%) and respiratory infection (14.3%). There was no significant difference between the survivor and non-survivor groups in terms of age, gender, and vital signs (Table I). Fluid overload was higher in non-survivors but not statistically significant (p=0.434). The stages of AKI did not show statistically significant differences in terms of mortality (p=0.130). The non-survivor group had an inconsiderably longer mechanical ventilation day (p=0.293) and the length of PICU days was insignificantly higher in the survivor group (p=0.158). The comparison of white blood cell count, hemoglobin level, pH, base deficit, lactate, liver function tests, and albumin

Table I. Demographics, clinical characteristics, and laboratory variables of survivors and non-survivors

Variables	Survivors (n=41)	Non-survivors (n=22)	p value
Age, months*	61 (142.25)	65.5 (164)	0.965[&]
Female gender, n (%)	23 (56.1)	7 (31.8)	0.115[Φ]
Respiratory rate, /min	36.95±13.50	36.36±12.43	0.866[†]
Heart rate, /min	141.31±35.70	147.95±36.61	0.488[†]
Systolic blood pressure, mmHg	89.41±15.22	86.59±19.24	0.525[†]
Most common four-admission diagnosis, n (%)			
Sepsis	12 (29.3)	13 (59.1)	0.097[¥]
Respiratory infections	8 (19.5)	1 (4.5)	
Cardiovascular disease	7 (17.1)	4 (18.2)	
Trauma	3 (7.3)	2 (9.1)	
Others	11 (26.8)	2 (9.1)	
Fluid overload, n (%)	4 (9.8)	4 (18.1)	0.434[£]
Duration of mechanical ventilation, days*	3 (7.5)	4 (12.25)	0.293[&]
Length of PICU stay, days*	6 (17.5)	5 (10.75)	0.158[&]
AKI stage, n (%)			
Stage 1	8 (19.5)	1 (4.5)	0.130[‡]
Stage 2	18 (43.9)	8 (36.4)	
Stage 3	15 (36.6)	13 (59.1)	
Hgb, g/dL	11.66±1.62	11.38±1.06	0.328[†]
WBC_{adm}, $\times 10^3/\mu L$	10.16±5.68	12.46±5.87	0.136[†]
PLT_{adm}, $\times 10^3/\mu L$	160.29±51.47	125.54±36.38	0.003[†]
PLT_{72h}, $\times 10^3/\mu L$	141.09±46.35	108.04±28.49	0.001[†]
MPV_{adm}, fL	10.97±0.80	11.11±0.63	0.474[†]
MPV_{72h}, fL	11.54±0.57	11.84±0.45	0.027[†]
MPR_{adm}	7.82±3,45	9.7±3,36	0.042[†]
MPR_{72h}	9.13±3.36	11.73±3.21	0.003[†]
AST (U/L)*	63 (68)	54.5 (36.25)	0.199[&]
ALT (U/L)*	44 (63)	57 (67.5)	0.349[&]
PRISM III score	16.04±8.1	21.45±7.62	0.012[†]
PELOD score	18.12±14.43	28.95±11.84	0.004[†]
pH	7.34±0.04	7.33±0.05	0.562[†]
Base deficit, mmol/L	-2.30 ± 1.76	-2.51 ± 2.13	0.676[†]
$Lactate_{adm}$, mmol/L*	1.8 (1.25)	1.8 (1.55)	0.994[&]
$Albumin_{adm}$, g/dL	3.56±0.57	3.53±0.48	0.808[†]
CRP_{adm}, mg/dL*	21 (8.5)	18 (8.25)	0.269[&]

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; Hgb: hemoglobin; Length of PICU stay: length of pediatric intensive care unit stay; MPR: MPV/PLT ratio; MPV: mean platelet volume; PELOD: pediatric logistic organ dysfunction; PLT: platelet; PRISM III score: pediatric risk of mortality III score; WBC: white blood cell.
* Median (interquartile range) values, [&]: Mann-Whitney U test, [†]: Independent samples t test, [¥]: Fisher-Freeman-Halton exact test, [£]: Fisher exact test, [Φ]: Chi square test with continuity correction, [‡]: Pearson chi square test.

levels between the two groups are presented in Table I. The non-survivors had a significantly higher PELOD and PRISM III score than the survivors (28.95±11.84 vs 18.12±14.43, p=0.004; 21.45±7.62 vs 16.04±8.10, p=0.012, respectively). While MPV values were similar between the two groups at admission, MPV_{72h} values were significantly higher in non-survivors

(MPV_{adm}: 11.11±0.63 vs 10.97±0.80; p=0.474; MPV_{72h}: 11.84±0.45 vs 11.54±0.57; p=0.027). Thrombocyte counts were significantly lower in non-survivors at admission and 72nd hours (PLT_{adm}(×10³/μL): 125.54±36.38 vs 160.29±51.47, p=0.003; PLT_{72h}(×10³/μL): 108.04±28.49 vs 141.09±46.35; p=0.001). Non-survivors exhibited a significantly higher MPR ratio than survivors at admission, and 72nd hours ($MPR_{adm:}$ 9.7±3.36 vs 7.82±3.45, p=0.042; MPR_{72h}: 11.73±3.21 vs 9.13±3.36; p=0.003, respectively).

Despite conducting correlation analysis between MPV_{adm}, MPV_{72h}, MPR_{adm}, MPR_{72h} and platelet counts, WBC, CRP, and albumin levels with the PRISM III score, no significant correlations were observed, as indicated in Table II. The relationship between admission diagnoses and MRP values was assessed using the Kruskal-Wallis test, which indicated no statistically significant impact on MRP values (MPR_{adm}: p=0.656; $MPR_{72h:}$ p=0.820).

Four variables (gender, PRISM III, length of PICU stay and WBC) in univariate analysis with a p-value < 0.25 and thrombocyte indices (PLT_{adm}, PLT_{72h}, MPV_{adm}, MPV_{72h}, MPR_{adm} and MPR_{72h}) were included in the multiple logistic regression analysis (Table III). PELOD was not included in the regression model due to the high correlation with PRISM III (r: 0.78, p<0.001). The variables MPR_{adm} and MPR_{72h}, derived from the PLT and MPV values on the relevant day, were added separately to the regression model in order to avoid multicollinearity issues. AKI stage and admission diagnosis were not included in the models due to an insufficient number of patients for analysis. Multiple logistic regression analysis demonstrated that both PLT_{adm} (AOR: 0.981, 95%CI (0.967-0.995); p=0.009) and PLT_{72h} (AOR: 0.972, 95% CI (0.945-1.000); p=0.046) were independent risk factors for mortality. Each increase of 1×10³/μL in PLT_{adm} and PLT_{72h} was associated with a 0.981 fold and 0.972-fold decrease in the risk of mortality, respectively. Increased MPR_{adm} (AOR: 1.184, 95% CI (0.991-1.414); p=0.063) was not significantly associated with mortality. MPR_{72h} (AOR: 1.537, 95% CI (1.081-2.184); p=0.017) was an independent risk factor for mortality in patients with AKI. Each increase in MPR_{72h} associated with a 1.537-fold increase in the risk of mortality. The discriminative ability of models was shown with the ROC curves for each model (Table IV).

Table III. Univariate analyses with binary logistic regression of risk factor of mortality

Variables	Univariate analysis		
	OR	95% CI	p value
Gender	2.74	0.92-8.1	0.070
PRISM III	1.01	1.02-1.18	0.018
AST	0.99	0.98-1.0	0.291
WBC	1.07	0.98-1.18	0.139
Length of PICU stay	0.99	0.96-1.02	0.635
PLT_{adm}	0.98	0.97-0.99	0.010
PLT_{72h}	0.97	0.96-0.99	0.007
MPV_{adm}	1.30	0.64-2.64	0.468
MPV_{72}	2.9	1.04-8.22	0.042
MPR_{adm}	1.0	1.0-1.03	0.051
MRP72	1.27	1.07-1.52	0.006

MPR: MPV/PLT ratio; MPV: mean platelet volume; OR: Odds ratio; PICU: Pediatric intensive care unit; PLT: platelet count; PRISM III score: Pediatric risk of mortality III score.

Table II. Correlation between MPV_{72h}, MPR_{adm}, MPR_{72h}, platelet counts and other variables

Variables	MPV_{adm}		MPV_{72h}		PLT_{adm}		PLT_{72h}		MPR_{adm}		MPR_{72h}	
	r	p	r	p	r	p	r	p	r	p	r	p
WBC	-0.35	0.78	-0.23	0.86	-0.20	0.11	-0.10	0.42	0.19	0.13	0.12	0.35
CRP	0.19	0.14	0.17	0.17	0.16	0.21	0.14	0.20	-0.13	0.31	-0.13	0.32
Albumin	0.01	0.93	-0.63	0.6	0.07	0.56	-0.03	0.79	-0.08	0.53	0.025	0.84
PRISM III	-0.06	0.62	0.17	0.18	0.08	0.49	0.14	0.26	-0.10	0.43	-0.10	0.40

CRP: C-reactive protein; MPR: MPV/PLT ratio; MPV: mean platelet volume; PRISM III score: pediatric risk of mortality III score; WBC: white blood cell.

