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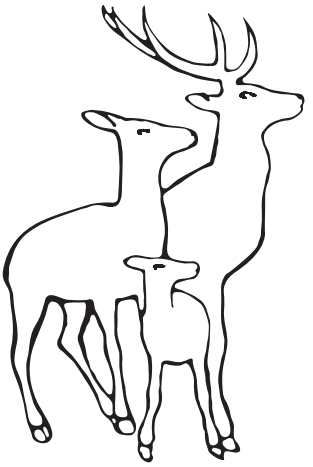

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Editorial

In memory of Prof. Enver Hasanoğlu: Honoring a legacy

Ali Düzova[1], Sinem Akgül[1], Eda Utine[1], Yılmaz Yıldız[1], Özge Başaran[1], Leman Akcan Yıldız[1], Esra Serdaroğlu[1], Yağmur Ünsal[1]

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As the Editorial Board of the *Turkish Journal of Pediatrics*, we are deeply saddened by the passing of Prof. Enver Hasanoğlu on March 7, 2026. Prof. Hasanoğlu dedicated his entire life to improving child health in Türkiye and worldwide, serving in numerous distinguished national and international roles. His passing represents not only a profound loss for Türkiye, but also for the global pediatric community. We sincerely thank the authors of the obituary published in this issue for providing our readers with a comprehensive and insightful account of his contributions to child health and pediatric science.[1]

Prof. Hasanoğlu served as the Administrator of the *Turkish Journal of Pediatrics* since 2004. Through his longstanding involvement in the Turkish National Pediatric Society, one of the scientific and financial pillars of our journal, he was a steadfast advocate for its growth and development. In recent years, he played a key role in organizing dedicated "Turkish Journal of Pediatrics sessions" at the annual National Pediatric Congresses. These sessions provided valuable opportunities to share developments related to the journal at both national and international levels, and to engage in constructive discussions on strategies for further advancement. In parallel, interactive "how to write a scientific paper" workshops led by members of our Editorial Board for young pediatricians were initiated at these congresses. Through these efforts, Prof. Hasanoğlu made substantial contributions to our mission of advancing academic publishing in pediatrics. We remember him with deep respect and sincere gratitude for his support.

Following his passing, the role of Administrator of the *Turkish Journal of Pediatrics* has been assumed by our esteemed colleague and mentor, Prof. Koray Boduroğlu. We are honored to announce this transition and look forward to working with him in this capacity. Prof. Boduroğlu served as President of the Turkish National Pediatric Society from 2018 to 2021 and continues to serve on its Executive Board. He is President of the Union of National Pediatric Societies of Turkic Republics and was a Standing Committee Member of the International Pediatric Association between 2021 and 2025.

As we honor the memory of Prof. Enver Hasanoğlu, we remain committed to upholding and advancing the quality and integrity of pediatric academic publishing. His leadership, dedication, and lifelong service to child health will continue to guide the *Turkish Journal of Pediatrics* in the years to come.

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1. Dağdemir A, Bideci A, Özmert EN, Okur İ, Boduroğlu K. Prof. Dr. Enver Hasanoğlu (1946-2026). Turk J Pediatr 2026; 68: 176-178. https://doi.org/10.24953/turkjpediatr.2026.8602

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Obituary

Prof. Dr. Enver Hasanoğlu (1946-2026)

Ayhan Dağdemir[1], Aysun Bideci[2], Elif N. Özmert[3], İlyas Okur[2], Koray Boduroğlu[3], on behalf of the Turkish National Pediatric Society

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Turkish National Pediatric Society mourns the passing of Prof. Dr. Enver Hasanoğlu on March 7, 2026. The global pediatrics community has lost a great human being, and the Turkish National Pediatric Society has lost its most important cornerstone. Prof. Dr. Enver Hasanoğlu was a leader who dedicated his life and efforts to the advancement of not only the treatment of diseases but also the promotion of child health and well-being nationally and internationally.

Prof. Dr. Enver Hasanoğlu was born in 1946 in Erbil, to which he has always been attached, missed, worked for and where he was widely respected and reputable. In 1969 he graduated from İstanbul University, İstanbul Faculty of Medicine, and in 1973 he completed his residency training in pediatrics at Hacettepe University, Faculty of Medicine, Department of Pediatrics in Ankara, Türkiye. Afterwards, he went to the University of Glasgow, Royal Hospital for Sick Children for his fellowship training in pediatric nephrology. He was among the pioneers of pediatric nephrology in Europe. He was appointed as Professor of Pediatrics in 1984 at Erciyes University. Thereafter, his efforts were not only devoted to preventing and treating children's diseases as a pediatrician, but also to the development of medical and higher education.

He served as the Dean of Erciyes University Faculty of Medicine (1984-1988) and Gazi University Faculty of Medicine (1988-1992). He also served as the Head of the Department of Pediatrics and made significant contributions to the development of the Departments of Pediatrics, Pediatric Nephrology, and Adult Nephrology within the Faculty of Medicine. He was appointed the Rector of Gazi University (1992-2000), where his great efforts led to the construction of the first modern hospital of the Faculty. During his tenure as Rector, he served as a member of the Higher Education Council's Medicine and Health Committee for two years. He also served as the Vice President of Bilkent University Board of Trustees and the President of the International Children's Center.

Prof. Dr. Enver Hasanoğlu

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He was a member of the Turkish Higher Education Council from 2006 to 2010. During his membership in the Higher Education Council, he put great effort into establishing new scientific pediatric subspecialties in Türkiye . His efforts in education and training of pediatricians was not only limited to within Türkiye. His leadership roles in regional and international organizations enabled him to extend these efforts to the international pediatrics community worldwide.

Prof. Hasanoğlu was Secretary General of the Union of National Pediatric Societies of Turkic Republics (UNPSTR) since 1993, a member of the UNICEF Turkey National Committee Board of Directors since 1993, President of the Turkish National Pediatric Society (1999-2001), Secretary General of the Turkish National Pediatric Society since 2003, Secretary General of the Union of Middle Eastern and Mediterranean Pediatric Societies (UMEMPS) since 2008, Member of Standing Committee of the International Pediatrics Association (IPA) since 2007, and Member of the Executive Committee of IPA Foundation. He worked with the mission of IPA for more than 20 years through participation in different committees of IPA in several countries worldwide.

For over 100 years, the IPA has been the only global institution representing the professional communities of pediatricians; it includes 168 pediatric societies operating in the field of child health across 149 countries and seven regional pediatric associations representing all regions of the world. In this context, as the largest child health institution in the world, the IPA represents more than one million pediatricians serving to improve the health of over one billion children and provides leadership in child health issues. Prof. Dr. Enver Hasanoğlu was elected President of the IPA at the General Assembly held in Panama in March 2019, attended by delegates from all member countries. Prof. Dr. Enver Hasanoğlu became the second Turkish physician elected to this position, 30 years after Prof. Dr. İhsan Doğramacı.

He served as IPA president for the 2021-2023 term. During his presidency, he made significant efforts to solve the problems of children worldwide and to inform pediatricians about these issues. He worked on topics such as vaccine hesitancy, climate change, malnutrition, children's rights, and preventive medicine. He led the Refugee Children Project (2015-2019), supported by IPAF, focusing on inclusion, support and well-being, at a time Türkiye was hosting the largest number of refugees—approximately four million, almost half of whom were children.

Prof. Hasanoğlu was a member of European Dialysis and Transplantation Association (EDTA), Middle East Societies for Organ Transplantation (MESOT), European Society for Pediatric Nephrology (ESPN), Turkish Nephrology and Hypertension Association, and served as the President of Azerbaijan-Turkish Foundation. Azerbaijan State Medical University (Baku), Macedonian St. Climent Ohridski University and Romanian Ovidius University awarded Prof. Hasanoğlu awarded him honorary doctorates. He was also an honorary member of the American Academy of Pediatrics and Honorary Professor at the Russian Scientific Center of Children's Health.

Prof. Hasanoğlu was the administrator of the Turkish Journal of Pediatrics, was a member of the editorial boards of *Çocuk Sağlığı ve Hastalıkları Dergisi* (Journal of Child Health and Diseases), *Türkiye Klinikleri* (Turkish Clinics), Journal of the Greek Paediatric Society, Journal of Romanian Pediatric Society, and Asian Journal of Pediatric Practice.

Prof. Hasanoglu authored more than 200 publications in English and Turkish, primarily in the fields of pediatrics and nephrology.

He married Prof. Dr. Alev Hasanoğlu in 1974, whom he met during his pediatrics residency at Hacettepe University. Prof. Dr. Alev Hasanoğlu was always his greatest supporter. This 52-year union was marked by achievements in the medicine, academia, administration, the

national and international scientific arenas, and leadership. Prof. Dr. Enver Hasanoğlu was the beloved father of Başak and Kerem, and the beloved grandfather of Can and Kaan.

Besides Turkish and English, he spoke Arabic fluently and frequently shared the original verses by renowned poets. He had a deep interest in history; you could always find him reading and learning until his final days. He was a devoted listener of Turkish classical music and an avid reader, often reading several books simultaneously.

With his leadership, scientific approach, dedication to education, determined stance, and his rich cultural and intellectual background, Prof. Dr. Enver Hasanoğlu played a significant role in the development of the Turkish National Pediatric Society, where he has served as President and later as Secretary General, as well as the development of pediatrics and pediatricians in Türkiye and around the world.

He was a true teacher, he was a visionary pioneer, he was a renowned guide.

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Review

Diagnostic dilemmas of child sexual abuse

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ABSTRACT

Globally, an estimated 12-13% of children experience sexual abuse, with prevalence rates of approximately 18% among girls and 8% among boys. Clinicians evaluating pediatric patients who present with anogenital complaints or lesions face considerable diagnostic challenges. The purpose of this narrative review is to outline the most frequently encountered conditions that can mimic child sexual abuse (CSA), thereby raising clinical awareness and helping to minimize both false-positive and false-negative diagnoses. We conducted a semi-systematic literature search in PubMed covering the period from 2000 to 2025, using the search terms "child sexual abuse," "differential diagnosis," "mimics," and "mimickers," supplemented by the German interdisciplinary guideline on child abuse and neglect. Notably, the vast majority of children who have been sexually abused present without detectable physical abnormalities. Conversely, an erroneous diagnosis of abuse—or the failure to identify a treatable underlying condition—can carry severe consequences. Many practitioners in primary care lack sufficient training to distinguish the wide range of dermatologic and systemic disorders that may affect the anogenital region. Precise recognition, careful documentation, and scientifically grounded interpretation of physical findings are critical to ensue child protection. Optimal medical care for suspected CSA victims requires that clinicians possess expertise in pediatric and adolescent gynecology and forensic medicine, recognize the constraints inherent to physical examination findings, and consistently employ up-to-date classification frameworks and clinical guidelines. Heightened awareness of CSA mimickers is essential both to prevent unfounded allegations and to ensure timely, appropriate management of genuine abuse.

Key words: child sexual abuse, differential diagnosis, mimickers, accidental anogenital injury, cutaneous lesions.

Child sexual abuse (CSA) constitutes a pervasive public health concern, with meta-analytic data indicating that 12-13% of children worldwide are affected—roughly 18% of girls and 8% of boys.[1] These figures, however, almost certainly underestimate the true scope of the problem, as a substantial proportion of cases remain undisclosed. Robust epidemiological data and standardized frameworks for addressing the medical and legal dimensions of CSA are still evolving.

CSA encompasses a spectrum of sexual activities imposed on children and adolescents who, by virtue of their developmental stage, are unable to provide informed consent or participate as equal partners.[2,3] Such acts transgress societal norms and are characterized by an inherent power asymmetry, whereby offending adults leverage age-related authority—through psychological manipulation, coercion, or physical force—to gratify their own sexual interests. The range of abusive behaviors extends from non-contact offenses (e.g., exposure, voyeurism) to penetrative assault. In most instances, CSA is a recurring and profoundly traumatizing experience, frequently perpetrated by family members or other individuals occupying

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positions of trust.[3,4] Victims commonly develop intense feelings of guilt, shame, diminished self-worth, and social withdrawal, with well-documented long-term repercussions for mental, emotional, and physical health.[4]

Given its high prevalence and far-reaching sequelae, CSA has attracted growing attention in both medical practice and the criminal justice system.[5] Media coverage regularly highlights cases of child victimization, yet professional awareness often becomes acute only in the aftermath of individual tragedies. Research consistently shows that many clinicians who encounter pediatric patients have insufficient training in recognizing, diagnosing, and managing CSA.[6] Diagnostic errors persist despite advances in the field, and conditions that mimic the presentation of sexual abuse remain poorly understood by many practitioners. Anogenital complaints in children demand careful clinical evaluation, as both failures to identify genuine abuse and a false attribution of abuse to an innocent cause can have devastating consequences. Accordingly, healthcare providers must be well versed in the differential diagnosis of CSA, due to the subsequent health of the victim and to the possible criminal consequences.

The aim of this review is to provide a comprehensive overview of the conditions most commonly mistaken for CSA, with the dual objective of reducing erroneous diagnoses and improving timely recognition of sexual abuse.

Because unexplained skin changes in the anogenital region are among the most frequent initial presentations that prompt suspicion of CSA, accurate differentiation of cutaneous mimickers from genuine abuse-related findings is of paramount importance.[7] Misidentification in either direction carries serious implications for the child, the family, and any individual wrongly accused.

By synthesizing the available evidence on CSA mimickers, we intend to equip clinicians across specialties with the knowledge needed to navigate these diagnostically challenging presentations and to reduce the burden of false accusations while strengthening the identification of true CSA.

Methods

We performed a semi-systematic review of the literature published between January 2000 and December 2024. PubMed was searched using the following terms in various combinations: "child sexual abuse," "differential diagnosis," "mimics," and "mimickers." In addition, the German interdisciplinary guideline on child abuse and neglect (S3-Leitlinie Kindesmisshandlung, -missbrauch, -vernachlässigung) was consulted. The initial search yielded 58 publications, of which 39 met our predefined inclusion criteria: (i) peer-reviewed original research addressing conditions that mimic CSA, (ii) pediatric study population (age <18 years), (iii) English-language publication, and (iv) publication date within the specified timeframe. We excluded practice guidelines, commentaries, editorials, opinion pieces, and studies focusing primarily on adult populations or published in languages other than English. Several limitations of the available evidence warrant acknowledgment. The heterogeneity of study designs and outcome measures precluded formal meta-analysis, and many included studies were case reports or small case series, limiting generalizability. Nevertheless, the growing recognition that CSA requires a multidisciplinary approach—integrating clinical, forensic, and psychosocial perspectives—underscores the importance of consolidating the existing knowledge base. Further research is needed to enhance the competency of healthcare professionals, particularly those with forensic responsibilities, in the differential diagnosis of CSA.

Anogenital findings in abused children

The spectrum of anogenital findings following CSA is broad and depends on multiple factors, including the nature and chronicity of the abuse,

any objects used, the degree of force applied, the victim's age, and the extent of resistance.[8] Among the variables most strongly associated with identifiable findings are the child's report of pain, the presence of vaginal bleeding, and the interval between the most recent abusive episode and the medical examination. Structured classification systems play a central role in the standardized assessment and interpretation of such findings. The Adams classification, which stratifies findings into three tiers, has gained wide acceptance as the principal framework for evaluating anogenital examination results in cases of suspected CSA. This system has undergone iterative, consensus-driven revision, with the most recent update published in 2023 (Table I).[9] Within this scheme, findings are categorized as those suggestive of abuse and those considered specific for abuse (Table II).[9,10]

Physiological anogenital findings

The morphology of the external genitalia, and particularly of the hymen, varies with age, constitutional factors, and hormonal status. Recognized hymenal configurations include semilunar, cribriform, septate, and imperforate variants. External hymenal ridges—thin, symmetric fibrous bands located lateral to the urethra that reinforce the superior hymenal margin—may be mistaken for scarring from prior trauma. These peri-urethral supporting ligaments typically course toward the lateral vaginal wall and are of no pathological significance.[3,11] Additional physiological variants include congenital absence of the superior hymenal rim, hymenal septa (Fig. 1A), protrusions, indentations, and punctuations of the inferior hymenal margin.[3,11] Longitudinal intravaginal ridges that traverse the vaginal columns may protrude and alter the contour of the hymenal opening, representing yet another normal anatomical variation best appreciated during examination in the knee-chest position. Certain structures in the vestibular and perineal region may closely resemble healed injuries. The linea vestibularis—an avascular, midline linear structure extending from the inferior hymen to the posterior fourchette—can be confused with a healed laceration.[12] Similarly, failure of midline fusion, which extends from the fourchette along the perineum toward the

Table I. Simplified version of the Adam`s classification.

Adams I	Normal findings or findings with a medical explanation other than abuse
Adams II	Findings of unclear significance that arouse the suspicion of CSA
Adams III	Findings of injury that establish the diagnosis of CSA

CSA: child sexual abuse.

Table II. Anogenital findings specific for abuse.

Moderate specificity for abuse	High specificity for abuse
• Acute lacerations, abrasions, or extensive bruising of the labia, peri-hymenal tissues, penis, scrotum, or perineum • Scar or fresh laceration of posterior fourchette, not involving the hymen • Hymenal notch or cleft that extends > 50% of the inferior hymenal rim • Perianal scar not in the midline • Condyloma acuminata in a child older than 3 years of age • Genital herpes beyond the neonatal period	• Acute laceration of the hymen • Ecchymosis of hymen • Perianal lacerations extending into the anal sphincter • Healed hymenal transaction • Absence of hymenal tissue • Newly healed scars in the posterior fourchette of the hymen • Purulent or malodorous vaginal discharge in a young girl • Pregnancy

anus, may mimic a fresh wound. Perianal skin tags, particularly when located in the midline, are another normal variant; lateral displacement of such tags, however, may warrant further evaluation for possible CSA.[13] A summary of physiological genital and anal findings in children is provided in Table III.[3,9] Importantly, a number of examination findings formerly interpreted as indicators of abuse are now understood to represent normal anatomical variation. Measurement of hymenal opening diameter, for example, is considered obsolete and of no diagnostic utility. Tampon use may widen the hymenal orifice in pubertal girls without causing tissue injury, and activities such as horseback riding, gymnastics, stretching, and masturbation have not been shown to produce hymenal damage.

Accidental anogenital injury

Accidental trauma to the anogenital region is one of the more frequently encountered differential diagnoses.[14] Such injuries are a source of considerable alarm for both caregivers and clinicians, who must determine whether the mechanism was unintentional or inflicted and, in the latter case, whether a report to child protective services is indicated. The hypoestrogenic state of the prepubertal genitalia predisposes to more profuse bleeding than might otherwise be expected.[15] Genital trauma in prepubertal children—particularly when the hymen is involved—invariably raises the question of sexual abuse. Distinguishing accidental from inflicted injury depends critically on the concordance between the reported mechanism and the observed pattern of trauma. Straddle injuries, in which the perineum strikes an object during a fall, are a common form of accidental genital trauma with a characteristic presentation that rarely involves the hymen. An example of such an injury is illustrated in Fig. 1B. When hymenal trauma is present, suggesting possible penetrating injury, the clinician must consider the potential for significant intravaginal or intra-abdominal visceral injury, which may occasionally present with deceptively mild symptoms.[16] Published reports of accidental anogenital trauma, while limited in number, consistently emphasize the critical role of a detailed, internally consistent history in formulating the differential diagnosis. Fortunately, genital and anal injuries requiring operative intervention are uncommon in prepubertal girls; in one series of 358 girls aged 0-16 years with blunt perineal trauma, only 9% required surgical repair.[17] Anorectal injuries in children are similarly uncommon and are most often attributed to falls during play or, alternatively, to CSA. Mechanistically, straddle injuries produce crush-type trauma from falls onto objects of varying shape, typically resulting in unilateral involvement of the labia and clitoral hood. Impalement injuries, by contrast, involve penetration by a pointed object.[16] Whenever hymenal injury is identified, the possibility of deeper vaginal or intraperitoneal penetration

Table III. Physiological genital and anal findings.

Physiological findings	
Genital findings in girls	Anal findings
Various hymenal configurations: septate, semilunar, microperforate, cribriform, imperforate	Perianal erythema
External hymenal ridges	Perianal pigmentation
Longitudinal intravaginal ridges	Circular venous engorgement
Hymeneal tags	Perianal polyp-like tags
Periurethral bands	Diastasis ani
Erythema in introitus	Perianal erythema
Congenital pigmentation	
Urethral dilatation	

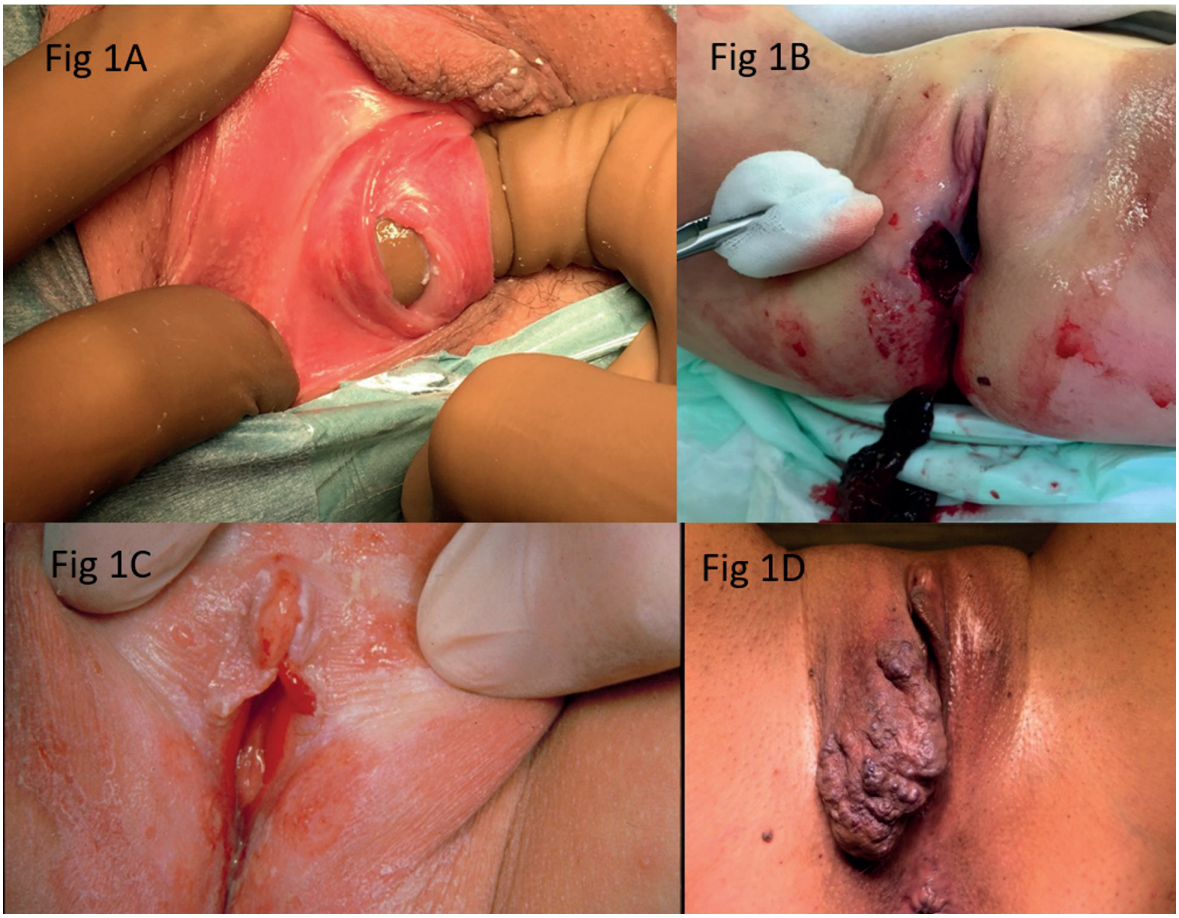

Fig. 1. A. Hymen septum, **B.** Inline-skating injury, **C.** Lichen sclerosus, **D.** Hemangioma of the right external labia.

must be excluded; evaluation may include vaginoscopy, hysteroscopy, laparoscopy, or sigmoidoscopy under anesthesia, supplemented by transrectal ultrasonography or abdominal computed tomography as clinically indicated. Among inline skating injuries, the upper extremities are involved in 50% to 86% of cases, with nearly half being fractures; pelvic or pubic injuries constitute only a small minority.[18] The distinguishing features of accidental versus inflicted anogenital injury are summarized in Table IV. Published reports consistently describe accidental genital injuries as predominantly minor, superficial, anterior, external, and unilateral. In the vast majority of accidental cases, the hymen remains uninjured; penetrating injuries of accidental origin are exceedingly rare.

Cutaneous mimickers of child sexual abuse

A variety of dermatologic conditions may produce anogenital findings that simulate CSA. Among the most important is lichen sclerosus (LS), a chronic autoimmune inflammatory dermatosis that causes epithelial atrophy, hypopigmentation, and—in some cases—prominent subcutaneous hemorrhage in the perivaginal and perianal region, creating the characteristic "hourglass" appearance (Fig. 1C). Approximately 95% of patients with LS develop genital lesions, whereas extragenital involvement occurs in only 6-15% of cases. The hymen itself is characteristically spared.[19,20] The haemorrhagic changes, fissuring, and ulceration associated with LS can closely resemble the sequelae of sexual abuse. Although the condition predominantly affects

Table IV. Accidental anogenital injuries vs child sexual abuse.

	Suggestive of accidental injury	Suggestive of sexual abuse
Anatomical localisation	Anterior, exterior	Deep
	Unilateral	Bilateral
	External Labia, Clitoris	External genitalia, Hymen
Characteristics	Superficial	Deep
	Mild	Serious
Form of Appearance	Bruises, hematomas	Tears, penetration
Invasiveness	Very rare	Common
Penetration	Very rare	Common
History	Acute, dramatic, consistent	Chronic, not consistent
Medical care	Acute, emergency	not acute, rare

postmenopausal women (with a 90% female preponderance overall), approximately 15% of cases occur in childhood. Extragenital lesions, when present, tend to involve the upper trunk, forearms, neck, and face. Patients typically report genital pruritus, pain, and bleeding; in chronic cases, labial fusion in girls or phimosis in boys may develop. The diagnosis is based on the clinical presentation and can be confirmed by targeted biopsy. While no curative therapy exists, topical corticosteroids provide significant symptomatic relief. When initially assessed by a multidisciplinary team including forensic specialists, the clinical picture can usually be distinguished from traumatic injury, and the diagnosis of LS established by routine methods. Despite its recognizable features, LS has been misdiagnosed not only as CSA but also as gonococcal vaginitis, lichen planus, psoriasis, and self-inflicted injury.[21] Several additional conditions merit consideration in the differential diagnosis of cutaneous CSA mimickers. Congenital dermal melanocytosis, phytophotodermatitis, and certain connective tissue disorders may all be erroneously attributed to abuse.[18] Infantile hemangiomas—the most common tumors of infancy, occurring with greater frequency in girls and premature infants—may present on cutaneous or mucosal surfaces within the first weeks of life.[20] Although the majority involute spontaneously, complications (most commonly ulceration, occurring in approximately 5% of cases) can occur.[22] Hemangiomas are classified as superficial (bright red, lobulated), deep (bluish subcutaneous masses), or mixed. When located in the perineal region, their red coloration and propensity for ulceration can be mistaken for abuse-related findings (Fig. 1D). Allergic contact dermatitis (ACD) is an additional diagnostic pitfall. This delayed-type hypersensitivity reaction produces well-demarcated, pruritic, eczematous plaques—with or without vesiculation—at sites of allergen exposure. In the genital area, common triggers include detergents, hygiene products, and nickel. The clinical history and distribution pattern typically suffice for diagnosis. Isolated case reports of ACD in the anogenital region being misinterpreted as CSA have been published.[23,24]

Vaginal and perianal infections mistaken as CSA

Vulvovaginitis is among the most common gynecologic complaints in prepubertal girls, attributable to several predisposing factors: the relatively small labia offer limited mechanical protection, the hypoestrogenic mucosa is thin and atrophic, and the neutral intravaginal pH favours pathogen colonization. Inadequate hygiene further promotes chronic irritation and secondary bacterial infection. Commonly implicated organisms include Staphylococcus aureus, group A β-haemolytic Streptococcus, Enterococcus, and Shigella species.

Streptococcal vulvovaginitis and perianal streptococcal cellulitis are particularly notable presentations; the latter typically manifests with painful defecation and constipation, occurs more frequently in boys, and is usually unaccompanied by systemic symptoms. In girls, vulvovaginitis may present with vaginal discharge, pruritus, and erythema. The clinical appearance of both conditions can prompt erroneous suspicion of CSA.[7] Anogenital warts (AGW) represent another challenging differential diagnosis. These papillomatous growths, caused predominantly by human papillomavirus (HPV) types 6, 11, 16, and 18, may be acquired through perinatal transmission, auto- or heteroinoculation (e.g., from hands or during diaper changes), or direct contact with symptomatic or asymptomatic HPV carriers. Perinatal acquisition is generally considered unlikely beyond the age of two years[25], although vertical transmission may explain lesions detected in infants under one year.[26] Non-sexual transmission routes—including shared bathing and towel use—have also been documented.[9] The warts are typically soft, small (<1 mm), and frequently asymptomatic, though pruritus may occur. While the presence of AGW in a child does not constitute definitive evidence of CSA, the possibility of abuse cannot be excluded regardless of the child's age, and alternative transmission routes should be actively explored.[27] Additional differential diagnoses of vulvovaginal vesicular lesions include herpes zoster and Epstein-Barr virus infection.[28]

Labial adhesion (also termed labial agglutination) describes partial or complete fusion of the labia minora or, less commonly, the labia majora, most often occurring posteriorly along the midline. The pathogenesis is not fully elucidated but is thought to involve hypoestrogenism and local inflammation. Topical estrogen cream is the first-line treatment for symptomatic cases; following pretreatment, gentle manual separation is often successful. The condition is most prevalent between the ages of one and three years; when observed in older children, the possibility of CSA should be considered.[8]

Vaginal bleeding in prepubertal girls is most frequently attributable to infection (approximately 70% of cases), with less common etiologies including foreign bodies, hemangiomas, and precocious puberty.[3] Intravaginal foreign bodies constitute a particular diagnostic challenge in pediatric gynecology; the most commonly identified foreign body is retained toilet paper, typically presenting with persistent malodorous discharge. Only 10% of affected patients initially present with the specific complaint of a possible foreign object. Ultrasonography demonstrates superior sensitivity (approximately 80%) compared with plain radiography (approximately 33%) for foreign body detection.[29] Vaginoscopy remains the diagnostic and therapeutic gold standard and is additionally required to exclude sarcoma botryoides.

Among the principal differential diagnoses of perianal findings suggestive of abuse are anal fissures secondary to chronic constipation or Crohn disease, rectal prolapse, and proctitis (e.g., due to cytomegalovirus infection).[3] Crohn disease, a chronic inflammatory bowel disorder with potential involvement of any segment of the gastrointestinal tract, frequently produces perianal fissures, fistulae, and skin tags that may raise suspicion of CSA.[30] Documented cases of Crohn disease initially misdiagnosed as CSA underscore the importance of considering this entity in the differential.[31]

Urogenital pathologies

Urethral pathologies—including hemangiomas, polyp-like tags, ureteroceles, and urethral prolapse—are infrequently encountered in pediatric practice and are consequently prone to misdiagnosis.[32] Urethral prolapse (UP) occurs predominantly in prepubertal girls between four and eight years of age, with a predilection for children of African descent. Contributing factors include increased intra-abdominal pressure (as in chronic constipation or

persistent coughing) and hypoestrogenism. The most common presenting symptom is bleeding (reported in approximately 86% of cases), followed by a visible mass at the introitus (47%) and dysuria (32%).[33] Dysuria itself is a frequent complaint associated with genital trauma of any cause, but it must also be differentiated from excessive self-stimulatory behaviour, exposure to genital irritants, and CSA.

Discussion

Pooled data from 39 prevalence studies spanning 28 countries and the period 1994-2007 indicate that 10-20% of girls and 5-10% of boys experience CSA, findings that are broadly concordant with earlier estimates.[34] A large-scale meta-analysis encompassing 323 studies and 9.9 million affected children calculated a global prevalence of 12.7%, with rates of 18.0% for girls and 7.6% for boys.[1] It has been noted that "Child sexual abuse is more common than childhood cancer, juvenile diabetes, and congenital heart disease combined…".[35] Nonetheless, an estimated 95% of cases are never reported to authorities.[36] Data from Germany remain particularly scarce, and reliable information on the frequency of specific abuse subtypes is limited. A substantial body of evidence links childhood sexual victimization to chronic mental and physical illness in adulthood.[2,3,9] Evidence-based research and consensus-driven clinical standards in this domain have gained traction in Germany and internationally only in recent years.[3]

The evaluation of a child with suspected CSA demands time, specialized training, and unwavering professional commitment. Clinicians must balance empathy with scientific rigor—an approach aptly described as "cool science for a hot topic." Although more than 90% of abused children present with unremarkable physical examination findings[9,35,37], the forensic component of the assessment remains indispensable: the absence of positive findings can itself be forensically significant. The objectives of the medical examination include corroborating or refuting the suspicion of abuse, providing acute care, screening for sexually transmitted infections, assessing for pregnancy and administering emergency contraception where appropriate, offering timely reassurance to the child and family, and collecting and documenting evidence for potential legal proceedings. In most cases, the diagnosis rests primarily on the child's disclosure, obtained through empathetic, non-leading questioning by a trained interviewer.[3] Suggestive or leading questions must be strictly avoided, and the child's statements should be recorded verbatim by professionals experienced in forensic interviewing. The physical examination, when conducted in a supportive and non-coercive manner, can have a therapeutic effect by affirming the child's bodily integrity. Where indicated, prophylaxis against sexually transmitted infections or pregnancy may be initiated. In Germany, the Bundeskinderschutzgesetz (Federal Child Protection Act) delineates the circumstances under which a physician may breach confidentiality to report relevant information to the Youth Welfare Office.