Table IV. Multiple logistic regression analysis and the model discriminative ability by area under the ROC curve

	AOR	95% CI	p value	AUC (95% CI)	p value
Model 1 –Binary logistic regression for PLT_{adm}					
Constant	0.451		0.563		
PLT_{adm}	0.981	0.967-0.995	0.009	0.834 (0.719-0.916)	<0.001
Variables Included in the Model: PLT_{adm}					
Confounding factors: Gender, PRISMIII, WBC					
Model Summary: Hosmer and Lemeshov Test χ^2=4.832; p=0.775; Nagelkerke R^2=0.375					
Model 2 –Binary logistic regression for PLT_{72h} and MPV_{72h}					
Constant	0.714		0.816		
PLT_{72h}	0.972	0.945-1.000	0.046	0.882 (0.777-0.950)	<0.001
Variables Included in the Model: $PLT_{72h.,}$ MPV_{72h}					
Elimination methods: Backward Wald					
Confounding factors: Gender, PRISMIII, WBC, $PLT_{adm,}$ MPV_{adm}					
Model Summary: Hosmer and Lemeshov Test χ^2=13, .758; p=0.088; Nagelkerke R^2=0.438					
Model 3 –Binary logistic regression for MPR_{adm}					
Constant	0.008		<0.001		
MPR_{adm}	1.184	0.991-1.414	0.063	0.813 (0.694-0.900)	<0.001
Variables included in the model : MPR_{adm}					
Confounding factors: Gender, PRISMIII, WBC					
Model Summary: Hosmer and Lemeshov Test χ^2=9.703; p=0.286; Nagelkerke R^2=0.291					
Model-4: Binary logistic regression analysis for MPR_{72h}					
Constant	0.001		<0.001		
MPR_{72h}	1.537	1.081-2.184	0.017	0.856 (0.745-0.932)	<0.001
Variables included in the model : MPR_{72h}					
Confounding factors: Gender, PRISMIII, WBC, MPRadm					
Elimination methods: Backward Wald					
Model Summary: Hosmer and Lemeshov Test χ^2=8.036; p=0.430; Nagelkerke R^2=0.413					

AOR: Adjusted odds ratio; AUC: area under the curve; CI: confidence interval; MPR: MPV/PLT ratio; MPV: mean platelet volume; PLT: platelet count; PRISM III score: Pediatric risk of mortality III score; WBC: White blood cell count.

An analysis using ROC curves for each of the variables was performed, showing the cut-off point of each one with greater specificity and sensitivity. The cut off levels for PLT_{adm} and PLT_{72h} were 79 $\times 10^3/\mu L$ (sensitivity 77.3%, specificity 82.9) and 76 $\times 10^3/\mu L$ (sensitivity 86.3%, specificity 85.3), respectively. The threshold level of MPR_{72h} was >8.35 (sensitivity 72.7%, specificity 90.2%) (Fig. 1).

Discussion

The current research was a retrospective clinical study that evaluated the MPR ratio as a prognostic factor in pediatric patients with AKI. The primary outcomes of this research were that the MPR ratio was significantly higher in non-survivors and revealed to be an independent risk factor for AKI patients, even after adjusting for acceptable parameters. Specifically, we

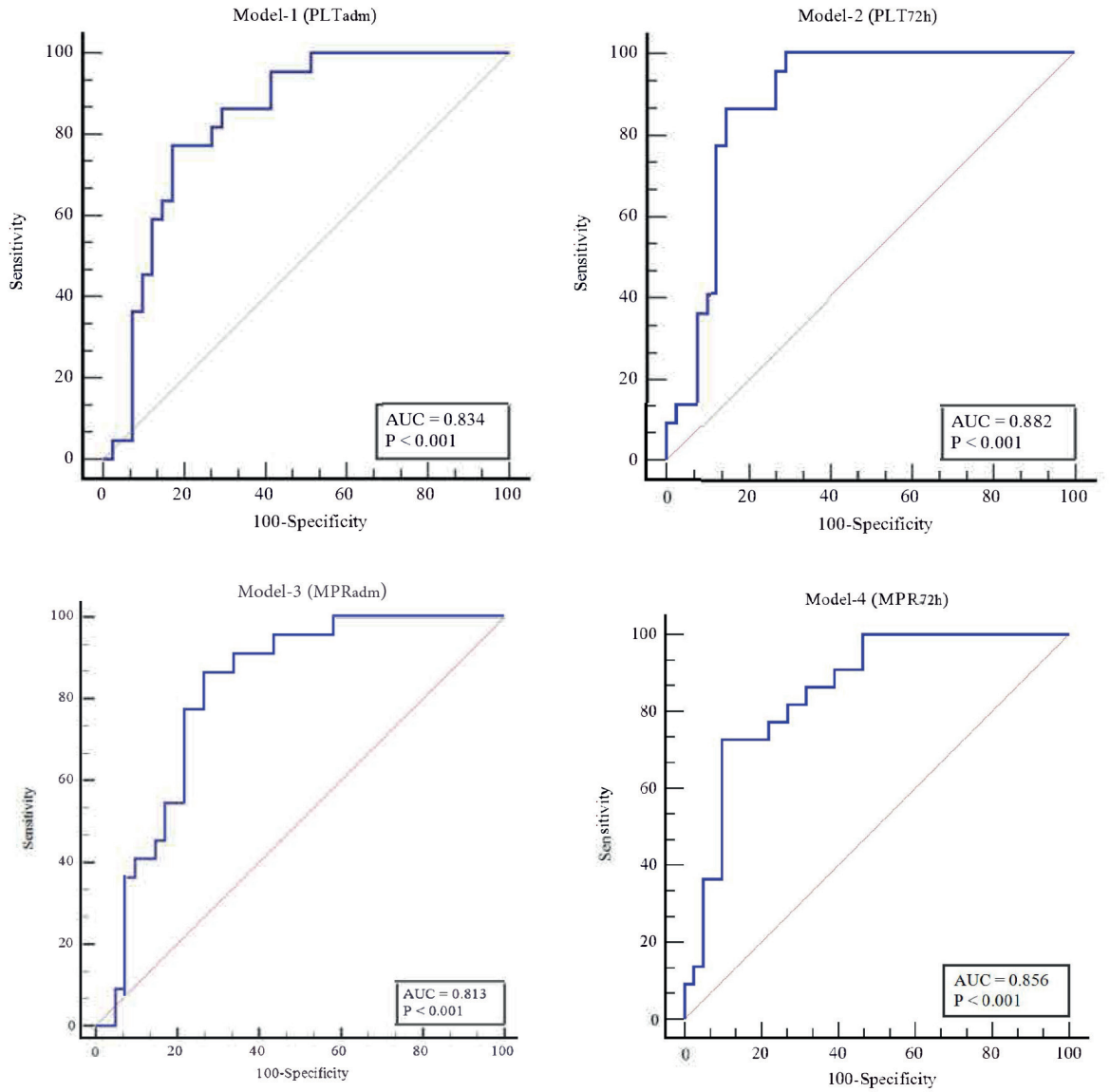

Fig. 1. The ROC curve of the logistic regression model with thrombocyte indices (PLT_{adm}, PLT_{72h}, MPR_{adm},MPR_{72h}). AUC: area under the curve; MPR: MPV/PLT ratio; PLT: platelet count.

should closely monitor AKI patients with a high MPR rate due to their elevated risk of mortality. According to our current knowledge, this is the first study to investigate the association between the MPR ratio and prognosis in children with AKI.

Despite advancements associated with its pathogenesis and management, AKI is still an independent risk factor related to mortality in critically ill patients.[19] Several investigations have suggested that the activation of platelets aggravates kidney damage.[6] Some studies have shown that thrombotic and inflammatory conditions might alter the platelet volume, larger platelets are more reactive and these alterations are related to an increase in morbidity and mortality in patients with various illnesses.[20,21] Although the mechanism of platelet volume control is not clearly known,

it is known that thrombopoietin stimulates megakaryopoiesis and results in increased ploidy and megakaryocyte size.[22] According to a study, MPV values positively correlated with thrombocyte activation, and higher MPV was a risk factor for mortality in cardiovascular diseases.[20] In another study, the authors found that among patients with chronic kidney disease, MPV levels were higher in diabetic patients than in non-diabetic patients.[23] In the current research, we excluded the majority of chronic and inflammatory diseases due to their potential impact on thrombocyte indexes. Clinical characteristics of non-survivors and survivors were compared, and MPV_{72h} level was found to be higher in non-survivors, however, MPV_{adm} was not statistically different between groups. Further analyses have shown that MPV measurements are not a risk factor for mortality. Additionally, we did not observe any association between platelet indices and laboratory markers or diagnoses at admission.

Thrombocytopenia is an independent risk factor and negative prognostic indicator in children with sepsis.[24] Activated thrombocytes interact with monocytes in the bloodstream, which causes the consumption of thrombocytes in circulation, signifying the relationship between activation of thrombocytes and suppressed thrombocyte counts during infection.[25] In a recent study of patients with rhabdomyolysis-induced AKI, low platelet count and myoglobin level were found to be independent risk parameters for kidney injury, and platelet numbers were superior to myoglobin for predicting the risk of kidney injury.[26] Research has shown that in patients with AKI receiving continuous renal replacement therapy, non-survivors had a lower platelet count.[27] Similarly, in the current study, among the non-survivors the thrombocyte count was found lower. Recent investigations recommend that the combination of thrombocyte count and MPV will present clinically more significant results than thrombocyte count or MPV alone.[9,14] Several studies have shown that total thrombocyte count was inversely associated with MPV levels.[28,29] A study hypothesized that the MPV/platelet count ratio could be a more beneficial predictor with higher sensitivity and specificity to detect deep vein thrombosis than MPV alone.[13] Research evaluating the effects of the MPV/PLT ratio on mortality in patients with pediatric septic shock presented that MPV/PLT ratios were statistically higher in the non-survivor group.[9] Although the pathophysiological mechanisms of the relationship between high MPR values and worse outcomes remain unclear, many different mechanisms have been demonstrated to explain the effect of increased inflammatory conditions on low platelet counts and high MPV levels.[10,30] Aligned with previous research findings, the present study revealed that MPV values were not statistically significant for mortality in AKI. However, lower thrombocyte counts and a higher MPR rates especially on the third day, were found to be significantly associated with mortality.