The differential diagnostic workup of suspected CSA presents a formidable challenge for healthcare professionals, pediatric and adolescent gynecologists, and forensic practitioners. Clinicians must be prepared to distinguish accidental or self-inflicted injuries and medical conditions that mimic maltreatment from genuine abuse. This process requires meticulous evaluation, adequate time, and subspecialty expertise spanning both pediatric gynecology and forensic medicine. The examiner must be conversant with the current evidence regarding the medical findings of CSA and their classification.[38] Given that normal examination findings are documented in 90-95% of evaluated cases, physical findings alone only rarely yield a definitive diagnosis. Indeed, only an estimated 5% of CSA cases are accompanied by examination findings that are

independently diagnostic. The most commonly observed genital injuries are superficial and typically heal before the abuse is disclosed or concern is raised.

Conclusions

The majority of primary care practitioners receive insufficient training in the recognition of dermatologic and systemic conditions affecting the anogenital region, while dermatologists may not routinely consider the possibility of sexual abuse in their differential. Accurate identification of CSA is of equal importance to the avoidance of false accusations, and the medical assessment constitutes only one component of a comprehensive, multidisciplinary evaluation. The consequences of diagnostic error, whether over- or under-diagnosis, extend to the child, the family, and any individual wrongly implicated. It is therefore imperative that all healthcare providers involved in pediatric care, particularly gynecologists and pediatricians, maintain a thorough awareness of conditions that mimic CSA. Careful attention to clinical clues such as congenital onset and a family history of similar dermatoses can be highly informative. Expert examination under optimal conditions, performed by a clinician familiar with the full spectrum of potential mimickers, is essential for reaching the correct diagnosis. Whenever diagnostic uncertainty persists, referral to a dermatologist should be pursued to exclude genuine skin disease. Healthcare professionals should be encouraged to report and publish cases in which non-abusive conditions were initially mistaken for CSA, thereby expanding the collective knowledge base and fostering greater diagnostic accuracy. The management of these diagnostically complex presentations demands forensic expertise, subspecialty clinical skill, and the involvement of a coordinated multidisciplinary team. Clinicians must also remain alert to the possibility that genuine abuse and coexisting medical conditions may occur simultaneously within the same patient.

Author contribution

The authors confirm contribution to the paper as follows: Review conception and design: RC; literature review: RC; analysis and interpretation of results: RC, ZAE; draft manuscript preparation: RC, ZAE. All authors reviewed the results and approved the final version of the manuscript.

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Original Article

Influenza vaccination rates in children: a multicenter nationwide study

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ABSTRACT

Background. Influenza remains a major cause of morbidity and mortality in children worldwide, yet vaccination coverage is still suboptimal in many countries. We aimed to understand parental awareness, attitudes, and determinants of vaccine uptake to guide effective strategies for increasing coverage and protecting vulnerable pediatric populations.

Method. A cross-sectional study was conducted between October 2023 and May 2024 in 38 hospitals across 23 provinces in Türkiye. Data were collected from 5002 families through face-to-face interviews, with 4404 valid responses analyzed.

Results. The overall influenza vaccination rate among children was 4.4% (n=195/4404). Vaccination coverage was slightly higher in high-risk groups compared to non-high-risk groups (5.2% vs. 3.5%, p=0.003). Factors positively associated with vaccination uptake included the presence of chronic illness in the child (15.1% in vaccinated vs. 4.7% in unvaccinated, p<0.001), higher parental education levels, and parental history of influenza vaccination (42.8% vs. 4.4%, p<0.001). Logistic regression identified poor attendance at routine pediatric check-ups, lack of awareness of influenza vaccination, and absence of private vaccination as the strongest predictors of non-vaccination.

Conclusion. Parental education and physician recommendation are the strongest determinants of childhood influenza vaccination. Embedding vaccination counseling into routine pediatric visits and implementing awareness strategies may help improve uptake, particularly in high-risk children.

Key words: children, influenza, vaccination.

Influenza is an acute respiratory viral infection caused by influenza viruses. Globally, annual seasonal influenza epidemics are estimated to result in approximately 1 billion clinical cases, 3-5 million cases of severe illness, and 290,000-650,000 deaths.[1,2] While influenza viruses can infect individuals across all age groups, children experience the highest infection rates.[3] The impact of seasonal influenza epidemics in low- and middle-income countries (LMICs) remains poorly understood. However, studies indicate that 99% of deaths due to influenza-associated lower respiratory tract infections in children under five occur in LMICs.[4]

Seasonal influenza vaccination is widely regarded as one of the most effective measures to prevent influenza and its associated complications.[4-6] The World Health Organization (WHO) recommends prioritizing children for influenza vaccination.[7] More than 40% of countries incorporate free seasonal influenza vaccination into their National Immunization Schedules, particularly in North and South America, Europe, and certain regions of Africa, Southeast Asia, and the Western Pacific.[8-12] Evidence suggests that seasonal influenza vaccination not only protects vaccinated individuals but also reduces influenza incidence in the general population.[13] Data from high- and middle-income countries highlight that vaccinating children, particularly school-aged children, yields the greatest impact on community transmission.[14,15] However, according to WHO data, Türkiye reported no data on influenza vaccine coverage rates in children for 2015 and 2017.[16,17] Despite WHO recommendations, the successful implementation of seasonal influenza vaccination programs for children faces significant challenges, leading to persistently low vaccination rates.

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Vaccine hesitancy, recognized as a critical barrier in childhood vaccination programs, was identified by the WHO in 2019 as one of the ten threats to global health. Since parents are the primary decision-makers regarding their children's healthcare, their attitudes and perceptions significantly influence vaccination decisions. Vaccine hesitancy is often driven by complex factors, including complacency, difficulties in vaccine access, and a lack of trust, as noted by a WHO-affiliated advisory group.[18]

This study aims to assess influenza vaccination rates and identify factors influencing vaccination uptake among pediatric patients in Türkiye, where influenza immunization is not included in the routine immunization schedule. The findings are expected to provide valuable insights to inform the development of effective influenza vaccination policies.

Materials and Methods

Study design and data source

This study was conducted across 38 hospitals in 23 provinces, representing various geographical regions of Türkiye. All pediatric infectious disease specialists in Türkiye were contacted and invited to participate, and the study was carried out in the centers where specialists accepted the invitation. Particular attention was given to ensuring representation from all seven geographical regions of the country. Data collection took place between October 1, 2023, and May 1, 2024, through face-to-face interviews with families of pediatric patients under 18 years of age. The questionnaire was administered by doctors, and responses from 5,002 participants who sufficiently completed the survey were included in the analysis. Ethical approval for the study was obtained from the Hacettepe University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Approval No: 2024/08-66).

The survey gathered data on influenza vaccination status, factors influencing vaccination, and demographic characteristics. The demographic section included variables such as the patient's age, gender, ethnicity, parents' age, occupation, education level, monthly income, number of children, the decision-maker regarding the child's healthcare, place of residence, number of household members, housing conditions (e.g., number of rooms), and prior visits to the same hospital or physician.

The questionnaire also included multiple-choice items regarding patients' medical history (e.g., underlying diseases), flu vaccination status and history, adherence to routine vaccination schedules, special vaccinations, and parents' flu vaccination status. Parents were queried about prior awareness of influenza vaccination, as well as their attitudes toward and perceptions of vaccination.

Attitudinal questions addressed six reasons for vaccination (e.g., belief that vaccination provides partial protection, reduces flu incidence and hospitalization, mitigates the risk of severe illness, or protects the individual and their family) and ten reasons for not vaccinating (e.g., religious objections, perceived lack of necessity or effectiveness, concerns about side effects, cost, lack of awareness, fear of social or familial disapproval, time constraints, or logistical barriers). Additionally, parents were asked about their sources of vaccination information, including doctors, pharmacists, neighbors, friends, and the media. Respondents could select multiple answers for each question.

Children identified as being in high-risk groups for severe influenza infection were specifically assessed. These included children under five years old, those aged 6 months to 18 years requiring long-term aspirin use, and those with chronic health conditions, such as metabolic diseases (e.g., diabetes), chronic respiratory diseases (e.g., asthma), chronic kidney disease, immunosuppressive conditions (e.g., chronic blood diseases, cancer, or immunosuppressive therapy), and chronic cardiovascular diseases.

Participants who declined to participate or provided insufficient or contradictory responses were excluded from the study.

Statistical analysis

The analyses were conducted using the free and open-source software R (version 4.4.1, https://cran.r-project.org) and the SPSS for Windows Version 23.0 statistical package (Chicago, IL), with the assistance of an academic biostatistician. Descriptive statistics were presented as mean±SD and frequencies (percentages) as appropriate. To compare the differences between the groups, Student's *t*-test, was used for continuous variables, and Pearson's chi-square test, Fisher's exact test and Fisher-Freeman Halton test, as appropriate, were used for categorical variables. The Fisher-Freeman-Halton test was calculated in R software using the "Fisher.test" function. Variables associated with non-vaccination in univariate analyses at a threshold of $p<0.20$ were included in the multiple binary logistic regression model. Multiple binary logistic regression analysis was performed to identify independent risk factors associated with non-vaccination status for influenza, and results were reported as odds ratios with 95% confidence intervals. Model fit was evaluated using the Hosmer–Lemeshow goodness-of-fit test, and the model's classification performance was summarized using the overall accuracy, sensitivity, and specificity. A p-value of less than 5% was considered statistically significant.

Results

This study, conducted across 38 hospitals in Türkiye, provides a comprehensive analysis of influenza vaccination rates and the factors influencing vaccination among pediatric patients (Table I). A total of 5,002 pediatric patients were surveyed. After excluding patients younger than 6 months and those with incomplete data, the analysis included 4,404 patients, of whom 195 (4.4%) had received an influenza vaccine, while 4,209 (95.6%) had not.

The mean age of vaccinated children was 7.77 ± 4.92 years, compared to 7.11 ±4.95 years in unvaccinated children, with no statistically significant difference in mean ages ($p = 0.067$). Among vaccinated children, 54.4% (n = 106) were male, while 52.3% (n = 2,200) of unvaccinated children were male.

However, the prevalence of underlying chronic conditions, such as pulmonary diseases (15.1%), neurological disorders (6.3%), and other chronic illnesses, was significantly higher in the vaccinated group compared to the unvaccinated group, with a significant difference ($p < 0.001$).

Overall influenza vaccination rates

Although the rate of being fully vaccinated with childhood vaccines was higher in the influenza-vaccinated group (97.4%) compared to the unvaccinated group (94%), the difference was not statistically significant ($p = 0.089$). None of the patients who received the influenza vaccine had completely avoided childhood vaccinations, whereas 1.7% (n = 73) of those in the unvaccinated group had never received any vaccines. Additionally, 2.6% (n = 5) of the influenza-vaccinated group were incompletely vaccinated with childhood vaccines, compared to 4.2% (n = 178) in the unvaccinated group.

Regarding special vaccines, in the vaccinated group, 6.4% (n = 12) had received the rotavirus vaccine, 5.9% (n = 11) the meningococcal vaccine, 35.1% (n = 66) both the rotavirus and meningococcal vaccines, and 3.7% (n = 7) a combination of rotavirus, meningococcal, and human papilloma virus (HPV) vaccines. Additionally, 0.5% (n = 1) received both HPV and meningococcal vaccines. In the unvaccinated group, 9.3% (n = 390) had received the rotavirus vaccine, 1.8% (n = 76) the meningococcal vaccine, 0.2% (n = 9) the HPV vaccine, 10.6% (n = 438) both the rotavirus and meningococcal vaccines, 1.1% (n = 45) a combination of rotavirus, meningococcal, and HPV vaccines, and 0.2% (n = 9) both HPV and meningococcal vaccines. The overall rate of receiving special vaccines was significantly higher in the influenza-vaccinated group compared to the unvaccinated group ($p < 0.001$).

Table I. Social characteristics of participants whom vaccinated and unvaccinated with influenza vaccine.

	Total (n=4404)	Influenza Vaccinated (n=195, 4.4%)	Influenza Unvaccinated (n=4209, 95.6%)	p-value
Demographic characteristics				
Age, years, mean±SD	7.14±4.95	7.77±4.92	7.11±4.95	0.067[a]
Male sex, n (%)	2306 (52.4%)	106 (54.4%)	2200 (52.3%)	0.568[b]
Underlying diseases, n (%)				<0.001[c]
No disease	3378 (76.9%)	113 (58.9%)	3265 (77.8%)	
Congenital heart	52 (1.2%)	2 (1%)	54 (1.2%)	
Endocrinological	73 (1.7%)	3 (1.6%)	70 (1.7%)	
Gastrointestinal	58 (1.3%)	2 (1%)	56 (1.3%)	
Hematologic	40 (0.9%)	3 (1.6%)	37 (0.9%)	
Immunodeficiency	33 (0.8%)	1 (0.5%)	32 (0.8%)	
Kidney	52 (1.2%)	4 (2.1%)	48 (1.1%)	
Malignancy	22 (0.5%)	3 (1.6%)	19 (0.5%)	
Metabolic	25 (0.6%)	2 (1%)	23 (0.5%)	
Neurologic	163 (3.7%)	12 (6.3%)	151 (3.6%)	
Pulmonary	225 (5.1%)	29 (15.1%)	196 (4.7%)	
Rheumatological	102 (2.3%)	4 (2.1%)	98 (2.3%)	
Others[*]	166 (3.8%)	14 (7.3%)	152 (3.6%)	
Childhood vaccination coverage, n (%)				0.089[b]
Never vaccinated	73 (1.7%)	-	73 (1.7%)	
Incompletely vaccinated	183 (4.2%)	5 (2.6%)	178 (4.2%)	
Full vaccinated	4136 (94.2%)	189 (97.4%)	3947 (94%)	
Special vaccinations coverage, n (%)				<0.001[c]
Never vaccinated	3242 (75.3%)	98 (50.3%)	3151 (76.5%)	
Rotavirus vaccine	402 (9.1%)	12 (6.4%)	390 (9.3%)	
Meningococcus vaccine	89 (2.1%)	11 (5.9%)	76 (1.8%)	
HPV vaccine	9 (0.2%)	-	9 (0.2%)	
Rotavirus+meningococcus	504 (11.7%)	66 (35.1%)	438 (10.6%)	
Rotavirus+meningococcus+ HPV	52 (1.2%)	7 (3.7%)	45 (1.1%)	
Meningococcus+ HPV	10 (0.2%)	1 (0.5%)	9 (0.2%)	
Parental characteristics				
Age, years, mean±SD				
Mother	35.96±6.89	37.19±6.74	35.90±6.92	0.012[a]
Father	39.55±7.44	40.56±7.41	39.51±7.46	0.060[a]
Education level of mother, n (%)				<0.001[b]
Illiterate	182 (4.1%)	6 (3.1%)	176 (4.2%)	
Primary education	120 (2.7%)	3 (1.5%)	117 (2.8%)	
Lower secondary education	1496 (34.1%)	60 (30.8%)	1436 (34.2%)	
Upper secondary education	1205 (27.4%)	51 (26.2%)	1154 (27.5%)	
Undergraduate	1122 (25.5%)	46 (23.6%)	1076 (25.6%)	
Graduate	267 (6.1%)	29 (14.9%)	238 (5.7%)	

Numerical data are presented as mean±SD. Categorical variables reported as frequency (percent).
Differences between groups were analyzed using: [a]Student's t-test, [b]Pearson chi-squared test, [c] Fisher-Freeman Halton test.
*: Bulgarian immigrant, Balkan, Afghan, Iraqi, Turkmen, Sudanese
HPV: human papilloma virus, SD: standard deviation.

Table I. Continued.

	Total (n=4404)	Influenza Vaccinated (n=195, 4.4%)	Influenza Unvaccinated (n=4209, 95.6%)	p-value
Education level of father, n (%)				<0.001[b]
Illiterate	71 (1.6%)	1 (0.5%)	70 (1.7%)	
Primary education	76 (1.7%)	5 (2.6%)	71 (1.7%)	
Lower secondary education	1325 (30.3%)	58 (29.7%)	1267 (30.3%)	
Upper secondary education	1382 (31.6%)	43 (22.1%)	1339 (32%)	
Undergraduate	1195 (27.3%)	49 (25.1%)	1146 (27.4%)	
Graduate	331 (7.6%)	39 (20%)	292 (7%)	
Working status of mother, n (%)				0.008[b]
Government employee	842 (19.2%)	53 (27.7%)	789 (18.8%)	
Homemaker	2950 (67.2%)	113 (59.2%)	2837 (67.6%)	
Other	596 (13.6%)	25 (13.1%)	571 (13.6%)	
Working status of father, n (%)				0.055[b]
Government employee	1025 (23.5%)	56 (29.2%)	969 (23.2%)	
Private-sector employee	1714 (39.3%)	61 (31.8%)	1653 (39.6%)	
Other	1626 (37.3%)	75 (39.1%)	1551 (37.2%)	
Number of siblings, n (%)				0.150[b]
Only child	880 (20.0%)	49 (25.1%)	831 (19.8%)	
Two children in the family	1916 (43.6%)	84 (43.1%)	1832 (43.7%)	
Three or more children	1594 (36.3%)	62 (31.8%)	1532 (36.5%)	
Decision maker for child, n (%)				0.009[b]
Mother	2428 (55.3%)	114 (58.5%)	2314 (55.2%)	
Father	405 (9.2%)	13 (6.7%)	392(9.3%)	
Other	79 (1.8%)	9 (4.6%)	70 (1.7%)	
Father and Mother	1478 (33.7%)	59 (30.3%)	1419 (33.8%)	
Socioeconomic indicators, n (%)				
Income status				0.677[b]
Under $1000	1712 (39.3%)	74 (37.9%)	1638 (39.4%)	
Over $1000	2370 (54.4%)	106 (54.4%)	2264 (54.4%)	
Not specified	272 (6.2%)	15 (7.7%)	257 (6.2%)	
Number of rooms in the house				0.023[b]
2+1	1314 (30.3%)	64 (32.8%)	1250 (30.2%)	
3+1	2479 (57.2%)	96 (49.2%)	2383 (57.6%)	
4+1	542 (12.5%)	35 (17.9%)	507 (12.2%)	
House type				0.092[b]
Slum	316 (7.2%)	9 (4.6%)	307 (7.3%)	
Apartment	3474 (79.2%)	151 (77.4%)	3323 (79.3%)	
Other	598 (13.6%)	35 (17.9%)	563 (13.4%)	

Numerical data are presented as mean±SD. Categorical variables reported as frequency (percent).
Differences between groups were analyzed using: [a]Student's t-test, [b]Pearson chi-squared test, [c] Fisher-Freeman Halton test.
*: Bulgarian immigrant, Balkan, Afghan, Iraqi, Turkmen, Sudanese
HPV: human papilloma virus, SD: standard deviation.