This study had several limitations. Primarily, although the medical data of all patients were collected with a high degree of precision from medical records, control of confounding parameters may be insufficient due to the retrospective design of the study. Secondly, the study's short-time calculation of MPR rates instead of long-time calculations was an important limitation. Third, the effects of drugs on platelet indices may be a factor causing bias in study results. Furthermore, the observational research design of this study did not allow for the investigation of metabolic or molecular mechanisms.

In conclusion, AKI is a common complication in critically ill patients, with adverse effects in the short and long term. Predicting and defining AKI with biomarkers is essential to reduce AKI-related mortality and morbidity. Thrombocyte counts and their indices are inexpensive and available in the complete blood count, which is usually used to evaluate the hematologic status of hospitalized patients. In this current study, the prognosis of AKI patients and the role of MPR in mortality prediction were analyzed.

The results show that MPR may be beneficial in predicting the short-term outcome of AKI. Therefore, we propose the calculation of MPR as a means to determine the prognosis of pediatric patients with AKI. Larger prospective multicenter studies are required to confirm the usefulness of the MPR as a predictive marker in children with AKI.

Ethical approval

The study was approved by Ethical Committee of Afyonkarahisar Health Sciences University Faculty of Medicine (date: 01.07.2022, number: 2022-08).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: KÇ; data collection: MÇ; analysis and interpretation of results: KÇ, MÇ; draft manuscript preparation: KÇ, MÇ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Case Report

Extremely rare cause of hyperkalemia: ileostomy–induced hyperkalemia in extremely low birth weight infants

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ABSTRACT

Background. Hyperkalemia is one of the most serious electrolyte disturbances, and it can cause lethal cardiac arrhythmia. Although hyperkalemia associated with ileostomies has been reported in adults, to the best of our knowledge, it has not previously been reported in neonates.

Case. We report ileostomy–induced hyperkalemia that persisted during the ileostomy and resolved promptly after the closure of the ileostomy in two extremely low birth weight (ELBW) infants, with birth weights of 850 g and 840 g and gestational ages of 27 weeks and 27 weeks 6 days.

Conclusions. These cases highlight that disruption of intestinal integrity in ELBW infants may cause hyperkalemia. Ensuring the integrity of the gastrointestinal tract plays an important role in the treatment of electrolyte disorders such as hyperkalemia in ELBW infants with an ileostomy.

Key words: extremely low birth weight, premature, ileostomy, hyperkalemia.

Hyperkalemia is defined as a serum or plasma potassium concentration exceeding 6 mEq/L in a non-hemolyzed specimen in neonates.[1] Renal dysfunction or immaturity, medications, massive tissue breakdown (asphyxia, hypotension, intraventricular hemorrhage, necrotizing enterocolitis and intravascular hemolysis), congenital adrenal hyperplasia or acute adrenal insufficiency may cause hyperkalemia in extremely low birth weight (ELBW) neonates. It can be life-threatening because of its effect on cardiac rhythm. Although hyperkalemia associated with ileostomies has been reported in adults, it has not previously been reported in neonates.[2-4] Herein, we present two ELBW premature newborns with ileostomy–induced hyperkalemia that persisted during ileostomy and resolved promptly after closure of the ileostomy.

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Case Presentations

Case 1

A female preterm infant with a birth weight of 850 g was delivered by caesarean section at 27 weeks of gestation. The mother did not receive antenatal steroids. The infant was admitted to the neonatal intensive care unit (NICU) due to being extremely preterm and respiratory distress syndrome. The patient had normal external genitalia without areolar or genital hyperpigmentation. Noninvasive mechanical ventilation support and less-invasive surfactant administration were provided. Total parental nutrition and minimal enteric nutrition with maternal milk were given just after the birth. On the 10th day of life, the patient had recurrent episodes of apnea, bradycardia, lethargy, abdominal distension and vomiting.

An abdominal X-ray showed evidence of intestinal pneumatosis and ileus. The patient was diagnosed with necrotizing enterocolitis (NEC) according to a combination of clinical and radiographic features. Enteral nutrition was discontinued, antibiotics (ampicillin, gentamicin and metronidazole) and parenteral nutrition were started. Nasogastric decompression was applied. On the 16th day of life, despite medical treatment, the patient did not improve, leading to the performance of an ileostomy 10 cm proximal to the cecum. Measured serum potassium levels were between 4.2 and 4.9 mEq/L before the operation. Serum potassium levels in non-hemolyzed serum were between 5.7 and 6.9 mEq/L during the ileostomy period and between 4.4 and 5.0 mEq/L after closure of the ileostomy (Fig. 1). Potassium chloride (KCl) (1 mEq/kg/d) was added to parenteral nutrition fluids before surgery. The patient was not receiving medications that contained potassium (total parenteral nutrition and antibiotics) or potassium sparing diuretics during the ileostomy period. The ileostomy closure was performed on the 113th day of life. No signs of hyperkalemia were detected on the electrocardiogram (ECG). Ultrasound imaging of the adrenal glands and urinary systems showed no pathology. Serum creatinine, blood urea nitrogen (BUN), sodium (Na), blood gases and urine output (ml/kg/h) were within normal limits during the ileostomy period (Table I). Renin, aldosterone and 17-hydroxyprogesterone levels were within the normal range (Table I). The low dose (1 mcg) adrenocorticotropic hormone (ACTH) stimulation test revealed a normal response (Table I).

Case 2

A preterm male infant with a birth weight of 840 g from a twin pregnancy was delivered by caesarean section at 27 weeks and 6 days of gestation. The pregnancy was complicated by preeclampsia. The mother received antenatal steroids. Neonatal resuscitation was performed in the delivery room. The Apgar scores were 3 and 6 at the 1st and 5th minute, respectively. The patient had normal external genitalia without areolar or genital hyperpigmentation. The infant was admitted to the NICU due to prematurity,

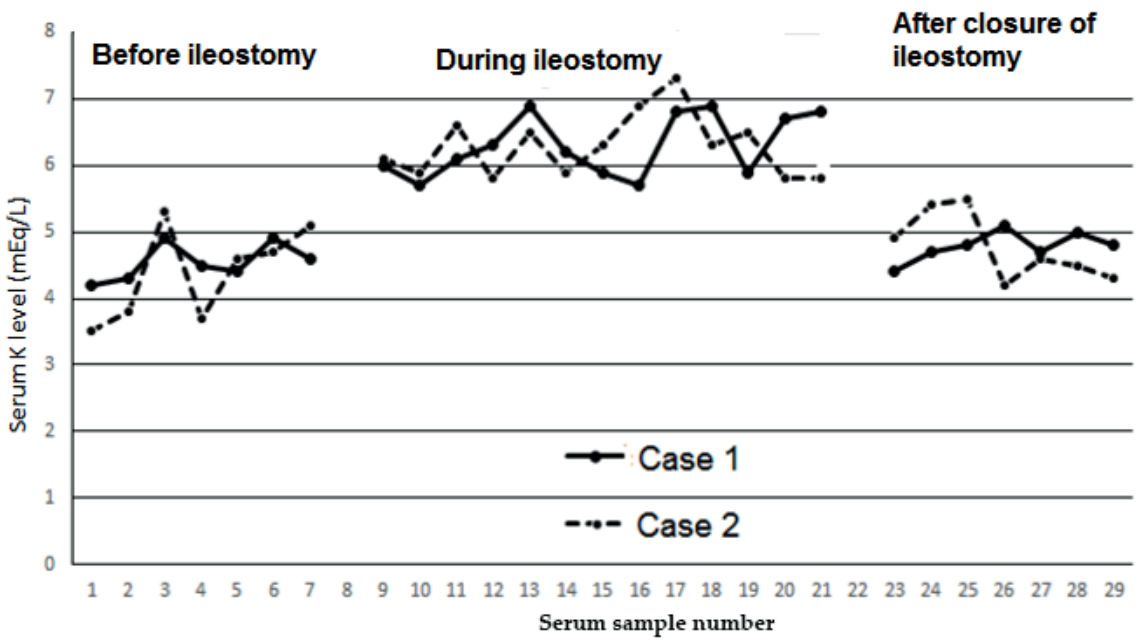

Fig. 1. Changes in serum potassium concentration before ileostomy, during ileostomy and after closure of ileostomy.

Table I. Laboratory values of the cases during ileostomy.