Table I. Continued.

	Total (n=4404)	Influenza Vaccinated (n=195, 4.4%)	Influenza Unvaccinated (n=4209, 95.6%)	p-value
Presence of grandparents or other individuals living in the same home				0.996[b]
No	3766 (85.6%)	167 (85.6%)	3599 (85.6%)	
Yes	632 (14.4%)	28 (14.4%)	604 (14.4%)	
Healthcare Behaviors, n (%)				
Routine control in the same doctor or hospital				<0.001[b]
Regular follow-up	2767 (63.0%)	170 (87.2%)	2597 (62%)	
Irregular follow-up	1201 (27.4%)	19 (9.7%)	1182 (28.2%)	
No prior follow-up	422 (9.6%)	6 (3.1%)	416 (9.9%)	
Influenza vaccination status of parents in this year				<0.001[b]
Yes	267 (6.1%)	83 (42.8%)	184 (4.4%)	
No	4111 (93.9%)	111 (57.2%)	4000 (95.6%)	
How many times have you had an influenza vaccine before?				<0.001[b]
Have received the vaccine at least once in your life	752 (17.2%)	75 (39.1%)	677 (16.2%)	
Getting the vaccine regularly	149 (3.4%)	51 (26.6%)	98 (2.3%)	
Never happened	3470 (79.4%)	66 (34.4%)	3404 (81.5%)	
Have you ever heard of the influenza vaccine?				<0.001[b]
Yes	3187 (72.7%)	181 (93.3%)	3006 (71.7%)	
No	1198 (27.3%)	13 (6.7%)	1185 (28.3%)	
Who recommended the influenza vaccine?				<0.001[b]
Doctor	1866 (51.4%)	156 (84.8%)	1710 (49.6%)	
Neighbor	125 (3.4%)	2 (1.1%)	123 (3.6%)	
Pharmacist	135 (3.7%)	2 (1.1%)	133 (3.9%)	
Media	491 (13.5%)	9 (4.9%)	482 (14%)	
Friend	227 (6.2%)	4 (2.2%)	223 (6.5%)	
Other	789 (21.7%)	11 (6%)	778 (22.6%)	
Ethnicity				NA
Not wanted to specify	909 (20.8%)	49 (25.5%)	860 (20.6%)	
Turkish	3108 (71.3%)	132 (68.8%)	2976 (71.4%)	
Kurdish	238 (5.5%)	6 (3.1%)	232 (5.6%)	
Arab	45 (1.0%)	2 (1.0%)	43 (1.0%)	
Syrian	38 (0.9%)	-	38 (0.9%)	
Other*	23 (0.5%)	3 (1.6%)	20 (0.5%)	

Numerical data are presented as mean±SD. Categorical variables reported as frequency (percent).
Differences between groups were analyzed using: [a]Student's t-test, [b]Pearson chi-squared test, [c] Fisher-Freeman Halton test.
*: Bulgarian immigrant, Balkan, Afghan, Iraqi, Turkmen, Sudanese
HPV: human papilloma virus, SD: standard deviation.

Parental sociodemographic characteristics

Both maternal and paternal education levels were significantly higher in the influenza-vaccinated group compared to the unvaccinated group ($p < 0.001$). The proportion of mothers employed as government employees was 27.7% (n = 53) in the vaccinated group, compared to 18.8% (n = 789) in the unvaccinated group, with this difference being statistically significant ($p < 0.001$). There was no significant difference between the groups regarding the number of siblings ($p = 0.150$). Notably, mothers were the primary decision-makers for their child's healthcare in 58.5% (n = 114) of cases in the vaccinated group, compared to 55.2% (n = 2,314) in the unvaccinated group, a difference that was statistically significant ($p = 0.009$).

There were no significant differences between the groups in terms of income status, number of rooms, or housing type ($p = 0.677$, $p = 0.023$, $p = 0.092$, respectively). Similarly, no significant difference was observed regarding the presence of other individuals in the household ($p = 0.996$).

Healthcare behaviors and parental vaccine history

The proportion of children attending the same doctor for regular check-ups was higher in the vaccinated group, and this difference was statistically significant ($p < 0.001$).

The rate of parents receiving influenza vaccination was 42.8% (n = 83) in the vaccinated group, compared to 4.4% (n = 184) in the unvaccinated group, a significant difference ($p < 0.001$). Furthermore, the rate of children receiving influenza vaccination either regularly or at least once in the past was higher in the vaccinated group ($p < 0.001$).

Among participants, 93.3% (n = 181) in the vaccinated group had heard of the influenza vaccine, while 71.7% (n = 3,006) in the unvaccinated group had heard of it, with the vaccinated group having significantly higher awareness ($p < 0.001$). Additionally, 84.8% (n = 156) of those in the vaccinated group learned about the influenza vaccine through a doctor's recommendation, compared to 49.6% (n = 1,710) in the unvaccinated group. This difference was also statistically significant ($p < 0.001$).

When examining the factors affecting the attitudes and perceptions of participants and participants in the risk group regarding influenza vaccination according to the vaccination status of their children, a high rate in both groups (Fig. 1) believed that vaccination would reduce the risk of serious illness in vaccinated individuals and that vaccinated individuals would have fewer flu attacks. Among those who were not vaccinated, a high rate in both groups were not informed about the necessity of vaccination and were unaware of the necessity of vaccination.

High-risk vs. non–high-risk groups

When assessing patients based on their risk group status, there were 2,327 patients in the risk group and 2,077 in the non-risk group (Table II). The mean age of the risk group was significantly lower (4.70 ± 4.65 years) compared to the non-risk group (9.87 ± 3.69 years), with a statistically significant difference ($p < 0.001$). The proportion of male patients in the risk group was 54.2% (n = 1,262), compared to 50.3% (n = 1,044) in the non-risk group, and this difference was statistically significant ($p = 0.008$).

The vaccination rate in the risk group was 5.2% (n = 123), significantly higher than the 3.5% (n = 72) in the non-risk group ($p = 0.003$). However, the full vaccination rate was lower in the risk group (93.2%, n = 2,167) compared to the non-risk group (95.2%, n = 1,969), and this difference was statistically significant ($p < 0.001$). Among those with incomplete vaccination, 5.2% (n = 121) were in the risk group, compared to 3% (n = 62) in the non-risk group. Those who had never been vaccinated comprised 1.5% (n = 36) in the risk group and 1.8% (n = 37) in the non-risk group.

In the risk group, the rates of receiving special vaccines were as follows: rotavirus vaccine

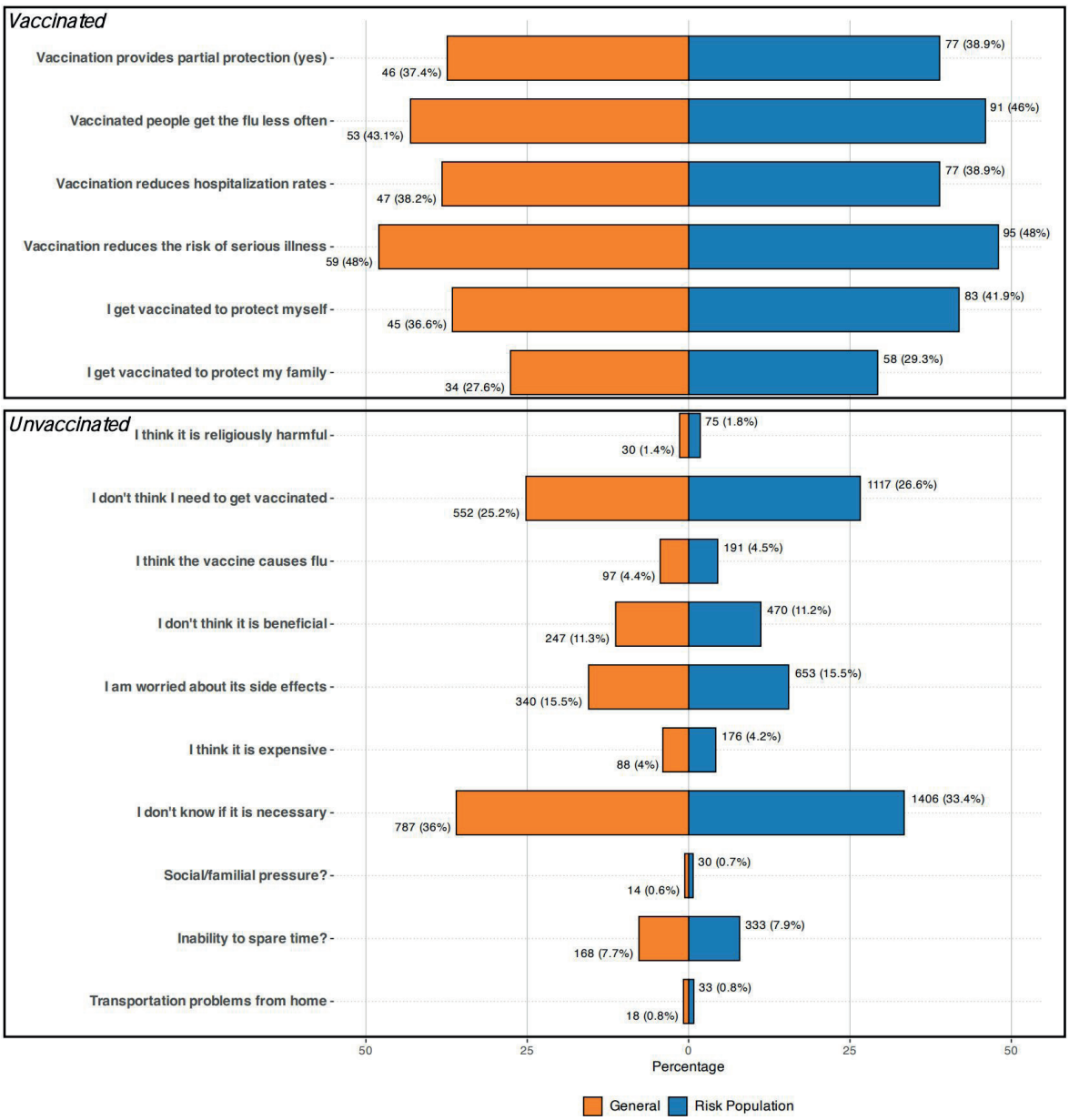

Fig. 1. Factors affecting the attitudes and perceptions of all participants and participants in the risk group about influenza vaccination according to children's influenza vaccination status.

10% (n = 230), meningococcal vaccine 2.1% (n = 48), HPV vaccine 0.1% (n = 2), rotavirus and meningococcal vaccines 13.5% (n = 309), rotavirus, meningococcal, and HPV vaccines 1.5% (n = 34), and HPV and meningococcal vaccines 0.3% (n = 6). In the unvaccinated group, the corresponding rates were: rotavirus vaccine 8.5% (n = 171), meningococcal vaccine 2% (n = 41), HPV vaccine 0.3% (n = 7), rotavirus and meningococcal vaccines 9.7% (n = 195), rotavirus, meningococcal, and HPV vaccines 0.9% (n = 18), and HPV and meningococcal vaccines 0.2% (n = 4). The prevalence of chronic diseases such as pulmonary (9.7%, n = 225) and neurological (7%, n = 163) conditions was significantly higher in the risk group ($p < 0.001$).

Table II. Social characteristics of participants in risk and non-risk group for severe influenza infection.

	Risk group (n=2327)	Non-Risk group (n=2077)	p-value
Demographic characteristics			
Age, years, mean±SD	4.70±4.65	9.87±3.69	<0.001[b]
Sex, male, n (%)	1262 (54.2%)	1044 (50.3%)	0.008[a]
Vaccination coverage, n (%)			
Influenza			0.003[a]
No	2189 (94.7%)	1991 (96.5%)	
Yes	123 (5.2%)	72 (3.5%)	
Childhood			<0.001[a]
Never had it done	36 (1.5%)	37 (1.8%)	
Incompletely vaccinated	121 (5.2%)	62 (3.0%)	
Full	2167 (93.2%)	1969 (95.2%)	
Special			<0.001[c]
Never had it done	1661 (72.5%)	1581 (78.4%)	
Rotavirus vaccine	230 (10.0%)	171 (8.5%)	
Meningococcus vaccine	48 (2.1%)	41 (2.0%)	
HPV vaccine	2 (0.1%)	7 (0.3%)	
Rotavirus+meningococcus	309 (13.5%)	195 (9.7%)	
Rotavirus+meningococcus+HPV	34 (1.5%)	18 (0.9%)	
Meningococcus+HPV	6 (0.3%)	4 (0.2%)	
Underlying disease, n (%)			
No disease	1303 (56.3%)	2075 (99.9%)	<0.001[a]
Congenital heart	54 (2.3%)	-	
Endocrinological	73 (3.2%)	-	
Gastrointestinal	58 (2.5%)	-	
Hematologic	40 (1.7%)	-	
Immunodeficiency	33 (1.4%)	-	
Renal	51 (2.2%)	1 (<0.1%)	
Malignancy	22 (1.0%)	-	
Metabolic	25 (1.1%)	-	
Neurologic	163 (7.0%)	-	
Pulmoner	225 (9.7%)	-	
Rheumatological	102 (4.4%)	-	
Others[*]	165 (7.1%)	1 (<0.1%)	
Parental characteristics			
Age, years, mean±SD			
Mother	34.03±6.92	38.14±6.22	<0.001[b]
Father	37.42±7.40	41.99±6.74	<0.001[b]

Numerical data are presented as mean±SD. Categorical variables reported as frequency (percent).
Differences between groups were analyzed using: [a]Pearson chi-squared test, [b]Student's t-test, [c] Fisher-Freeman Halton test.
HPV: human papilloma virus, SD: standard deviation.

Table II. Continued.

	Risk group (n=2327)	Non-Risk group (n=2077)	p-value
Education level of mother, n (%)			<0.001[a]
Illiterate	100 (4.3%)	82 (4.0%)	
Primary education	61 (2.6%)	59 (2.9%)	
Lower secondary education	763 (32.8%)	733 (35.4%)	
Upper secondary education	634 (27.3%)	571 (27.6%)	
Undergraduate	650 (28.0%)	472 (22.8%)	
Graduate	116 (5.0%)	151 (7.3%)	
Education level of father, n (%)			0.003[a]
Illiterate	46 (2.0%)	25 (1.2%)	
Primary education	30 (1.3%)	46 (2.2%)	
Lower secondary education	693 (29.9%)	632 (30.6%)	
Upper secondary education	743 (32.1%)	639 (31.0%)	
Undergraduate	654 (28.2%)	541 (26.2%)	
Graduate	152 (6.6%)	179 (8.7%)	
Working status of mother, n (%)			<0.001[a]
Government employee	428 (18.4%)	414 (20.0%)	
Homemaker	1624 (70.0%)	1326 (64.1%)	
Other	268 (11.6%)	328 (15.9%)	
Working status of father, n (%)			0.416[a]
Government employee	534 (23.1%)	491 (23.9%)	
Private-sector employee	928 (40.2%)	786 (38.2%)	
Other	847 (36.7%)	779 (37.9%)	
Number of siblings, n (%)			<0.001[a]
Only child	625 (26.9%)	255 (12.3%)	
Two children in the family	951 (41.0%)	965 (46.7%)	
Three or more children	746 (32.1%)	848 (41.0%)	
Decision maker for child, n (%)			<0.001[a]
Mother	1354 (58.4%)	1074(51.9%)	
Father	173 (7.5%)	232 (11.2%)	
Other	37 (1.6%)	42 (2.0%)	
Father and Mother	755 (32.6%)	723 (34.9%)	
Socioeconomic indicators, n (%)			
Income status			<0.001[a]
Under $1000	967 (42.0%)	745 (36.3%)	
Over $1000	1211 (52.6%)	1159(56.5%)	
Not specified	126 (5.5%)	146 (7.1%)	
Number of rooms in the house			<0.001[c]
2+1	754 (32.7%)	559 (27.5%)	
3+1	1255 (54.5%)	1224(60.2%)	
4+1	293 (12.7%)	249 (12.3%)	

Numerical data are presented as mean±SD. Categorical variables reported as frequency (percent).
Differences between groups were analyzed using: [a]Pearson chi-squared test, [b]Student's t-test, [c] Fisher-Freeman Halton test.
HPV: human papilloma virus, SD: standard deviation.