	Case 1	Case 2
Glucose (mg/dL)	70-95	82-122
BUN (mg/dL)	4-21	2-20
Cr (mg/dL)	0.13-0.4	0.14-0.49
Na (mEq/L)	131-140	131-137
K (mEq/L)	5.7-6.9	5.8-7.3
Urine Na (mEq/L)	5-7	6.2-25
Urine K (mEq/L)	11.2-48	1.6-71
Blood pH	7.34-7.418	7.34-7.42
HCO_3^- (mEq/L)	19.9-22.8	21.0-23.0
Renin (N: 2.4 – 37 ng/ml/h)	8.99	-
Aldosterone (N: 19-141 ng/dL)	75.69	-
ACTH (N: <46 ng/L)	13.7	23.7
Cortisol (μg/dL)	5.97	11.62
30-min cortisol	48.4	-
17OHP (N: 6.3-10 ng/mL)	1.82	3.56

Intervals indicate min-max values.
ACTH: Adrenocorticotropic hormone,
17OHP: 17-hydroxyprogesterone.

being an ELBW infant, and respiratory distress syndrome. Surfactant and mechanical ventilation support were administered. Total parental nutrition was immediately started, and minimal enteric nutrition with maternal milk was started at 24 hours of life. The patient had bradycardia, lethargy, feeding intolerance, recurrent vomiting, and abdominal distension and vomiting on the 12th day of life. Abdominal X-ray showed evidence of dilated loops of the bowel, pneumatosis intestinalis, and portal venous air. Thrombocytopenia and metabolic acidosis were determined on laboratory examination. The patient was diagnosed with NEC according to a combination of clinical, laboratory and radiographic features. Enteral nutrition was discontinued, antibiotics (meropenem and vancomycin) and parenteral nutrition were started. Nasogastric decompression was applied. KCl (2 mEq/kg/d) was added into the parenteral nutrition fluid before surgery. The patient underwent an ileostomy on the 18th day of life. Measured serum potassium levels were between 3.5 and 5.1 mEq/L before the operation. Serum potassium levels in non-hemolyzed serum were between 5.8 and 7.3 mEq/L during the ileostomy period and between 4.2 and 5.5 mEq/L after closure of the ileostomy (Fig. 1). When the serum potassium level was measured at 7.3 mEq/L, sinus rhythm with peaked T-waves was observed on the ECG and was treated with insulin and dextrose, bicarbonate and calcium gluconate. The patient was not receiving medications containing potassium (total parenteral nutrition and antibiotics) or potassium-sparing diuretics during the ileostomy period. Serum creatinine and BUN, Na, pH, HCO_3, urine output (ml/kg/h) were within normal limits during the ileostomy period (Table I). ACTH, cortisol and 17-hydroxyprogesterone levels were within normal limits (Table I). Ultrasound imaging of the adrenal glands and urinary systems showed no pathology. The ileostomy closure was performed on the 91st day of life. A blood transfusion was not given to the patients after the ileostomy was opened.

A written consent form was obtained from the families for this publication.

Discussion

In the present report, ileostomy–induced hyperkalemia was presented in two extremely preterm infants. To the best of our knowledge, this has not been previously reported in neonates. In both cases, although the serum potassium levels were within normal limits before the ileostomy, it increased and persisted in the ileostomy period, and recovered after the closured of the ileostomy.

Potassium is critical for maintaining cellular function. 98% of total body potassium is intracellular. Plasma potassium concentration is kept within narrow limits (3.5-5.0 mEq/L). The plasma potassium level in neonates is elevated compared to that of older infants. In the early postnatal period, premature neonates with a birthweight of <1000 grams and a postmenstrual age of <30 weeks have higher serum potassium concentrations due to renal function immaturity

and an inadequate response to hormones that control potassium levels. The highest level (>6 mEq/L) is observed at around 24 hours of life. After the third day of life, it starts to gradually decrease and stabilize over the next 4-5 days.[5]

Hyperkalemia is one of the most serious electrolyte disturbances because it can cause lethal cardiac arrhythmia. Hyperkalemia may be caused by excess potassium intake, impaired potassium excretion, drugs that can cause hyperkalemia, maldistribution between intra- and extracellular space or pseudohyperkalemia.[6] Acute kidney injury, adrenal insufficiency, congenital adrenal hyperplasia, metabolic acidosis or increased plasma osmolality, such as hyperglycemia, massive tissue breakdown such as asphyxia, hypotension, intraventricular hemorrhage, rhabdomyolysis, and blood cell transfusions can result in hyperkalemia. None of these conditions were present in these patients. Potassium-sparing diuretics (spironolactone), trimethoprim, non-steroidal anti-inflammatory drugs (ibuprofen, indometacin) angiotensin converting enzyme inhibitors, digoxin, heparin, beta blockers, mannitol and calcium channel blockers may cause hyperkalemia.[7] The patients did not receive any medication that could cause hyperkalemia during the hyperkalemic period. No potassium was added to the total parenteral nutrition fluid, and a potassium rich formula was not given in the ileostomy period. There was no condition such as mechanical hemolysis, lymphocytosis or thrombocytosis.

Ou et al.[8] reported that seven newborns with pseudo-hyperkalemia and high levels of aldosterone and renin were diagnosed with secondary pseudohypoaldosteronism, due to excessive gastrointestinal losses from ileostomy or jejunostomy. In our cases, hyponatremia and dehydration were not observed, aldosterone and renin levels were measured in only one patient, and the level was within normal limits.

Potassium homeostasis is maintained by oral intake, absorption from the gastrointestinal tract, and excretion through the colon and kidney. The kidneys are responsible for approximately 90% of excess potassium excretion in the body, the remaining 10% of potassium is excreted in the colon.[6,7] The colon has the capacity to absorb or excrete potassium depending on the serum potassium status. When the renal excretion of potassium is limited, as in ELBW infants or in individuals with chronic kidney disease, colonic excretion acquires a more prominent role in regulating extracellular potassium.[5] We assume that the hyperkalemia observed in our patients was caused by reduced colonic potassium excretion due to the disabling of the colon as a result of the ileostomy.

Hyperkalemia has been reported in adult patients with an ileostomy due to impaired intestinal continuity.[6,7] After the bowel continuity was restored, hyperkalemia improved as in our patients. High fecal potassium levels after ostomy closure could explain this situation. We could not measure the fecal potassium concentration before and after the stoma. However, the high serum potassium during the ileostomy period, which decreased to the normal range after closure of the ileostomy, supports this situation.

Hyperkalemia (≥7 mEq/L) is a severe acute problem in ELBW infants[1] and should be treated when hyperkalemia when it exceeds 7 mEq/L or hyperkalemic changes occur on the ECG with insulin and dextrose, bicarbonate and calcium gluconate. It should be kept in mind that an ileostomy may lead to hyperkalemia when other conditions that may cause hyperkalemia in ELBW neonates are excluded.

Ethical approval

A written consent form was obtained from the families for this publication.

Author contribution

Study conception and design: MM, YA; data collection: MM, ŞK, EAC, GŞ; analysis and interpretation of results: MM, YA, ŞK; draft manuscript preparation: MM, ŞK, EAC, GŞ. All

authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Case Report

Severe myxedema coma and pericardial effusion in a child with Down syndrome: the importance of adherence to levothyroxine therapy

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ABSTRACT

Background. Myxedema coma is a rare, but life-threatening endocrinological emergency. Myxedema is characterized by altered mental status, and is accompanied by hypotension, bradycardia, hypothermia, bradypnea, hyporeflexia, hyponatremia, and hypoglycemia, all stemming from reduced metabolism due to severe hypothyroidism. Additionally, patients may exhibit signs of low cardiac output, edema in the extremities, peripheral circulatory disturbances, shock, and the development of pericardial and pleural effusions, ultimately leading to confusion and coma. We present a successfully treated case of severe myxedema coma with recurrent pericardial effusion and hypotensive shock. This case is characterized by an unusual clinical presentation and required a distinct treatment strategy highlighting its exceptional rarity.

Case. A 2-year-old boy with Down syndrome presented with recurrent pericardial effusion attributed to medication non-adherence. The critically-ill patient, experiencing a severe cardiogenic shock required mechanical ventilation and inotropic infusions in the pediatric intensive care unit. Elevated thyroid stimulating hormone (TSH), and low free T4 (fT4) and free T3 (fT3) levels prompted consideration of myxedema coma. Upon reviewing the patient's medical history, it was ascertained that he had an ongoing diagnosis of primary hypothyroidism, and exhibited non-adherence to the prescribed treatment regimen and failed to attend scheduled outpatient clinic appointments for follow-up assessments. The treatment plan, devised by the pediatric endocrinology team, included the peroral administration of L-thyroxine (L-T4) at a dose of 50 micrograms per day. After beginning regular oral L-T4 treatment, a gradual improvement in the patient's condition was observed. Notably, by the 15th day of oral therapy, the patient had made a full recovery. Contrary to the recommended intravenous treatment for myxedema coma, this patient was successfully treated with oral levothyroxine, due to the unavailability of the parenteral form in Türkiye.

Conclusions. This case report presents an instance of non-adherence to L-T4 therapy, which subsequently progressed to severe myxedema coma. Changes in neurologic status and hemodynamic instability in a patient with a history of hypothyroidism should raise the concern of nonadherence and, though rare, myxedema coma should be in the differential diagnosis.

Key words: Hypothyroidism, recurrent myxedema coma, cardiogenic shock, levothyroxine, child.

Myxedema coma is a rare and life-threatening endocrinological emergency with an incidence of 0.22/1,000,000 persons per year and a mortality rate of 30-50%.[1,2] Symptoms and findings such as altered mental status, hypothermia, hypotension, bradycardia, hypoventilation, bradypnea, hyponatremia, hyporeflexia, and hypoglycemia are observed with decreased metabolism.[3] These symptoms are followed by low cardiac output and associated edema of the hands and feet, vasoconstriction, peripheral circulatory disturbance, shock, pericardial and pleural

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effusion, cerebral anoxia, confusion, and coma. The main treatment strategy, alongside supportive care, involves the administration of thyroid hormone replacement.[4] The risk of hypothyroidism in children with Down syndrome is 28 times higher than other children.[5] Furthermore, children with Down syndrome showed a significant decline in thyroid hormone levels, dropping from 90.8% to 41.7% in a follow-up study.[6]

In this case report, we present a successfully treated case of severe myxedema coma in a 2-year-old child with Down syndrome, featuring recurrent pericardial effusion and hypotensive-cardiogenic shock. This case is particularly intriguing due to its rare clinical presentation, and unique treatment strategies employed.

Case Report

A 2-year-old boy with Down syndrome (regular trisomy 21) was admitted to the pediatric emergency department due to altered mental status and respiratory distress. The patient, who was born at term via normal spontaneous vaginal birth from a healthy mother, was using hydrochlorothiazide and spironolactone as regular medications due to a known atrial septal defect and pulmonary stenosis and was additionally using levothyroxine (L-T4) therapy due to hypothyroidism. Thyroid agenesis had been identified as the cause of the patient's hypothyroidism through ultrasonography. The parents were not consanguineous, did not have a known hereditary disease, and had a healthy 5-year-old girl. His family stated that the patient was able to sit without support and walk on his own in his daily life and was able to take solid and liquid foods by mouth.

At the time of admission, his weight was 10 kg (3.75p; -1.78 SDS) and length was 78-cm- (1.07p; -2.3 SDS) he had bradypnea (respiratory rate 10/min (<-2 SDS)), bradycardia (heart rate 72/min (<-2 SDS)), hypotension [blood pressure 72/36 mmHg (13p, -1.13 SDS; 34p, -0.41 SDS)], altered mental status [Glasgow coma scale (GCS) score: 13], hearth sounds were barely audible and a cardiac murmur on auscultation, hypothermia (body temperature 35.5°C), capillary refill time was increased (4 seconds), cutis marmoratus, extensive dry skin with hard, non-pitting edema on the dorsum of the hands and feet, tongue edema (Fig. 1). The patient had a typical Down syndrome facial appearance with slanted eyes, a flat nose, small ears, and a large tongue. The patient also had short stature, brachydactyly and Simian creases. There was no hepatosplenomegaly on abdominal palpation. According to his medical history, he had experienced pericardial tamponade and underwent pericardiocentesis on two separate occasions. The family stated that the patient had benefited clinically from

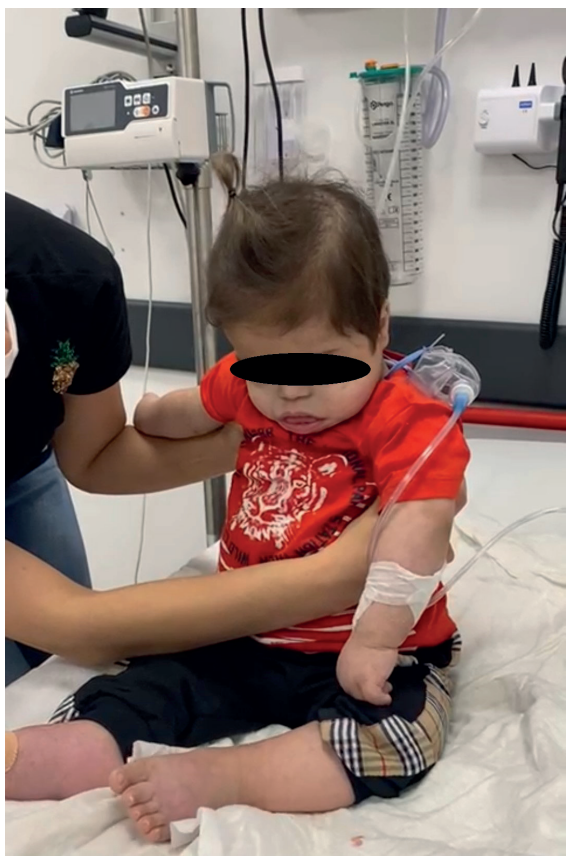

Fig. 1. The apperance of the patient on admission: typical phenotypes of Down syndrome and extensive dryness of the skin with hard, non-pitting edema on the dorsum of the hands and feet, and tongue edema.

previous pericardiocentesis procedures, but the same clinic developed after a period of time. In previous hospitalizations, hormone tests were not performed because the family stated that the patient had regular outpatient check-ups and was taking his medications regularly.

The patient's arterial blood gas, complete blood count, organ function tests (heart, liver, kidney), and serum electrolyte levels were within normal limits. The chest X-ray revealed an enlarged heart silhouette (Fig. 2), while the electrocardiogram (ECG) indicated a reduction in QRS voltage. Given the patient's altered mental status and hemodynamic instability, he was promptly transferred to the pediatric intensive care unit (PICU) for close monitoring, further assessment, and treatment.

Intravenous bolus administration of normal saline and an adrenergic inotropic infusion with adrenaline were initiated. However, the patient exhibited persistent refractory hypotension. Adrenaline and noradrenaline infusion rates were meticulously adjusted based on age-appropriate criteria. Endotracheal intubation was performed to reduce respiratory effort. A bedside echocardiography, overseen by the pediatric intensive care team, revealed a normal ejection fraction. Nonetheless, a diffuse pericardial effusion, not indicative of tamponade, was observed (Fig. 3). Adrenaline and noradrenaline doses were incrementally increased to 0.6 μg/kg/min to maintain normotension. Stress-related hyperglycemia was considered the cause of the patient's high serum glucose level of 243 mg/dL, given the absence of diabetes symptoms and the spontaneous resolution of hyperglycemia. Additionally, the urine ketone test was negative. Therefore, HbA1c and C-peptide levels were not tested. Empirical antibiotics were administered to address potential sepsis, and a hydrocortisone infusion (85 mg/m^2/day) was initiated due to suspected catecholamine resistant septic shock. Following hemodynamic stabilization, fluid restriction was implemented, and diuretic therapy was initiated. Given the patient's history of primary hypothyroidism and treatment non-adherence, thyroid function tests were performed, revealing markedly elevated thyroid stimulating hormone (TSH) level (311.24 mlU/L), along with suppressed free T3 (<1.07 pg/ml) and free T4 (<0.40 ng/dL) levels. In the patient's previous history, although he was diagnosed with primary hypothyroidism and his parents were giving him 50 μg of L-T4, thyroid function tests were not checked and cardiac causes were considered first because

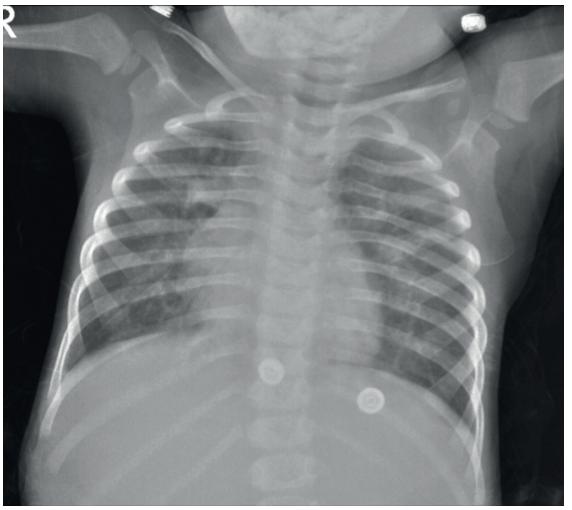

Fig. 2. The chest X-ray shows an enlarged heart silhouette.

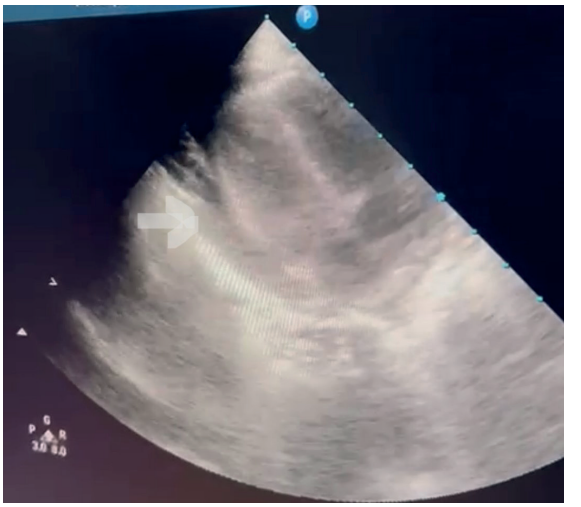

Fig. 3. Bedside ecocardiography: Diffuse pericardial effusion that did not cause tamponade (white arrow) with a normal ejection fraction.

the family reported that the treatment was being given regularly and that the patient had regular pediatric endocrinology visits. The patient was followed up because he benefited from pericardiocentesis. However, due to the severe clinical picture at the last hospitalization and the recurrence of the pericardial effusion, myxedema coma was considered. Before the diagnosis of myxedema coma, blood, urine, and endotracheal aspirate cultures were obtained for differential diagnosis. Hemodynamic instability prevented imaging, but we performed a detailed neurological examination and hourly GCS calculation of the patient. Due to the possibility of intoxication, the family was interviewed and urine toxicology tests were performed.