Table II. Continued.

	Risk group (n=2327)	Non-Risk group (n=2077)	p-value
House type			0.007[a]
Slum	193 (8.3%)	123 (5.9%)	
Apartment	1805 (77.8%)	1669 (80.7%)	
Other	321 (13.8%)	277 (13.4%)	
Presence of grandparents or other individuals living in the same home			0.016[a]
No	1963 (84.4%)	1803 (87%)	
Yes	362 (15.6%)	270 (13%)	
Routine control in the same doctor or hospital			<0.001[a]
Regular follow-up	1561 (67.3%)	1206 (58.2%)	
Irregular follow-up	541 (23.3%)	660 (31.9%)	
No prior follow-up	217 (9.4%)	205 (9.9%)	
Influenza vaccination status of parents in this year			0.722[a]
Yes	144 (6.2%)	123 (6%)	
No	2171 (93.8%)	1940 (94%)	
How many times have you had an influenza vaccine before?			0.006[a]
Have received the vaccine at least once in your life:	367 (15.8%)	385 (18.8%)	
Getting the vaccine regularly:	92 (4%)	57 (2.8%)	
Never happened:	1859 (80.2%)	1611 (78.5%)	
Have you ever heard of the influenza vaccine?			0.504[a]
Yes	1696 (73.1%)	1491 (72.2%)	
No	624 (26.9%)	574 (27.8%)	
Who recommended the influenza vaccine?			0.373[a]
Doctor	971 (50.6%)	895 (52.2%)	
Neighbor	62 (3.2%)	63 (3.7%)	
Pharmacist	78 (4.1%)	57 (3.3%)	
Media	274 (14.3%)	217 (12.7%)	
Friend	112 (5.8%)	115 (6.7%)	
Other	423 (22%)	366 (21.4%)	

Numerical data are presented as mean±SD. Categorical variables reported as frequency (percent).
Differences between groups were analyzed using: [a]Pearson chi-squared test, [b]Student's t-test, [c] Fisher-Freeman Halton test.
HPV: human papilloma virus, SD: standard deviation.

Parents in the risk group were older ($p < 0.001$). The education levels of both mothers and fathers in the risk group were lower, and these differences were statistically significant ($p < 0.001$ and $p = 0.003$, respectively). A higher proportion of mothers in the risk group were homemakers ($p < 0.001$). Additionally, the risk group had a higher number of children, with this difference being statistically significant ($p < 0.001$).

Mothers acted as decision-makers for the child's healthcare in 58.4% (n = 1,354) of cases in the risk group, compared to 51.9% (n = 1,074) in the non-risk group, with this difference

being statistically significant. The proportion of families with an income below $1,000 was higher in the risk group (42% vs. 36.3%), with a statistically significant difference ($p < 0.001$). The risk group lived in smaller homes and more often in substandard housing, with significant differences in both categories ($p < 0.001$ and $p = 0.007$, respectively). The presence of additional individuals living in the same household was higher in the risk group.

The proportion of individuals in the risk group who followed up regularly with the same doctor was higher (67.3% vs. 58.2%), and this difference was statistically significant ($p < 0.001$). The rate of parents who received the influenza vaccination during the current season was higher in the risk group.

The rate of individuals who did not receive the flu vaccine in previous years was higher in the risk group, with a statistically significant difference ($p = 0.006$). The proportion of individuals who had previously heard of the influenza vaccine was higher in the risk group (73.1%, n = 1,696) compared to the non-risk group (72.2%, n = 1,491). Additionally, there was no significant difference between the two groups in terms of those who recommended the influenza vaccine ($p = 0.373$).

The multiple binary logistic regression analysis of individuals who did not receive the vaccine revealed that the most significant independent variables were not attending routine doctor check-ups and not having previously heard of the influenza vaccine (Table III).

In the multiple binary logistic regression analysis (Table III), living in an apartment was associated with higher odds of non-vaccination compared with the reference housing category ("Other") (odds ratio [OR]=2.059, 95% confidence interval [CI]: 1.318-3.218; p=0.002). Compared with individuals who reported attending routine check-ups ("Yes"), those attending occasionally (OR=3.270, 95% CI: 1.933-5.532; p<0.001) and those who never attended (OR=3.317, 95% CI: 1.408-7.815; p=0.006) had higher odds of non-vaccination. Additionally, variables referenced to "Yes" were significantly associated with non-vaccination, including influenza vaccination status this year (OR=4.280, 95% CI: 2.689-6.812; p<0.001), having heard of the influenza vaccine previously (OR=3.510, 95% CI: 1.715-7.187; p<0.001), and private vaccination (OR=2.126, 95% CI: 1.422-3.178; p<0.001). Regarding vaccination frequency, compared with "Regular" vaccination, being vaccinated at least once was associated with higher odds of non-vaccination (OR=2.738, 95% CI: 1.652-4.539; p<0.001), while never being vaccinated showed a markedly higher odds (OR=7.614, 95% CI: 4.124-14.056; p<0.001). Model fit was assessed using the Hosmer–Lemeshow test (χ^2=2.498; p=0.962), indicating no evidence of poor fit. At the 0.50 probability cutoff, the fitted model showed 99.7% sensitivity for identifying non-vaccinated individuals and 10.7% specificity

Table III. Results of logistic regression analysis for risk factors affecting non-vaccination status of Influenza

Variables	OR (95% CI)	p-value
House type (reference category: other)		
Slum	1.535 (0.650 – 3.625)	0.329
Apartment	2.059 (1.318 – 3.218)	0.002
Routine control in the same doctor or hospital (reference category: regular)		
Irregular follow-up	3.270 (1.933 – 5.532)	<0.001
No prior follow-up	3.317 (1.408 – 7.815)	0.006
Not having heard of the influenza vaccine before (reference category: yes)	3.510 (1.715 – 7.187)	<0.001
No special vaccination (reference category: yes)	2.126 (1.422 – 3.178)	<0.001

Hosmer-Lemeshow chi-squared=2.498, p-value=0.962; overall accuracy=95.9.
CI: confidence interval, OR: odds ratio.

for identifying vaccinated individuals, with an overall accuracy of 95.9%. The relatively low specificity is likely related to the pronounced class imbalance (a substantially smaller vaccinated group), which can bias classification toward the majority class.

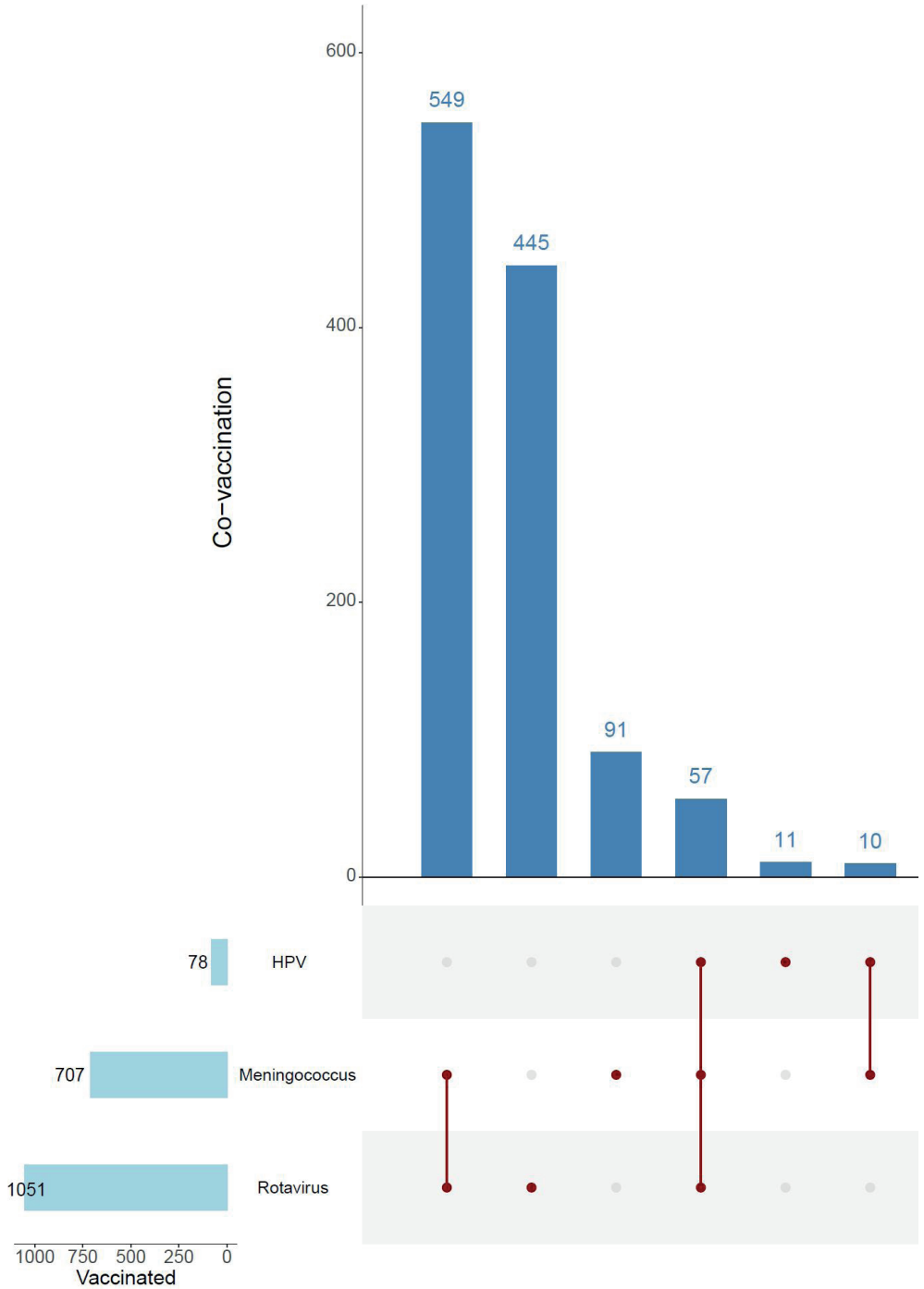

Fig. 2. Proportion of children vaccinated with non-national vaccination programme, special vaccines in total data.

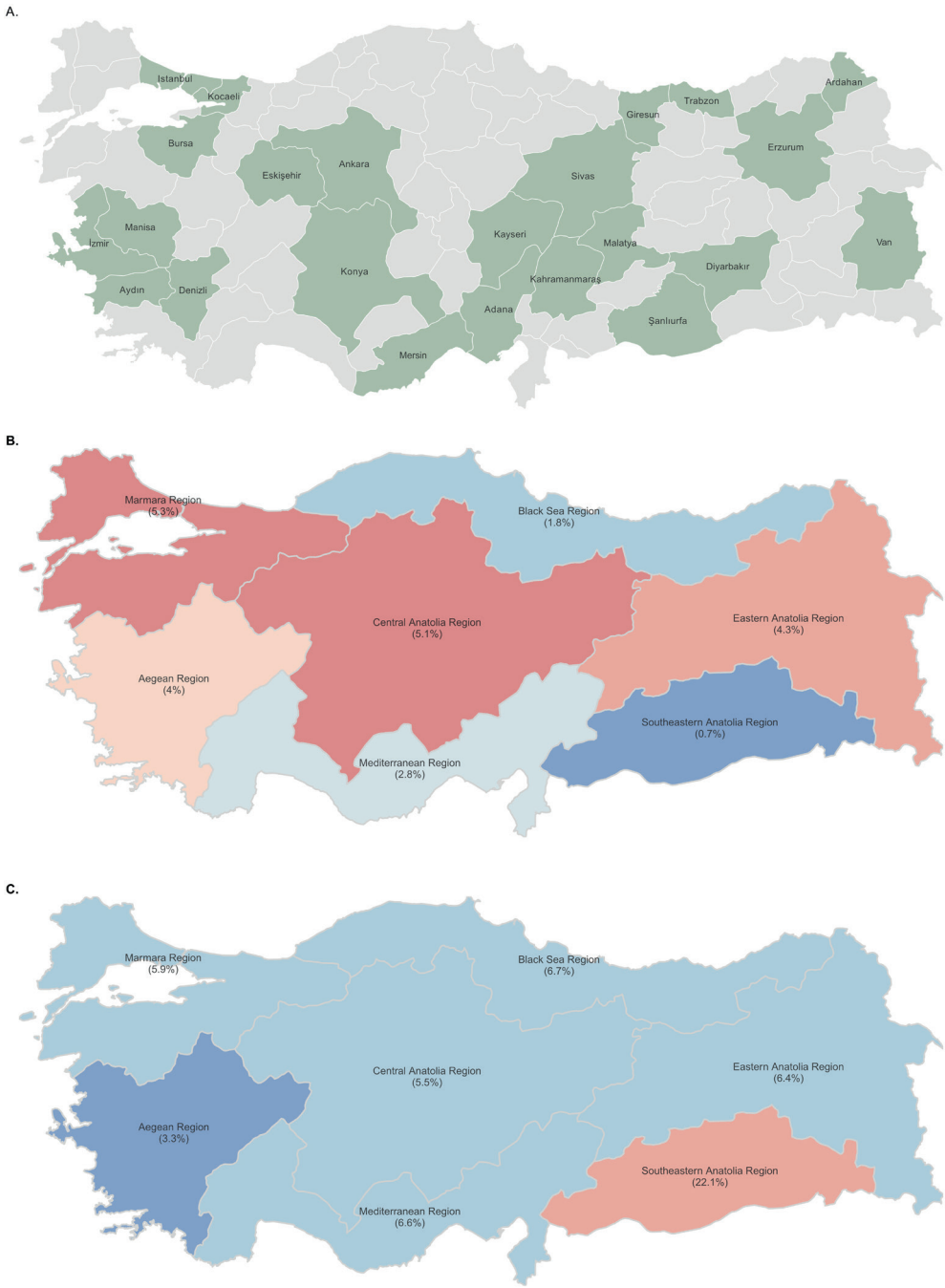

Fig. 3. Regional distribution of influenza vaccination and childhood immunization status in Türkiye. **(A)** Map of Türkiye showing the 23 provinces across all seven geographical regions that contributed survey data (n=4404). **(B)** Regional influenza vaccination coverage among children, ranging between 3–6% across different regions, with an overall vaccination rate of 4.5%. Children in the risk group (n=2327) had a significantly higher vaccination rate (5.2%) compared to those in the non-risk group (3.5%). **(C)** Regional distribution of children who had not received routine childhood vaccines included in the national immunization schedule. Overall, 73 children (1.7%) were never vaccinated, while 4.2% were incompletely vaccinated. The majority (94.2%) were fully vaccinated, though the proportion of unvaccinated children varied slightly across regions.

Among the 5002 patients included in the survey, 93% were fully vaccinated, 5% were incompletely vaccinated, and 2% had not been vaccinated at all. Of the patients, 3716 had not received any special vaccinations, while 1051 had received the rotavirus vaccine, 707 had received the meningococcal vaccine, and 78 had received the HPV vaccine (Fig. 2).

The distribution of provinces contributing survey data to our study is shown on the map of Türkiye (Fig. 3A). According to the obtained data, the regional distribution of influenza vaccination rates in Türkiye and the rates of not having childhood vaccines included in the Ministry of Health vaccination calendar are shown (Fig. 3B and Fig. 3C).

Discussion

In Türkiye, influenza vaccination rates among children have been found to be quite low at only 4.4%, largely because it is not routinely included in the national immunization schedule outside of target groups. Furthermore, even when specific groups are included, no childhood group has a vaccination rate exceeding 5.2%. Although data on influenza vaccination rates among children in Türkiye are limited, existing studies provide a consistent picture. For instance, data published from the 2016-2017 autumn-winter period revealed that the influenza vaccination rate among hospitalized pediatric patients stood at just 1.6%.[19] In a study conducted under the leadership of our department, involving approximately 19 centers and including 1032 hospitalized pediatric patients with influenza, the vaccination rate among children was found to be 1.2% (unpublished data). Another Turkish study focusing on both adult and pediatric cases reported vaccination rates of only 0.3% and 2.1% for children under five in the 2014-2015 and 2015-2016 seasons, respectively.[20] In stark contrast, countries like the United Kingdom and the United States report much higher influenza vaccination coverage in young children. For instance, the United Kingdom has a combined vaccination rate of 44.4% among children aged 2-3 years during recent seasons.[21] Similarly, influenza vaccination rates for American children between 6 months and 17 years exceeded 55% annually from 2019 to 2023. However, despite these seemingly high rates, it is still observed that the majority of children who die from influenza in the United States are unvaccinated. According to estimates from the Centers for Disease Control and Prevention (CDC), during the 2022-2023 influenza season, approximately 21,000 individuals died from flu-related illnesses or complications, including 176 children, the majority of whom had not received the influenza vaccination.[22] An interesting point is that even in countries such as Peru, where influenza vaccination is provided free of charge, vaccination rates can remain very low.[23]

Therefore, in this study, our primary aim was to understand the factors, particularly from the parents' perspective, that contribute to vaccination uptake, or rather the lack thereof.

In the current study, it is observed that individuals with underlying health conditions are more likely to be vaccinated. For these children, the most motivating factor for vaccination appears to be information provided by their doctors. On the other hand, those who did not receive the vaccine were mostly influenced by information they encountered in the media. These data highlights that the most reliable and accurate information comes from healthcare professionals. Additionally, this finding emphasizes the importance of enhancing risk communication strategies to promote vaccination, with a particular focus on high-risk groups such as children, pregnant women, and older adults, who are more vulnerable to influenza-related complications.[23-25]

Our logistic regression analysis further confirmed this, showing that poor attendance at routine pediatric check-ups, lack of awareness of influenza vaccination, and absence of private vaccinations were strong predictors of non-vaccination. These findings highlight critical gaps in both preventive healthcare utilization and public awareness. From a policy perspective,

integrating influenza vaccination counseling into routine pediatric visits and implementing nationwide awareness campaigns could be effective strategies to improve uptake. Strengthening these preventive healthcare opportunities may therefore play a pivotal role in reducing influenza-related morbidity and mortality in children.

Higher educational levels appear to significantly influence vaccine acceptance. The proportion of mothers with higher education is 14.9%, which is three times higher than the rate among parents in the unvaccinated group. This becomes even more significant considering that nearly 60% of decision-making within the household is typically made by mothers. Similarly, the percentage of fathers with higher education is 20%, which is also three times higher than the rate observed among parents in the unvaccinated group. Another piece of evidence supporting the importance of parental awareness is the high vaccination rate among the parents themselves. In light of the data from our study, the primary behavioral pattern behind not being vaccinated against influenza is not, as commonly believed, concerns about vaccine side effects. Rather, it is the lack of awareness regarding the necessity of the influenza vaccine and, in some cases, the importance of vaccinating their children. Similarly, a systematic review reported that sociodemographic factors, including age and education, along with the lack of recommendations from healthcare professionals to the primary decision-makers (i.e., parents of children aged 6–59 months), were identified as the most common barriers to seasonal influenza vaccine uptake in children.[24] In our study, a considerable proportion of parents also reported "fear of side effects," highlighting the need for physicians to address safety concerns through clear, evidence-based communication.

Although factors such as a physician's guidance take precedence in general vaccination, economic reasons appear to be influential in the vaccination of high-risk groups. A previous study conducted by our center demonstrated that underlying diseases in children are the most significant risk factor for both hospital admission and intensive care unit (ICU) admission. Furthermore, the median age of children requiring ICU admission due to influenza was reported to be under 2 years.[26] In another study, which included our department, comparing pediatric patients with coronavirus disease 2019 (COVID-19) and influenza, it was observed how influenza particularly affects children under the age of five.[27] When examining the data from our study, it is evident that the vaccinated individuals tend to be older. These findings, therefore, underscore the critical importance of including children under 5 years of age in healthcare coverage, particularly in resource-limited countries like Türkiye.

The vaccination rate for all childhood vaccines among those vaccinated for influenza is 97.4%. However, our study identified that 73 (1.7%) children had not received any vaccinations as part of the national immunization program. The overall vaccination rate within our cohort was found to be 94.2%. This rate is notably lower than the figures reported to the World Health Organization on Türkiye.[28] This decline is a significant indicator of the extent to which vaccine refusal in Türkiye has contributed to recent years. It was also observed that 35.4% of parents in this group had administered private vaccines that are not included in Türkiye's national immunization schedule to their children, a rate that is three times higher than that of children who were not vaccinated against influenza. This finding further illustrates the willingness of families who have vaccinated their children against influenza to pursue additional vaccinations, independent of financial considerations. It reinforces the notion that, for parents, the key determinant in vaccination decisions is not cost, but rather awareness and understanding of the importance of immunization.

This study has several limitations. Although the survey was conducted face-to-face, which

generally enhances the accuracy of responses compared to anonymous surveys, it still carries the potential for interviewer bias. The presence of the interviewer may have influenced participants' answers, especially when it comes to sensitive topics like vaccination decisions. Additionally, while the sample included over 5,000 children and their parents, the study sample may not be fully representative of the wider population, limiting the generalizability of the findings. Other factors, such as healthcare access, socioeconomic status, and cultural beliefs, were not comprehensively explored, which could affect vaccination decisions but were outside the scope of this survey. Finally, as the study was cross-sectional, it provides a snapshot of associations at a single point in time and does not allow for the determination of causal relationships.

In conclusion, this study highlights the alarmingly low influenza vaccination rates among children in Türkiye, particularly in comparison to other countries with more established vaccination programs. The findings suggest that parental awareness plays a crucial role in vaccination uptake, with factors such as educational level, healthcare guidance, and awareness of the importance of the vaccine being significant contributors. Importantly, the data suggests that the primary barrier to vaccination is not vaccine side effects but rather a lack of understanding of the necessity of influenza vaccination, especially for children under the age of five. Healthcare professionals, particularly physicians, are key influencers in encouraging vaccination, and their guidance proves to be more effective than information from media sources. The study also underscores the need for targeted interventions aimed at high-risk groups, particularly young children and those with underlying health conditions, who remain vulnerable to severe influenza outcomes. The higher vaccination rates observed among children whose parents are more educated further emphasize the importance of increasing awareness and providing accurate information to parents. Given the limitations of the study, future research should explore broader socio-economic, cultural, and healthcare access factors that may also influence vaccination behavior. Additionally, longitudinal studies are necessary to understand the causal factors behind low vaccination rates and to evaluate the effectiveness of public health campaigns. Addressing the gaps in vaccination uptake in Türkiye, particularly through enhanced education and policy interventions, is critical for improving childhood influenza vaccination rates and reducing the burden of this preventable disease.

It is crucial to strengthen public health strategies in Türkiye. Free influenza vaccination should be considered for high-risk groups to increase coverage and reduce disease burden. Moreover, standardization of physician recommendations could play a key role in improving parental trust and ensuring more consistent uptake of the vaccine nationwide.

Ethical approval

The study was approved by Hacettepe University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (date: March 05, 2024, number: 2024/08-66).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: HY, KA, OOD, YO; data collection: HY, SI, HK, GG, EA, EGC, MSS, PK, MG, AO, DDG, SET, BCCY, OK, AK, DSO, MG, OMA, DBA, GA, SI, LG, TBD, AT, ESI, ND, FDA, EC, SC, NMA, AS, ECT, MIN, OE, Dİ, SSK, GA, BO, ME, ACG, EKO, GOP, ZGGA, BY, ZU, SBS, CE, GA, HSU, SO, AS, YEK, EK, OGS, AHT, MKC, UC, NG, EY, NK, AB, GM, OK, BC, MK, NE, SS, ZNC, HKK, SKY, HKA, HT, CO, ASD, GTU, KC, OC, EA, AH, HM; analysis: OOD, HA; interpretation of results: ABC, YO; draft manuscript preparation: HY, KA, OOD, YO. 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

Factors for poor outcomes of neonatal bacterial meningitis: a retrospective multicenter study

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ABSTRACT

Background. Neonatal bacterial meningitis remains a severe infectious disease associated with substantial mortality and long-term neurological sequelae. This study aimed to identify factors associated with poor outcomes and to determine independent prognostic predictors in neonates with bacterial meningitis.

Methods. This retrospective multicenter cohort study included neonates diagnosed with bacterial meningitis. Clinical characteristics, laboratory findings, microbiological data, treatment responses, and outcomes were analyzed. Univariate and multivariable logistic regression analyses were performed to identify factors associated with poor outcomes.

Results. A total of 85 neonates were included in the final analysis. 31 neonates (36.5%) experienced poor outcomes, including death or long-term neurological sequelae. In multivariable analysis, the presence of neurological signs at admission (odds ratio [OR]: 7.315; 95% confidence interval [CI]: 1.875–28.535) and the development of acute neurological complications during hospitalization (OR: 7.541; 95% CI: 2.045–27.807) were the only factors independently associated with poor outcomes. Several variables, including elevated cerebrospinal fluid protein levels, early administration of blood-brain barrier (BBB)-permeable antibiotics prior to lumbar puncture, and adequate response to initial antimicrobial therapy, were significantly associated with outcomes in univariate analyses but did not retain statistical significance after multivariable adjustment.

Conclusions. Neurological involvement at presentation and acute neurological complications are key independent predictors of poor outcomes in neonatal bacterial meningitis. Other clinical and laboratory variables may reflect disease severity or early clinical course and may assist in early risk stratification.

Key words: neonatal bacterial meningitis, prognosis, neurological complications, cerebrospinal fluid, outcomes.

Neonatal bacterial meningitis (NBM) continues to pose a serious clinical burden worldwide, with a particularly high disease severity and fatality rate in resource-limited settings.[1] Survivors of NBM frequently experience unfavorable neurological outcomes, and previous studies have reported that up to half of affected neonates may develop moderate to severe long-term disabilities, including impairments in language, hearing, vision, motor function, and cognition.[2] In addition, a proportion of survivors, estimated at approximately 5-20%, may subsequently develop epilepsy during later childhood or adolescence.[3]

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Early recognition of neonates with NBM at risk for poor outcomes is crucial for ensuring timely management and identifying those who require long-term follow-up and early intervention. Although several studies on NBM have been conducted, data on long-term epidemiological trends and prognostic factors remain limited.[4,5] This retrospective study analyzed six years of epidemiological data on culture-confirmed NBM from two medical centers in Eastern China, aiming to identify predictors of poor outcomes and support the early identification of high-risk neonates.

Materials and Methods

This retrospective multicenter study reviewed the inpatient electronic medical records of neonates diagnosed with neonatal bacterial meningitis (NBM) who were admitted to the neonatal intensive care units of Yuying Children's Hospital and the Department of Pediatrics, Jingmen Central Hospital from January 2017 to December 2022, as well as their outpatient follow-up electronic medical records. This study protocols were approved by the Yuying Children's Hospital Ethics Committee (date: 01.01.2021, number: 2021-K-167-02). Inpatient data collection encompassed demographic data, clinical characteristics, laboratory findings and additional assessments for each case. Demographic data included age at onset, sex, weight at admission, gestational age, and maternal and perinatal conditions. The clinical characteristics documented included detailed body temperature profiles (including peak and nadir values), initial clinical presentations (such as poor feeding, irritability, lethargy, vomiting, seizures), neurological symptoms and signs at admission, and antibiotic exposure prior to and during hospitalization.

Laboratory findings included a complete blood count (CBC), C-reactive protein (CRP), procalcitonin (PCT) levels, blood cultures, as well as cerebrospinal fluid (CSF) analysis, which consisted of a white blood cell count and differential, protein concentration, glucose level, Gram staining, and bacterial culture. Additional assessments consisted of cranial magnetic resonance imaging (MRI), hearing evaluations, and documentation of acute neurological complications during hospitalization. All clinical, laboratory, imaging, and treatment-related data were retrospectively extracted from electronic medical records using a standardized data collection form by trained investigators at each participating center.

The follow-up duration was at least 2 years for preterm infants and at least 1 year for term infants and was conducted through scheduled outpatient clinic visits. Follow-up data primarily focused on neurodevelopmental outcomes and long-term neurological sequelae associated with bacterial meningitis.

Inclusion criteria

1. Clinical diagnosis of NBM confirmed by CSF Gram-stained smear or CSF bacteriological culture.
2. Onset of NBM within the first 28 days of life.
3. Gestational age greater than 34 weeks and birth weight above 1500 grams.

Exclusion criteria

1. Recent neurosurgical interventions, such as CSF shunts or reservoirs.
2. Presence of acquired or congenital anatomical defects.
3. Immunological abnormalities.

Definitions and clarifications applied in this study

1. We defined CSF pleocytosis as a CSF white blood cel (WBC) count >16 cells per mm^3 for infants ≤ 28 days.[6]
2. An abnormal CSF profile was defined as a positive Gram-stain result, CSF pleocytosis, neutrophil predominance on the CSF WBC

differential (>50% neutrophils), an elevated CSF protein level (>128 mg/dL for infants ≤ 28 days),or a low CSF glucose level (<25 mg/dL for infants ≤ 28 days of age).[6]

3. Bacterial meningitis was defined as either a positive CSF culture yielding a pathogenic organism or a positive CSF Gram stain demonstrating bacteria (e.g., Gram-positive cocci, Gram-negative rods). For cases diagnosed solely by Gram staining, the diagnosis required both exclusion of contamination by laboratory assessment and the presence of an abnormal CSF profile.[6]
4. For infants with traumatic lumbar punctures (ie, CSF RBC count >10 000 cells per mm^3), we used an RBC/WBC correction factor of 1000:1 to determine the corrected CSF WBC count.[7]
5. Neurological sequelae were defined as impairments persisting for more than six months, including intellectual or motor deficits and cranial nerve dysfunction (e.g., hearing loss, visual impairment, facial or oculomotor nerve palsy). Intellectual and motor development was evaluated using the Gesell Developmental Diagnosis Scale (GDDS). The GDDS assesses five developmental domains: adaptability, gross motor, fine motor, language, and personal-social behavior. For each domain, a developmental quotient (DQ) is calculated as the ratio of developmental age to chronological age multiplied by 100. A total DQ score is derived by averaging the domain scores. A DQ score <85 was defined as developmental delay. The GDDS has been widely applied in pediatric neurodevelopmental assessment and has demonstrated acceptable reliability and validity in clinical practice.[8] Muscle strength, muscle tone, and cranial nerve dysfunction were assessed through physical examination and relevant instrumental tests. Secondary epilepsy was diagnosed based on medical history, clinical manifestations, and electroencephalography findings.
6. An adequate response to initial antimicrobial therapy was defined as an afebrile period of 48 consecutive hours (maximum tympanic temperature ≤ 37.5 °C), negative meningeal irritation signs, a CRP level ≤ 20 mg/L, and a neutrophil count ≤ 10,000/mm^3 within the first 3-5 days of treatment.[9,10]
7. Patients who died or developed neurological sequelae were regarded as having a poor outcome.
8. Cases with fatal outcomes were not included in the analysis of antibiotic duration and recurrence. Those who were lost to follow-up were excluded.
9. Neonatal fever (rectal temperature):
   Low-grade fever: 38.0-38.4 °C,
   Moderate fever: 38.5-38.9 °C,
   High fever: 39.0-40.0 °C,
   Hyperpyrexia: > 40.0 °C.
10. Neonatal hypothermia (rectal temperature):
    Mild hypothermia: 36.0-36.4 °C,
    Moderate hypothermia: 32.0-35.9 °C,
    Severe hypothermia: < 32.0 °C.
    Temperature instability:
    Maximum rectal temperature ≥ 39.0 °C,
    Minimum rectal temperature < 36 °C.
11. Early-onset meningitis was defined as bacterial meningitis occurring within the first 7 days of life, whereas late-onset meningitis referred to cases diagnosed after 7 days of age, in accordance with commonly used neonatal infection classifications.[11]

Statistical analysis

Continuous variables with a normal distribution were expressed as means ± standard deviations, whereas non-normally distributed variables were presented as medians with interquartile ranges (IQRs) (median [Q1, Q3]). Categorical variables were summarized as frequencies and percentages.

Comparisons between groups were performed using the independent-samples t test for normally distributed continuous variables, the Mann–Whitney U test for non-normally distributed continuous variables, and the chi-square test for categorical variables, as appropriate.

Variables included in the univariate analysis were selected a priori based on previous literature and clinical relevance to neonatal bacterial meningitis. Univariate logistic regression analysis was performed to identify variables associated with poor outcomes. Variables with a p value <0.05 in univariate analysis were subsequently entered into the multivariable logistic regression model to determine factors independently associated with poor outcomes.

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. All statistical tests were two-sided, and a p value <0.05 was considered statistically significant. Statistical analyses were conducted using SPSS software (version 23.0).

Results

Patient characteristics

Between January 2017 and December 2022, a total of 92 neonates hospitalized at the neonatal intensive care units of Yuying Children's Hospital and the Department of Pediatrics, Jingmen Central Hospital met the diagnostic criteria for bacteriologically confirmed bacterial meningitis. Seven neonates (7.6%) were lost to follow-up; subsequent analyses were conducted on the remaining 85 neonates.

Among these 85 neonates, the mean gestational age was 36.8 ± 1.73 weeks (range: 34–40 weeks). The median age at symptom onset was 6 days after birth (IQR: 2–15; range: 0–28 days), with 43 (50.6%) classified as early-onset meningitis. The median duration of illness before admission was 12 hours (IQR: 7.5–23.5; range: 2–48 hours). The mean admission weight was 3.36 ± 0.64 kg (range: 1.9–5.1 kg), and 46 neonates (52.9%) were male. A total of 22 neonates (25.9%) had identifiable maternal or intrapartum risk factors, with one (12.2%) presenting with two such factors. These included premature rupture of membranes (n = 10, 11.8%), intrapartum fever (n = 7, 8.2%), prolonged labor (n = 2, 2.4%), antepartum hemorrhage (n = 2, 2.4%), and meconium-stained amniotic fluid (n = 2, 2.4%).