A pediatric endocrinology consultation was sought, and a decision was made to continue the patient's oral L-T4 treatment at the same dosage (50 μg/day), with close monitoring of thyroid function tests. Upon conducting an in-depth review of the patient's medical history, it was ascertained that non-adherence to the prescribed treatment for hypothyroidism and irregularities in attending routine medical evaluations had been observed. Beginning on the 3rd day of PICU hospitalization, inotropic support was gradually tapered. The noradrenaline infusion ceased on day 11, followed by the discontinuation of the adrenaline infusion on day 12. On the 13th day, the patient underwent extubation and was transitioned to noninvasive respiratory support. After achieving hemodynamic stability, the hydrocortisone infusion was gradually tapered and ultimately discontinued on the 15th day. Subsequent thyroid function tests on the 3rd, 6th, and 10th days following the diagnosis of myxedema coma indicated a decreasing trend in TSH levels and an increasing trend in free T4 levels, as detailed in Table I. On the 15th day, the patient achieved hemodynamic stability, exhibited normal neurological, cardiac, and respiratory functions, showed regression of skin findings and edema, and was able to resume total oral feeding. The patient experienced a complete recovery from a severe and life-threatening myxedema coma, with no residual sequelae or complications.

Discussion

We present a successfully treated patient with Down syndrome who had severe myxedema coma accompanied by recurrent pericardial effusion and hypotensive shock. This case is characterized by an unusual clinical presentation and a different treatment strategy, highlighting its exceptional rarity. This case report underscores the importance of adherence to LT-4 therapy in children with hypothyroidism. The life-threateing presentation emphasizes the significance of timely diagnosis and treatment of severe hypothyroidism.

The thyroid hormones act as fundamental regulators of metabolism, exerting pleiotropic effects on numerous organs. They play vital roles in orchestrating normal physiological growth, governing protein and lipid metabolism, enhancing the absorption of carbohydrates from the intestine, and activating red blood cell 2,3-diphosphoglycerate, which aids in the dissociation of oxygen from hemoglobin. In the cardiovascular system, particularly through the actions of T3, thyroid hormones increase ejection fractions, reduce vascular resistance, and promote coronary angiogenesis. Beyond their cardiovascular effects, thyroid hormones also regulate the metabolism of various internal organs such as the liver, pancreas,

Table I. Laboratory changes of thyroid function tests day by day under L-T4 treatment.

	1st day	3th day	6th day	10th day	Normal
TSH (mlU/L)	311.24	65.01	31.01	2.91	0.35-4.94
fT4 (ng/dL)	<0.40	0.46	0.90	1.32	0.7-1.48
fT3 (pg/ml)	<1.07	-	-	-	1.71-3.71

fT3: free T3, fT4: free T4, L-T4: L-thyroxine, TSH: thyroid stimulating hormone.

and muscles. Furthermore, they contribute to the carbohydrate metabolism by maintaining plasma insulin and glucose levels.[7,8]

Decompensation due to severe hypothyroidism, also known as myxedema coma, is an endocrinologic emergency that can lead to altered mental status and, in severe cases, coma. All clinical signs and symptoms associated with myxedema coma are a consequence of a metabolic slow-down.[9,10] In line with the typical presentation, our patient, like most individuals with myxedema coma, exhibited primary hypothyroidism. This was substantiated by low serum levels of fT4 and fT3, accompanied by elevated levels of TSH.[4,11,12]

Severe hypothyroidism can lead to the development of pericardial effusion, although this accumulation typically occurs gradually. Consequently, it is unexpected for this condition to produce clinically significant acute cardiovascular effects. Although rare, there are patients who are monitored in the PICU for myxedema coma. A 10-year-old male patient with the phenotype of Down syndrome and 1q deletion also presented with a low GCS and hemodynamic instability that was severe enough to require intubation. Similar to our patient, he was successfully treated with oral L-T4 but at high doses (400 μg/day) and intravenous hydrocortisone (3 mg/kg/day) for 14 days.[2] In our pediatric patient, who has Down syndrome, an extraordinary and exceptionally rare occurrence was observed. This involved severe myxedema coma with recurrent pericardial effusion, leading to a life-threatening hypotensive shock. It is noteworthy that such a combination of factors and clinical presentation has been reported very rarely in the literature. Complications arising from hypothyroidism may include pericardial effusions, which have been reported in 3-37% of hypothyroidism patients. Typically, pericardial effusions are associated with severe and long-standing hypothyroidism. However, on rare occasions, they can manifest as an initial clinical presentation of severe hypothyroidism or even mild thyroid dysfunction. Pericardial fluid shares a composition similar to plasma, and its drainage is facilitated by the thoracic and lymphatic ducts. Various theories exist regarding the development of pericardial effusion in hypothyroidism, with the most well-known theory attributing it to increased albumin permeability in pericardial capillaries. This increased permeability is a result of both the direct effects of hypothyroidism and the subsequent increase in histamine release. Consequently, the elevated intrapericardial oncotic pressure leads to an accumulation of pericardial fluid. Furthermore, pulmonary hypertension resulting from hypothyroidism can disrupt lymphatic drainage and elevate right-sided pressures.[13] In the context of myxedema coma, similar cardiac manifestations have been observed. For instance, a 5-year-old autoimmune thyroiditis patient presented with right ventricular conduction delay and mild pericardial effusion. Similarly, another 6-year-old patient diagnosed with autoimmune thyroiditis displayed prolonged QT interval, mild pericardial effusion, and anuria.[14,15] In 2019, a more severe clinical presentation was noted in a 2-year-old patient with congenital primary hypothyroidism, who also had acute viral bronchiolitis. Echocardiography revealed pericardial effusion and biventricular hypertrophy in the untreated hypothyroid patient, who presented with altered mental status, hypothermia, and bradycardia. The treatment and follow-up approach for this patient mirrored our previous case. With regular L-T4 treatment, the patient's thyroid function returned to normal, pericardial effusion decreased within a month, and heart dimensions improved within two months. Additionally, this patient displayed additional findings of rhabdomyolysis and liver failure, which responded positively to treatment.[16] Another patient with clinical and treatment similarities to the previously mentioned cases was a four-year-old male child experiencing recurrent abdominal pain. Ultrasonography revealed a significant pericardial effusion, which was later confirmed by echocardiography to be approximately 23 mm in size with a volume of

around 600 mL. Despite minimal impairment of heart kinetics, thyroid function testing revealed extremely high thyrotropin levels and low serum-free thyroxine levels, leading to a diagnosis of myxedema coma with pericardial effusion. Treatment involved LT4 replacement therapy administered gradually. Remarkably, after just one month, complete regression of the effusion and normalization of thyroid function indexes were observed.[17]

The differential diagnosis of myxedema coma is essential for proper management. There are many clinical conditions that may mimic the myxedema coma, such as sepsis, drug intoxications, central nervous system disorders, or drug-related adverse effects.[18,19] In our patient, the related disorders had been excluded by physical examination, laboratory, and radiological tests. It is important to note that hypothyroidism leading to coma in children is a very rare condition. Given the limited number of cases in the medical literature, it is challenging to establish a precise mortality rate for this specific population. However, in adults, myxedema coma is associated with a reported mortality rate ranging from 20% to 50%. Even when early diagnosis and prompt treatment are initiated, a poor prognosis has been linked to factors such as advanced age, bradycardia, and prolonged or resistant hypothermia.[3,20] Euthyroid sick syndrome (non-thyroidal illness) was also considered because of the extremely low fT3. However, euthyroid sick syndrome was ruled out due to the extremely high TSH levels in our patient, rather than the normal/low TSH level typically seen in euthyroid syndrome.[21]

Following the diagnosis of myxedema coma, therapeutic interventions include correction of electrolyte imbalances, implementation of passive warming measures, administration of antimicrobial agents for infection control, initiation of respiratory and hemodynamic support, provision of stress-dose glucocorticoids, and initiation of thyroid hormone replacement therapy. Vigilant monitoring and management within an intensive care unit are essential, given the concurrent presence of multiple issues, such as hypotension, hyponatremia, hypoglycemia, and hypothermia. Furthermore, it is noteworthy that when thyroid hormone replacement therapy is employed in conjunction with these supportive measures, a gradual resolution of all symptoms is typically observed.[4]

Myxedema coma can occur when compensatory mechanisms for hypothyroidism are overwhelmed by a precipitating cause, leading to life-threatening consequences. The diagnosis of myxedema coma hinges on a thorough assessment of differential diagnoses, clinical suspicion, patient history, and thyorid function tests. In children with known or suspected hypothyroidism—particularly those predisposed to hypothyroidism, such as individuals with Down syndrome—myxedema coma should be considered in cases of altered mental status.[2] An illustrative case involves a 17-year-old girl with growth and developmental delay who was followed in the PICU due to confusion, bradycardia, hypothermia, and severe hypotension, requiring vasopressors and hydrocortisone. She had myxedema coma due to severe hypothyroidism and promptly treated with intravenous levothyroxine.[22] Similarly to our patient, a 10-year-old cihld with Down syndrome, was admitted to the PICU with severe myxedema coma accompanied by shock. Mechanical ventilation was initiated for respiratory support, and vasopressors and hydrocortisone were administered to maintain normal blood pressure. Oral thyroid hormone replacement therapy was initiated at a dose of 400 μg/day, with subsequent doses adjusted based on thyroid hormone levels. Unfortunately, despite treatment efforts, the patient succumbed to severe cardiac arrhythmia on the 14th day.[2] Cases of myxedema coma reported in the literature are usually at the time of the initial diagnosis of hypothyroidism. In our case, the fact that the patient was previously diagnosed is important because it is a clear indicator of treatment noncompliance.

The basis therapeutic approach for myxedema coma patients revolves around optimizing the absorption and distribution of thyroid hormone

replacements, with a focus on achieving safe and efficacious outcomes. It has been reported that treatment with L-T4 may be less effective in cases where the conversion of L-T4 into T3 is impaired. In accordance with the guidelines reported by the American Thyroid Association, IV administration of L-T4 is considered the preferred treatment for managing myxedema coma. It's important to note that intravenous L-T4 is not readily available in many countries, making oral administration a more common approach. In children with myxedema coma, there is a scarcity of available data and established protocols regarding the oral administration of L-T4. Despite this, it remains a viable option. In this case report, oral L-T4 was administered due to the unavailability of the intravenous form of L-T4 in our country. Additionaly, it was also discovered that the patient had not been consistently taking the previously prescribed oral L-T4. To assess the effectiveness of the treatment, regular monitoring of thyroid function, including TSH and fT4 levels, was carried out in collaboration with the pediatric endocrinology team. Clinical symptoms and overall well-being were also closely observed and taken into consideration during the treatment course.[23]

According to the guidelines, intravenous L-T4 is used in myxedema coma but this form is not available in our country. If oral administration is preferred, a high dose is recommended, but we discovered that our patient did not take the medication regularly or showed noncompliance by spitting it out when he did take it. For this reason, even before the diagnosis was made, he was followed with close clinical monitoring in the PICU when the normal daily dose was started.

A myxedema coma diagnostic scoring system has been developed for adults. The clinical findings, including thermoregulatory dysfunction, central nervous system involvement, gastrointestinal findings, precipitating factors, cardiovascular dysfunction findings, and metabolic disorders, form the basis of the scoring system.[24] Although challenging to apply to children due to age-related changes in vital signs, a separate scoring system for children is necessary.

In summary, our case report highlights a pediatric patient with Down syndrome and a prior diagnosis of hypothyroidism. This patient presented with a severe clinical condition characterized by recurrent pericardial effusion and was effectively treated. Myxedema coma, although rare, carries a high risk of mortality. Consequently, it should be considered as a potential diagnosis in cases of shock and multi-organ involvement, ensuring its inclusion in the differential diagnosis.

Altered neurologic status and hemodynamic instability in a patient with a history of hypothyroidism should raise the concern of nonadherence and, although rare, myxedema coma should be in the differential diagnosis. In addition, regular medication use and outpatient clinic follow-ups should be questioned at every encounter with patients diagnosed with hypothyroidism for any reason, and thyroid function tests should be examined when L-T4 treatment noncompliance is suspected.

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Ethical approval

We obtained informed consent from the patient's parents for this report.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: HFA and AA; data collection: HFA, AA, ŞD, SFÇ; analysis and interpretation of results: HFA and AA; draft manuscript preparation: HFA and AA. All authors reviewed the results and approved the final version of the manuscript.

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Case Report

A surprise during hernia surgery: inguinoscrotal megaureter

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ABSTRACT

Background. Ureteroinguinal herniation is a rare occurrence that is typically diagnosed during the surgical repair of inguinal hernias.

Case Presentation. We present the case of a 4-year-old male who underwent inguinal hernia repair, during which a megaureter was discovered within the hernia sac. The surgical intervention included high ligation of the hernial sac and repositioning of the ureter back into the retroperitoneum. Postoperative investigations confirmed a diagnosis of primary non-refluxing and nonobstructive megaureter.

Conclusion. Although ureteral herniation is rare in infants, it is crucial to remain vigilant about the possibility of encountering the ureter during hernia repair to prevent potential ureteral injuries. Additionally, any associated urinary tract anomalies should be thoroughly investigated and ruled out.

Key words: hernia, ureteroinguinal hernia, herniation of the ureter, child.

Inguinal hernia repair is one of the most frequently performed surgical procedures worldwide.[1] While inguinoscrotal hernias typically encompass various intraperitoneal organs such as the small intestine, colon, appendix, and ovaries, ureteric herniation into the inguinal canal is exceedingly rare due to the ureter's retroperitoneal location. To date, fewer than 150 cases have been reported in adults, and the condition is even more uncommon in the pediatric population, with only 12 documented cases in children.[2] The literature reveals that most ureteral inguinal hernias are discovered during surgical interventions rather than in preoperative evaluations.[3] In this article, we present the case of a 4-year-old male who underwent inguinal hernia repair, during which a megaureter was discovered within the hernia sac.

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Case Presentation

A 4-year-old male patient presented to the pediatric surgery clinic complaining of right-sided inguinal swelling. Physical examination identified a reducible mass in the right inguinal region, with both testes appropriately located in the scrotum, and no other remarkable findings. The patient's medical history was free of comorbidities, and pre-operative blood tests were within normal limits. Based on the typical presentation, he was scheduled for a right inguinal hernia repair under general anesthesia, without the need for preoperative imaging.

During the surgical procedure, an open exploration of the right inguinal canal was performed, which revealed a peritoneal sac with a herniated luminal structure behind the sac (Fig. 1). Initially, the nature of this structure was unclear, including whether it represented an anatomical variation or was part of a direct hernia. Aspiration was performed using an injector to elucidate the identity of the luminal structure, and the presence of a

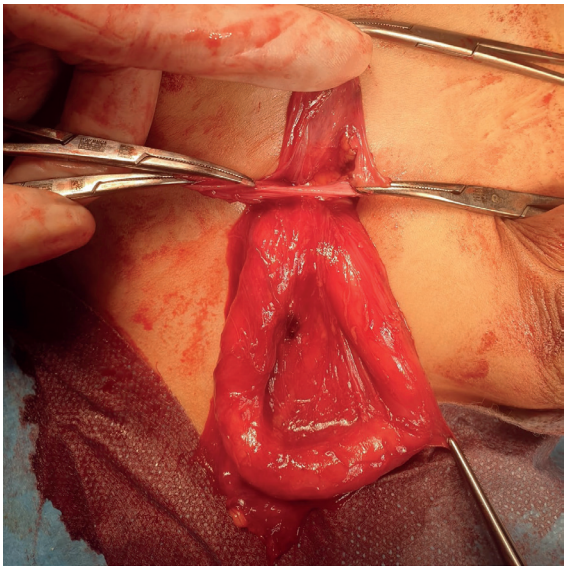

Fig. 1. Ureteral herniation showing the ureter behind the peritoneal sac

urine-like fluid indicated that the structure was the ureter. The ureter was found to originate from the retroperitoneum, with a portion looping within the inguinal canal. The surgical intervention included high ligation of the hernial sac and repositioning of the ureter back into the retroperitoneum. Furthermore, the internal inguinal ring was narrowed to prevent recurrence. The patient was successfully discharged on the same day, a few hours following surgery, without any postoperative complications.

Postoperative assessments were planned for further investigation of the patient's condition. Urinary system ultrasonography (US) revealed a minor degree of hydronephrosis, along with bilateral dilatation of the ureters, measuring 15 mm in diameter on the left and 12 mm on the right with normal bladder. Voiding cystourethrography (VCUG) ruled out vesicoureteral reflux (VUR). During the micturition phase, the posterior urethra was observed to be normal, thereby eliminating the diagnosis of posterior urethral valves (PUV). Additionally, diuretic scintigraphy using Mercapto-acetyltriglycine (MAG-3) was performed to exclude obstructive causes of the megaureter. The MAG-3 renography revealed normal split renal function (right: 48%, left: 52%), with evidence of bilateral megaureter and slow urinary drainage. Near complete drainage was observed after the diuretic injection, with no obstructive urinary pattern detected. The calculation of the half-time ($T_{1/2}$) was recorded as 13.5 minutes on the right and 15.2 minutes on the left. These findings led to a diagnosis of primary non-refluxing and nonobstructive megaureter. Given the absence of any history of urinary tract infections, the patient was recommended for intermittent follow-up in the outpatient clinic. A written informed consent was obtained from the parents of the patient for the publication of this case report.

Discussion

Inguinal hernia is a common diagnosis, often requiring surgical intervention.[1] However, inguinal herniation of the ureter is a rare occurrence, primarily seen in obese, middle-aged men.[4] In infants, this condition is extremely rare, with only 12 cases reported in the literature (as summarized in Table I).[2,3,5-14] In adults, risk factors for ureteral inguinal hernias include male sex, age over 50, collagen synthesis disorders, a history of kidney transplant, and obesity.[4] Although risk factors have not been identified in the pediatric population, it is noteworthy that all reported cases have involved male infants, with no instances documented in females to date.