Clinical manifestations and neurological signs

Clinical symptoms were generally nonspecific and atypical. The most common manifestation was abnormal body temperature. Fever was observed in 78 neonates (91.8%), of whom 38 (44.7%) had high fever/hyperpyrexia. Hypothermia was present in 20 neonates (23.5%), including 19 with mild hypothermia and 1 with moderate hypothermia. Both high fever/hyperpyrexia and hypothermia were recorded in 9 cases (10.6%). Only 5 neonates (5.9%) maintained body temperature within the normal range. Other common symptoms included poor feeding in 41 (48.2%), irritability in 20 (23.6%), lethargy in 15 (17.6%), seizures in 11 (12.9%), and jaundice in 11 (12.9%). Less frequent symptoms (<10% each) were vomiting, dyspnea, cyanosis, irregular respiration, gaze preference, ocular deviation, and stupor. Neurological signs were present in 25 neonates (29.4%), including bulging or tense fontanelle in 20 (23.5%), abnormal muscle tone (hypertonia or hypotonia) in 11 (12.9%), and nuchal rigidity in 3 (3.5%).

Microbiological findings

A total of 51 neonates were caused by Gram-positive organisms, including group B *Streptococcus* (GBS, n = 22, 25.9%), *Streptococcus pneumoniae* (n = 7, 8.2%), *Staphylococcus aureus* (n = 6, 7.1%), *Enterococcus* spp. (n = 4, 4.7%), and unspecified Gram-positive cocci (n = 12, 14.1%). The remaining 34 cases were caused by Gram-negative bacteria, including *Escherichia*

coli (n = 20, 23.5%), *Enterobacter* spp. (n = 1, 1.2%), *Haemophilus influenzae* (n = 1, 1.2%), and unspecified Gram-negative rods (n = 12, 14.1%). The most frequently isolated pathogens were GBS and *E. coli*.

Cerebrospinal fluid (CSF) findings

Among the 85 neonates, 83 (97.6%) exhibited elevated CSF total leukocyte counts (>20/mm^3). Neutrophil predominance (>70%) and elevated CSF protein levels (>1.0 g/L) were each observed in 80 cases (94.1%), while decreased CSF glucose concentrations (<2.2 mmol/L) were noted in 68 cases (80.0%).

Timing and administration of antibiotics

Among the 85 neonates, 13 received immediate intravenous administration of standard-dose antibiotics at their outpatient visit, all of which were cefotaxime, a third-generation cephalosporin with good blood-brain barrier (BBB) penetration. After hospital admission, all neonates underwent lumbar puncture as the first procedure, and empirical antimicrobial therapy (initial antimicrobial therapy) was initiated immediately after the CSF routine results became available (approximately 1 hour later). Antibiotic selection and dosing followed the neonatal bacterial meningitis guidelines: ampicillin (150-200 mg/kg/day) plus cefotaxime (100-200 mg/kg/day) in 73 cases, and vancomycin (30-45 mg/kg/day) plus cefotaxime (150-200 mg/kg/day) in 12 cases. Following the CSF culture or Gram-stained smear results, the antibiotic regimen was maintained if an adequate clinical response was achieved; in cases of an inadequate clinical response, treatment was adjusted according to the findings of the CSF Gram stain or culture.

Response to initial antimicrobial therapy and treatment duration

Among the 85 neonates, 54 (63.5%) exhibited an adequate clinical response to initial antimicrobial therapy, while the remaining 31 (36.5%) showed an inadequate response and subsequently underwent repeat lumbar puncture. Excluding the three fatal cases, the median duration of antibiotic therapy was 23 days (IQR: 18.5–33.5; range: 14–76 days), with 28 neonates (34.1%) receiving treatment for 30 days or more.

Acute neurologic complications

Complications during hospitalization occurred in 33 (38.8%) neonates, including subdural effusion, defined on MRI as CSF-like signal intensity without diffusion restriction (n = 11, 12.9), hydrocephalus (n = 11, 12.9), brain abscess (n = 9, 10.6%), symptomatic seizure-like episodes (n = 9, 10.6%), subdural empyema, defined on MRI as subdural collections with restricted diffusion on diffusion-weighted imaging (n = 8, 9.4%), unilateral hearing loss (n = 6, 7.1%), intracerebral hemorrhage (n = 4, 4.7%), and ventriculitis (n = 2, 2.4%).

Outcomes

Long-term neurological sequelae were identified based on clinical evaluation and GDDS assessment during follow-up. Excluding the three fatal cases, 28 of the 82 surviving neonates (34.1%) developed at least one neurological sequela, including hypertonia (n = 14, 17.1%), paresis (n = 7, 8.5%), unilateral hearing loss (n = 6, 7.3%), secondary epilepsy (n = 5, 6.1%), motor developmental delay (n = 1, 1.2%), and global developmental delay (n = 1, 1.2%). The remaining 54 neonates (65.9%) achieved complete recovery.

Factors associated with outcomes

Table I compares the clinical characteristics between neonates with good outcomes (n = 54) and those with poor outcomes (n = 31). In univariate analyses, several factors were significantly associated with poor outcomes, including the presence of neurological signs at admission ($p < 0.001$), elevated initial CSF protein levels ($p = 0.036$), lack of BBB-

permeable antibiotic use before lumbar puncture (p = 0.019), inadequate response to initial antimicrobial therapy (p = 0.002), and the occurrence of acute neurological complications during hospitalization (p < 0.001).

Receiver operating characteristic (ROC) analysis demonstrated that a CSF protein level > 3.08 g/L was the optimal cutoff value for discriminating poor outcomes, with a sensitivity of 41.9% and a specificity of 87.0%.

Table I. Comparison of clinical characteristics in neonates with bacterial meningitis based on different outcomes.

Variables	Neonates with good outcomes (n=54)	Neonates with poor outcomes (n=31)	P value
Sex, male	31 (57.4%)	15 (48.4%)	0.500
Age at onset (days)	6 (2.75–15)	10 (1–16)	0.851
Gestational age (weeks)	36.96±1.78	36.61±1.67	0.375
Weight on admission (g)	3.42±0.62	3.25±0.68	0.252
Positive maternal or labor factors	8 (15.4%)	8 (24.2%)	0.230
Maximum rectal temperature (°C)	38.89±0.556	39.01±0.74	0.369
High fever or hyperpyrexia	20 (37.0%)	18 (58.1%)	0.099
Hypothermia	12 (22.2%)	8 (25.8%)	0.913
Temperature instability	5 (9.26%)	4 (12.9%)	0.873
Duration of illness before admission (h)	12 (7.75–22.25)	12 (6–24)	0.562
Neurological signs positive	8 (14.8%)	17 (54.8%)	<0.001**
Peak blood parameters before antibiotic use			
TLC (10^6/mL)	16.41±7.08	18.38±10.94	0.315
Neutrophil (%)	0.674±0.167	0.664±0.199	0.810
CRP (mg/L)	51.09±47.37	69.44±52.26	0.102
PCT (ng/mL)	3.00±2.88	2.94±1.89	0.918
Initial blood pathogens			
Positive culture	34 (63%)	19 (61.3%)	0.878
Negative culture	20 (37%)	12 (38.7%)	
Initial CSF parameters			
CSF-TLC (cell/mL)	3323.43±5297.33	2976.35±4170.96	0.755
CSF-Neutrophil (%)	0.779±0.167	0.750±0.233	0.509
CSF glucose (mmol/L)	1.879±0.558	1.620±0.671	0.060
CSF protein (g/L)	2.047±1.525	2.852±1.912	0.036*
Initial CSF pathogens			
Positive culture	20 (74.1%)	19 (61.3%)	0.218
Gram-stained smear (Gram-positive)	32 (59.3%)	22 (71.0%)	0.280
Use of BBB-permeable antibiotics before LP	12 (22.2%)	1 (3.2%)	0.019*
Adequate response to initial antibiotic therapy	41 (75.9%)	13 (41.9%)	0.002*
Complications	10 (18.5%)	23 (74.1%)	<0.001**

Data presented as n (%), median (Q1-Q3) or mean ± standard deviation; BBB, blood-brain barrier; CRP, C-reactive protein; CSF, cerebrospinal fluid; Neutrophil (%), absolute neutrophil count/total leukocyte count ratio; PCT, Procalcitonin; TLC, total leukocyte count; *p<0.05; **p<0.01.

Table II. Multivariate logistic regression analysis to identify risk factors for poor outcomes in neonates with bacterial meningitis.

Variables	B	Standard error	Wald	Odds ratio	95% CI	P value
Neurological signs	1.990	0.649	8.211	7.315	1.875-28.535	0.004**
CSF protein (g/L) > 3.08	0.229	0.731	0.098	1.258	0.300-5.274	0.754
Use of BBB-permeable antibiotics before LP	-1.081	1.137	0.904	0.339	0.037-3.150	0.342
Adequate response to initial antibiotic therapy	-0.840	0.690	1.482	0.432	0.112-1.668	0.223
Complications	2.020	0.666	9.209	7.541	2.045-27.807	0.002**

BBB, blood-brain barrier; CI, confidence interval; CSF, cerebrospinal fluid; LP, lumbar puncture; *p<0.05; **p<0.01.

As shown in Table II, in the multivariable logistic regression analysis, only the presence of neurological signs at admission (OR: 7.315; 95% CI: 1.875–28.535) and the occurrence of acute neurological complications during hospitalization (OR: 7.541; 95% CI: 2.045–27.807) remained independently associated with poor outcomes.

Discussion

This retrospective cohort study provides a comprehensive overview of NBM, with particular emphasis on clinical presentation, etiological patterns, treatment response, and prognostic factors. Our findings highlight the persistent diagnostic and therapeutic challenges of NBM, largely attributable to its nonspecific early manifestations and the high risk of long-term neurological morbidity.

Consistent with previous reports, the majority of clinical manifestations in our cohort were nonspecific, with abnormal body temperature, poor feeding, and irritability being the most frequent presentations.[12,13] Classical neurological signs, including lethargy, focal seizures, vomiting, and abnormal muscle tone, were relatively infrequent but were closely associated with severe disease.[11,14]These observations underscore the diagnostic difficulty of NBM and emphasize the indispensable role of CSF analysis and microbiological testing for definitive diagnosis.[15] Clinicians should therefore maintain a high index of suspicion for NBM in neonates presenting with sepsis-like features, even in the absence of overt meningeal signs.[12,13]

The reported frequency of fever in NBM varies across studies, ranging from approximately 67.9%[12] to 84.1%.[16] In our cohort, the rate was higher (91.8%), which may reflect referral bias to tertiary centers and the relatively small sample size. Notably, hypothermia occurred in 17.6% of cases, and 8.2% of neonates experienced both hyperpyrexia and hypothermia during the course of illness, indicating that temperature instability is not uncommon in NBM, consistent with the findings of Haque et al.[17] Despite these abnormalities, a small proportion (5.9%) of neonates in our study maintained entirely normal body temperatures, reinforcing that the absence of fever does not exclude the diagnosis of NBM.

Regarding microbiological findings, GBS and *E. coli* were the leading pathogens, together accounting for nearly half of all cases. This distribution is consistent with epidemiological patterns reported in high-and middle-income regions, likely reflecting vertical transmission from maternal colonization.[18,19] The relatively high proportion of GBS meningitis suggests that gaps may exist in the implementation of maternal screening, risk stratification, and intrapartum antibiotic prophylaxis.[20]

Typical CSF abnormalities in NBM include neutrophilic pleocytosis (80–95%), elevated protein, and decreased glucose.[21,22] However, normal reference values for CSF vary with gestational and postnatal age, complicating

both diagnosis and monitoring.[15,23] In our study, several culture-proven cases had normal CSF white cell counts, protein, or glucose levels, consistent with findings by Garges et al. and others, which demonstrate that meningitis cannot be excluded based on a single CSF parameter.[24-26] Despite these limitations, CSF culture, microscopy, and biochemical analysis remain the diagnostic gold standard, while next-generation sequencing may serve as a valuable adjunct in complex or culture-negative cases.[5,27,28]

Importantly, in multivariable logistic regression analysis, only the presence of neurological signs at admission and the occurrence of acute neurological complications during hospitalization remained independently associated with poor outcomes. Neurological abnormalities at presentation, although relatively infrequent, were strongly associated with adverse prognosis (OR: 7.315; 95% CI: 1.875–28.535), supporting previous reports that early central nervous system involvement reflects more severe disease and a higher risk of irreversible brain injury.[29,30]

Acute neurological complications during hospitalization, including subdural effusion, hydrocephalus, brain abscess, ventriculitis, intracranial hemorrhage, seizure-related events, and hearing impairment, were independently associated with poor outcomes (OR: 7.541; 95% CI: 2.045–27.807). Nearly all infants who developed long-term neurological sequelae experienced at least one acute neurological complication during the acute phase, emphasizing the critical importance of early neuroimaging, close neurological monitoring, and timely intervention to mitigate secondary brain injury.[31]

Several variables, including elevated CSF protein levels (>3.08 g/L),[32-34] early administration of BBB–permeable antibiotics,[35,36] and a favorable initial response to antimicrobial therapy, were associated with outcomes in univariate analyses[37] but did not retain statistical significance after multivariable adjustment. These findings are consistent with previous reports suggesting that such factors may reflect disease severity, timing of diagnosis, or early clinical course rather than serving as independent prognostic determinants.

Despite advances in antimicrobial therapy and neonatal intensive care, 34.1% of surviving infants in our cohort developed long-term neurological sequelae, a prevalence consistent with the 20-50% range reported in previous studies.[38] These sequelae included abnormalities in muscle tone, paresis, hearing impairment, epilepsy, and developmental delay, underscoring the necessity of structured neurodevelopmental follow-up, routine audiological screening, and early rehabilitative interventions for survivors of NBM.

Several limitations of this study should be acknowledged. First, the retrospective design may limit causal inference and generalizability, and the availability of clinical data depended on the completeness of medical records. In addition, data from the most recent three years were not available, which may have limited the representativeness of current clinical practices and treatment strategies. Second, neurodevelopmental outcomes were assessed using the GDDS, rather than more comprehensive neuropsychological assessment tools, which may have resulted in underestimation of subtle cognitive or behavioral impairments. Moreover, the duration of follow-up was limited to at least one year for term infants, and although preterm infants were followed for a longer period, some neurodevelopmental sequelae may manifest later in childhood and therefore could have been missed. Third, the relatively small sample size may have limited the statistical power to identify additional factors independently associated with poor outcomes. Finally, potential selection bias and information bias inherent to multicenter retrospective studies cannot be completely excluded, including referral bias to tertiary centers and variability in diagnostic and management practices across institutions.

Conclusions

In this multicenter retrospective study, neurological signs at admission and acute neurological complications during hospitalization were independently associated with poor outcomes in neonatal bacterial meningitis. Other factors, including elevated CSF protein levels, early administration of BBB-permeable antibiotics, and response to initial therapy, were associated with outcomes in univariate analyses but did not retain independent significance after multivariable adjustment. These findings underscore the importance of early neurological assessment, close monitoring for complications, and structured long-term follow-up in affected neonates.

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Ethical approval

This study was conducted in accordance with the International Conference on Good Clinical Practice Standards and the Declaration of Helsinki. All study protocols were approved by the Ethics Committee of The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (date: 01.01.2021, number: 2021-K-167-02). The requirement for informed consent from study participants or their guardians was waived due to the de-identification of information in this retrospective study. Additionally, the study was registered with the Chinese Clinical Trial Registry (ChiCTR-INR-17012884).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: SL, LF; data collection: YDD, SYP, XHH, LF; analysis and interpretation of results: SL, YDD, SYP, XHH; draft manuscript preparation: SL, LF. 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

Carotid-femoral pulse wave velocity and strain echocardiography in neonates: impact of maternal diabetes and hypertension

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ABSTRACT

Background. The arterial wall tends to stiffen owing to prolonged exposure to cardiovascular disease risk factors such as high blood pressure, hyperglycemia, and chronic inflammation. Epidemiological research has demonstrated that maternal factors, demographic characteristics, and clinical data influence arterial stiffness and echocardiographic findings. This study aimed to evaluate the association between arterial stiffness and echocardiographic findings with maternal factors and demographic and clinical characteristics in infants of mothers with gestational diabetes or hypertension during the neonatal period.

Methods. A total of 67 newborns between 12-29 days of age, including 15 neonates of hypertensive mothers, 26 neonates of diabetic mothers, and 26 neonates in the control group, were included. Carotid-femoral pulse wave velocity (cfPWV) was used as a marker of arterial stiffness and measurements were performed using echocardiography. Basic echocardiographic evaluations and atrial and ventricular strain assessments were performed.

Results. The mean cfPWV value of infants of diabetic mothers (6.34 m/s) was significantly higher than that of infants of hypertensive mothers (4.65 m/s) and the control group (4.56 m/s) ($p<0.001$). Multivariate linear regression analysis revealed that increasing maternal age and the presence of diabetes in the mother were predictors of carotid-femoral pulse wave velocity values. The right ventricular free wall longitudinal strain z-scores were higher in hypertensive infants, while no significant difference was found in other strain measurements.