Ureteroinguinal hernias are classified into two main types: paraperitoneal (80%) and extraperitoneal (20%). Paraperitoneal hernias involve a true hernia sac that pulls the ureter into the inguinal canal through traction. In contrast, extraperitoneal hernias lack an associated sac and are thought to arise from incomplete differentiation of the ureter from the Wolffian duct or adhesion between the primitive ureter and the genitofemoral ligaments.[8,15] Notably, numerous cases of extraperitoneal hernias are associated with renal and urinary tract malformations, such as wandering kidney and transverse renal ectopia. Extraperitoneal hernias

Table I. Reports of cases of inguinal ureteral hernia in children

No	Author	Year	Age/Sex/Side	Type	Associated urinary anomaly	Management
1	Cianci et al.[5]	2024	2 mo/M/R	Paraperitoneal	Hydroureteronephrosis, VUR	Reduction to the retroperitoneal space
2	Delgado-Miguel et al. [6]	2024	2 mo/M/L	Paraperitoneal	Hydroureteronephrosis, VUR	Reduction to the retroperitoneal space, ureteroneocystostomy
3	Hosoda et al. [2]	2022	14 y/M/L	Paraperitoneal	A past medical history of left inguinal hernia surgery	Inguinal exploration
4	Wishani et al. [7]	2021	4 mo/M/L	Paraperitoneal	Primary obstructed megaureter	Reduction to the retroperitoneal space
5	Cao et al. [8]	2018	12 y/M/L	Extraperitoneal	Cloacal exstrophy, cross-fused pelvic kidney	Transureteroureterostomy
6	Bosschieter et al. [3]	2018	3 mo/M/R	Paraperitoneal	Hydroureteronephrosis, VUR	Ureteroneocystostomy
7	Handu et al. [9]	2012	18 mo/M/R	Paraperitoneal	Solitary kidney	Ureteroneocystostomy with appendiceal interposition
8	Sripathi et al. [10]	2011	10 mo/M/L	Paraperitoneal	VUR	End ureterostomy
9	Burgu et al. [11]	2010	4 mo/M/L	Paraperitoneal	Posterior urethral valve	End ureterostomy
10	Powell et al. [12]	1985	4 wk/M/L	Paraperitoneal	Megaureter	Reduction to the retroperitoneal space
11	Morris et al. [13]	1977	6 wk/M/B	Paraperitoneal	Multicystic dysmorphic kidney	Not mentioned
12	Jewett et al. [14]	1953	9 y/M/L	Extraperitoneal	Hydroureteronephrosis	Transureteroureterostomy

B: Bilateral, L: Left, M: Male, R: Right, VUR: Vesicoureteral reflux.

are more frequently associated with coexisting anomalies compared to paraperitoneal hernias, according to the literature.[9,11,12] Additionally, extraperitoneal herniation can be an acquired condition due to retroperitoneal fat prolapse and is reported to be relatively more common after renal transplantation.[4] Among the 12 reported pediatric cases in the literature, 2 were of the extraperitoneal type.[8,14] The patient presented here was diagnosed with the paraperitoneal type.

In both types of ureteroinguinal hernias, symptoms are often nonspecific, with the most common presentation being distension of the inguinal region due to ureteral slippage.[2,9] The majority of patients are asymptomatic, and routine radiological studies are typically not conducted preoperatively.[3] Consequently, the diagnosis of ureteroinguinal hernia is often missed until surgical exploration, as in the presented patient. If an ureteroinguinal hernia is encountered during routine herniotomy, the presence of associated urinary tract anomalies should be investigated. In the case presented, no prior diagnosis related to the urinary system was known, as the patient had no previous symptoms. However, postoperative investigations revealed the primary nonobstructive, nonrefluxing megaureter. The literature reports that extraperitoneal hernias are more likely to present with symptoms such as back pain or hernia incarceration due to ureteral obstruction or strangulation, compared to paraperitoneal hernias.[8,14] Although preoperative diagnosis is challenging, the possibility of an inguinal ureteral hernia should be considered in cases of inguinal herniation, especially if accompanied by symptoms and signs of ureteral obstruction such as hydronephrosis or hydroureter.

Despite their rarity, surgeons should remain vigilant for the possibility of a ureteroinguinal hernia to avoid inadvertent ureteral injury during herniotomy. Cases of ureteral injury during hernia surgery have been documented in the literature.[9] Once the diagnosis is confirmed

during surgical exploration, various treatment options exist based on the specific presentation of the herniated ureteral loop.[3,6,9] Most experts advocate for repositioning the ureter back into the retroperitoneum. However, in cases of ureteral redundancy or injury, resection and anastomosis are recommended.[8,14] End-ureterostomy has been reported as a management option for extremely dilated ureters, with subsequent plans for reimplantation.[10,11] The laparoscopic approach in these cases remains controversial. In cases involving adult patients, it has been reported that although laparoscopy may offer enhanced visualization of the ureter entering the inguinal canal, managing hernia repair and achieving vascular control of the ureter may pose challenges.[4] However, there is currently no literature on laparoscopic repair of ureteroinguinal hernia in children for comparative analysis in this regard.

In the present case, the standard open approach was chosen. Given the lack of information regarding the patient's etiology, a further postoperative investigation was planned, and a reduction of the ureter into the retroperitoneum along with hernia repair was performed. However, intraoperative identification of the herniated structure proved challenging. It is possible that a laparoscopic approach would have facilitated a clearer understanding of the anatomy and aided in the diagnostic process during the procedure.

Conclusion

Even though ureteral herniation in infants is rare and sporadic, it is important to consider the possibility of encountering the ureter during hernia repair, and precautions should be taken to prevent ureteral injury. Additionally, potential associated urinary tract anomalies should be thoroughly investigated and ruled out.

Ethical approval

Informed consent was obtained from the parents of the child.

Author contribution

The author confirms contribution to the paper as follows: study conception and design: GG, data collection and literature review: GG, draft manuscript preparation; GG. The author reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The author declares that there is no conflict of interest.

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Lipid emulsion resuscitation for intractable calcium channel blocker toxicity in pediatric patients

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To the Editor:

I read with interest the report entitled, "Effect of intravenous lipid therapy in critically ill pediatric patients with calcium channel blocker toxicity," recently published in The Turkish Journal of Pediatrics.[1] Previous studies have shown lipid emulsion, initially designed for intravenous nutrition, in treating cardiovascular collapse due to toxic levels of non-local anesthetics in pediatric patients.[2,3] I would like to comment on the fundamental mechanism and recommend a dosing regimen for lipid emulsion. First, the underlying mechanism of lipid emulsion resuscitation involves both direct and indirect effects.[2] The widely accepted theory behind this resuscitation method is the lipid shuttle mechanism.[2] According to this theory, the lipid component of the lipid emulsion absorbs highly lipid-soluble drugs (with a log P [octanol to water partition coefficient] value exceeding 2, such as bupivacaine, verapamil, and amlodipine with log P values of 3.41, 3.79, and 3, respectively) from the heart and brain.[2] Subsequently, the lipid emulsion containing the lipid-soluble drugs is transported to the liver, muscle, and adipose tissue for detoxification and storage.[2] The direct effects of lipid emulsion resuscitation encompass a range of actions such as positive inotropic effects, supplying fatty acids, inhibiting mitochondrial dysfunction, restraining nitric oxide release, and promoting glycogen synthase kinase-3β phosphorylation.[2] In light of previous findings, the increase in ejection fraction and blood pressure following the administration of lipid emulsion in this study could be linked to two factors: first, the removal of highly lipid-soluble calcium channel blockers like verapamil and amlodipine from the heart, and, second, the positive inotropic effect mediated by the lipid emulsion itself.[2-4] Second, the lipid emulsion dosing regimen described by Yavuz et al. is as follows: "A recommended dosing regimen for lipid emulsion is an infusion of 20% solution, 1 mL/kg over 1 minute, repeated every 3 to 5 minutes for a maximum of 3 mL/kg followed by 0.25 mL/kg/min."[1,5] This dosing regimen was proposed in 2004, predating the recommended lipid emulsion regimen for local anesthetic systemic toxicity by the American Society of Regional Anesthesia and Pain Medicine:[5,6] An initial intravenous bolus of 1.5 mL/kg of 20% lipid emulsion, followed by a continuous infusion at a rate of 0.25 mL/kg/min of 20% lipid emulsion.[6] However, local anesthetic systemic toxicity primarily occurs as a result of intravascular injection of local anesthetic agents, whereas toxicity from non-local anesthetics such as calcium channel blockers typically stems from oral administration of these drugs. Consequently, the pharmacokinetics of toxicity is different. In addition, there is no established lipid emulsion dosing regimen specifically for managing non-local anesthetic drug toxicity. A 1% plasma triglyceride concentration triggers both a positive inotropic effect and scavenging of lipid-soluble drugs.[4,7] On the basis of previous findings, a suggested dosing regimen for lipid emulsion to achieve 1% plasma triglyceride levels for managing drug toxicity due to non-local anesthetic drugs is as follows: Initially administer 1.5 mL/kg of 20% lipid emulsion

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over 1 min, followed by 0.25 mL/kg/min over 3 min, and then maintain a continuous infusion of 0.025 mL/kg/min of 20% lipid emulsion.[4,7-9]

Author contribution

Study conception and design: JTS; draft manuscript preparation: JTS. The author reviewed the results and approved the final version of the article.

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Conflict of interest

The author declares that there is no conflict of interest.

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Response to "Lipid emulsion resuscitation for intractable calcium channel blocker toxicity in pediatric patients"

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To the Editor:

We express our gratitude to Dr. Sohn for their interest in our research and wish to respond to the correspondence titled "Lipid emulsion resuscitation for intractable calcium channel blocker toxicity in pediatric patients".[1]

The additional information Dr. Sohn has provided[2] regarding the mechanism of action of intravenous lipid emulsion (ILE) treatment substantiates the mechanisms described in our article and will serve as a valuable resource for readers seeking guidance on this subject, where information remains limited.[3] In our publication on the recommended dose of ILE, we detailed the dosing regimen utilized in cases of local anesthetic toxicity.[4] As Dr. Sohn has stated in their letter, we adhered to the current recommended dosage for critical patients, such as those with calcium channel blocker poisoning. Specifically, we administered an initial intravenous bolus of 1.5 mL/kg of 20% lipid emulsion, followed by a continuous infusion at a rate of 0.25 mL/kg/min of 20% lipid emulsion.[5]

Author contribution

The authors confirm their contribution to the paper as follows: SY, AA, RGS, MMK, DA were responsible for writing and evaluating the letter. All authors reviewed and approved the final version of the manuscript.

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CASE REPORTS

LETTERS TO THE EDITOR

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