Conclusion. The analysis of arterial stiffness in infants of diabetic mothers, infants of hypertensive mothers, and controls showed that advanced maternal age and maternal diabetes were particularly associated with increased cfPWV. This study highlights the potential influence of maternal metabolic status on neonatal cardiac morphology and vascular function. Based on the data presented, further research is warranted to investigate whether the observed effects on arterial stiffness in infants of diabetic mothers persist into older ages and have long-term implications for the health of these patients.

Key words: neonates, gestational diabetes mellitus (GDM), gestational hypertension, arterial stiffness, strain echocardiography, relative wall thickness.

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Arterial stiffness reflects the mechanical properties of the vascular wall and is commonly expressed as the elastic modulus. As arterial pressure and diameter increase, circumferential wall stress is gradually transferred from extensible elastin fibers to relatively inextensible collagen fibers, resulting in progressive stiffening of the arterial wall.[1,2] Exposure to cardiovascular risk factors, including hypertension, hyperglycemia, dyslipidemia, and inflammation, accelerates this process and leads to early vascular remodeling.[3,4]

Pulse wave velocity (PWV) measured in central arterial segments is accepted as the gold standard for the assessment of arterial stiffness.[5] In adults, aortic pulse wave velocity (aPWV) is a strong independent predictor of cardiovascular mortality and has been shown to outperform conventional parameters such as systolic blood pressure and pulse pressure.[6,7] Increasing evidence suggests that the origins of cardiovascular disease begin early in life. Elevated blood pressure becomes clinically detectable in childhood when values exceed the 90th percentile for age[8], and increased aPWV predicts the later development of hypertension. Importantly, increased PWV in the neonatal period has also been associated with future cardiovascular disease and target-organ damage.[9]

The concept of fetal programming proposes that intrauterine conditions influence cardiovascular structure and function in later life. Maternal characteristics, perinatal factors, and neonatal clinical parameters have been shown to affect vascular function and arterial stiffness.[9-12] However, vascular changes do not occur in isolation; they are closely linked to cardiac performance. Increased arterial stiffness leads to elevated left ventricular afterload, which may result in subtle alterations in myocardial mechanics even before conventional echocardiographic parameters become abnormal.[13]

Advanced echocardiographic techniques, particularly speckle-tracking echocardiography, allow the evaluation of myocardial deformation and provide a sensitive assessment of cardiac function. Strain and strain-rate parameters can detect subclinical myocardial dysfunction earlier than traditional measurements such as ejection fraction. Therefore, the simultaneous assessment of arterial stiffness and myocardial deformation may improve the understanding of early cardiovascular adaptation in the neonatal period.[14,15]

In this study, we aimed to investigate the relationship between aortic pulse wave velocity and echocardiographic parameters, including myocardial strain measurements, and to evaluate their association with maternal factors and with the demographic and clinical characteristics of newborns.

Methods

Patient selection

This study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (Date: 20 September 2022, Project No: GO 22/887, Decision No: 2022/18–34). Informed consent was obtained from the families for study participation. Healthy newborns aged 12-29 days, evaluated at the Department of Pediatric Cardiology, Hacettepe University between November 2022 and April 2023, were divided into three groups: infants of mothers with diabetes or hypertension, and infants of healthy mothers. Children with neurologic disease, coagulopathy, malignancy, renal and hepatic failure, heart disease or genetic disease were excluded. The mothers were followed-up by Hacettepe University Department of Obstetrics and Gynecology during the antenatal period. Diagnoses of gestational diabetes mellitus, pre-gestational diabetes mellitus, gestational hypertension and preeclampsia were determined according to international standards.[16,17]

Sex, birth weight, current weight, gestational age, delivery mode, echocardiographic findings, number of births, age, hypertension

status, diabetes mellitus, HbA1c value, body mass index (BMI) calculated from prenatal weight and final prenatal hemoglobin value of mothers were recorded.

Echocardiographic measurements were performed in accordance with the American Society of Echocardiography standards[18] using a Philips Healthcare EPIQ CVx (Philips Medical Systems, Andover, MA, USA) equipped with a Philips S9-2 (PureWave sector array transducer) probe. For standard echocardiographic measurements, parasternal long-axis (PSLAX) M-Mode, apical four-chamber (A4C), apical three-chamber (A3C) and apical 2-chamber (A2C) images were obtained. The left ventricular end-diastolic diameter (LVEDD), interventricular septum end-diastolic diameter (IVSd) and left ventricular posterior wall thickness (PWd) were recorded. The left ventricular mass (LVM), LVM index (LVMI) and relative wall thickness (RWT) values were calculated from these values. Doppler recordings of the aortic isthmus were obtained from the suprasternal notch and Doppler recordings of the femoral artery were obtained from the right femoral artery. Left ventricular, right ventricular and left atrial strain values of the patients were calculated and recorded using the Philips Healthcare EPIQ CVx system software. Image windows for which the optimal strain values could not be obtained from the recorded images were excluded from the calculation. The left ventricular global longitudinal peak strain (LV GLPS), right ventricular free wall longitudinal strain (RVFW LS), global longitudinal peak strain (RV GLPS), left atrial reservoir strain (LArS), conduit strain (LAconS) and contraction strain (LAcS) values were recorded.

LVM and LVMI were calculated using the following formulas:

$$\mathrm{LVM} = 0.8 \times \left\{1.04 \times \left[(\mathrm{LVEDD} + \mathrm{IVSd} + \mathrm{PWd})^3 - \mathrm{LVEDD}^3\right]\right\} + 0.6$$

$$\mathrm{LVMI} = \frac{\mathrm{LVM}}{\mathrm{Body\ \ surface\ \ area}}$$

There are two methods for measuring the RWT:

$$\mathrm{RWT} = \frac{2\times\mathrm{PWd}}{\mathrm{LVEDD}} \text{ or } \mathrm{RWT} = \frac{\mathrm{IVSd}+\mathrm{PWd}}{\mathrm{LVEDD}}$$

$$\mathrm{PWd} = \text{posterior wall thickness}$$

In our study, the second method was preferred because IVSd values were different between the groups, and it is known that IVSd values are high in infants of diabetic mothers.[19]

PWV measurements were performed between 14.00 and 17.00 hours in a temperature-controlled room using the same device. Measurements were taken when infants were at their calmest, with calculations performed three times. The calculation involved taking pulse waves and simultaneous ECG images from the sternal notch and femoral artery. The pulse wave was measured on the descending aorta from the sternal notch, and the distance from notch to measurement site was calculated. Then, the femoral artery pulse wave was measured, and the distance between sternal notch and femoral artery measurement site was measured. The distance (d) was calculated by subtracting the sternal notch-to-aorta distance from the sternal notch-to-femoral artery distance. The time to pulse wave onset was calculated from the QRS waves on ECG. The carotid-femoral pulse wave velocity (cfPWV) was obtained by dividing distance (d) by the difference between the QRS-to-femoral and QRS-to-aorta pulse wave times (Fig. 1).

Statistical analysis

Statistical analysis was performed using SPSS 22.0 (Statistical Package for the Social Sciences) software. The Kolmogorov–Smirnov test or Shapiro–Wilk test was used to determine whether the data were normally distributed. In the evaluation of the data, frequencies and percentages were given for qualitative data, arithmetic means and standard deviations were used for quantitative data, and median and minimum-maximum values were given for non-normally distributed data. The chi-square test or Fisher's exact test was used for the comparison

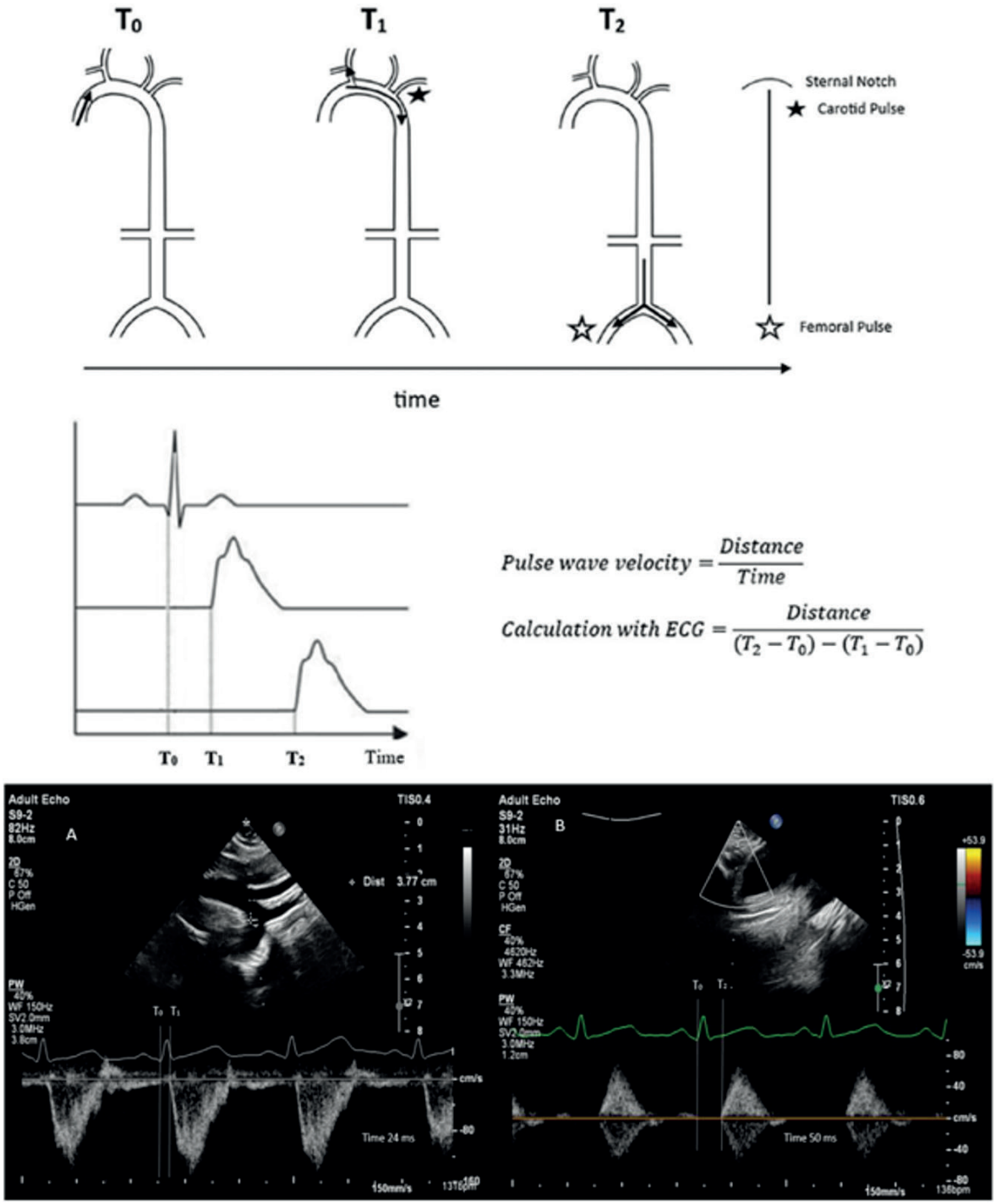

Fig. 1. Carotid-femoral pulse wave velocity (cfPWV) measurement scheme and ECG-assisted cfPWV calculation using echocardiography. The time measured over the femoral artery (B) was subtracted from the time measured over the descending aorta (A) and cfPWV was calculated by dividing the distance by time. The distance was calculated superficially from the sternal notch to where the probe was placed over the femoral artery, and subtracted from the distance between the sternal notch and the cursor shown in A.

of categorical data, whereas Student's t-test was used for the comparison of quantitative data between two groups with normally distributed data. One-way ANOVA was used for normally distributed data consisting of three groups, and the Kruskal-Wallis test was used for non-normally distributed data. The relationship between continuous data was evaluated using Pearson correlation analysis for normally distributed data and Spearman correlation analysis for non-normally distributed data. The receiver operating characteristic (ROC) curve analysis was applied to determine the cut-off value for cfPWV in infants of hypertensive and diabetic mothers. Univariate and multivariate linear regression analyses were applied to identify the factors affecting cfPWV. All statistical calculations were evaluated at a 95% confidence interval and a significance level of $p < 0.05$.

Results

A total of 67 infants were evaluated, and all had adequate echocardiographic and Doppler measurements. Therefore, all 67 infants (26 infants of diabetic mothers, 15 infants of hypertensive mothers, and 26 control infants) were included in the final analysis. The general characteristics of the infants and their mothers are presented in Table I.

Table I. General characteristics of the infants and mothers included in the study.

	Mean ± SD (range), or n (%)
Infant	
Age, day	21.5±5.0 (12-29)
Sex	
Male	28 (41.8%)
Female	39 (58.2%)
Birth weight, gr	3,231±484 (2,070-4,240)
Gestational age at birth, wk	38.1±0.9 (37-40)
Method of birth	
C/S	45 (67.2%)
NSVD	22 (32.8%)
IVF	9 (13.4%)
Mother	
Age, year	31±6 (21-42)
BMI, kg/m^2	29.8±4,5 (19.7-42.9)
Parity	2.2±1.4 (1-9)
Hemoglobin, gr/dL	11.3±1.5 (7.3-14.9)
HbA1c, %	5.48±0.48 (4.5-6.5)
Additional diseases	
Preeclampsia	4 (6.0%)
Hypertension	21 (31.3%)
Pre-gestational DM	4 (6.0%)
Gestational DM	21 (31.3%)

BMI: body mass index, C/S: Cesarean section, DM: diabetes mellitus, IVF: in vitro fertilization, NSVD: Normal spontaneous vaginal delivery, SD: standard deviation.

The results of the comparison of infants of hypertensive mothers, infants of diabetic mothers and the control group in terms of maternal and infant demographic characteristics are presented in Table II. Compared to the control group, infants of diabetic and hypertensive mothers were born earlier and cesarean sections were significantly more frequent in these groups ($p = 0.001$ and $p = 0.002$, respectively). The age of mothers in the diabetic mother group was higher than in the other groups ($p=0.005$).

The results of the comparison of echocardiographic characteristics of infants of hypertensive mothers, infants of diabetic mothers and infants in the control group are given in Table III. The cfPWV values of the infants of diabetic mothers were found to be significantly higher than those of the other groups ($p<0.001$), whereas the cfPWV values of the infants of hypertensive mothers were similar to those of the control group (Fig. 2). The right ventricular free wall longitudinal strain values were more negative in hypertensive infants than in the control group. Both hypertensive and diabetic infants had higher IVSd values than the control group. ($p=0.01$) RWT values of the infants of diabetic mothers were generally higher than those of the other groups; however, this difference was statistically significant only when compared with the control group

Table II. Comparison results of infants and mothers between groups in terms of demographic characteristics.

	Control group (n=26)	Infants of hypertensive mothers (n=15)	Infants of diabetic mothers (n=26)	p
Infant				
Age, day	22.58±4.66	21.13±5.79	20.65±5.10	0.382
Sex				0.638
Male	12 (46.2%)	7 (46.7%)	9 (34.6%)	
Female	14 (53.8%)	8 (53.3%)	17 (65.4%)	
Birth weight, g	3,198±451	3,139±459	3,317±533	0.483
Gestational age at birth, wk	38.6±0.9	37.6±0.7	37.9±0.9	0.001[a,b]
Method of birth				0.002[a, b]
C/S	11 (42.3%)	13 (86.7%)	21 (80.8%)	
NSVD	15 (57.7%)	2 (13.3%)	5 (19.2%)	
IVF	3 (11.5%)	1 (6.7%)	5 (19.2%)	0.659
Mother				
Age, yr	29±4	28±4	34±7	0.005[b,c]
BMI, kg/m^2	29.02±4.30	31.67±5.36	29.66±4.17	0.198
Parity	2 (1-9)	2 (1-4)	2 (1-5)	0.678
Hgb, g/dL	11.2±1.6	10.9±1.4	11.5±1.3	0.410
HbA1c, %	5.09±0.34	5.58±0.51	5.60±0.45	0.025[a,b]

Continuous data showing normal distribution were expressed with arithmetic mean±SD; continuous data that did not show normal distribution with median (min-max), and categorical data with number (percentage). Continuous data were compared with one way ANOVA test or Kruskal-wallis test, while categorical data were compared with chi-square or Fisher exact test.

[a]Significant difference between infant of control and hypertensive mother group, [b]Significant difference between infant of control and diabetic mother group, [c]Significant difference between infant of hypertensive mother and diabetic mother group BMI: body mass index, C/S: cesarean section, Hgb: hemoglobin, IVF: in vitro fertilization, NSVD: Normal spontaneous vaginal delivery, SD: standard deviation

(p=0.015). There was no difference between the groups in atrial strain echocardiographic evaluation data.

Univariate and multivariate linear regression analyses were performed to determine the factors affecting cfPWV values of the 67 infants included in the study and the results are presented in Table IV. Regression analyses were conducted to evaluate the relationship between maternal, obstetric, and neonatal factors and the outcome variable. In the univariate linear regression analysis, maternal age (β=0.299, p=0.014), neonatal sex (β=0.342, p=0.005), and maternal diabetes (β=0.664, p<0.001) were significantly associated with the outcome. Maternal BMI (p=0.066) and mode of delivery (p=0.078) demonstrated borderline associations. Other variables, including parity, birth weight, maternal hemoglobin level, conception via *in vitro* fertilization (IVF pregnancy), HbA1c

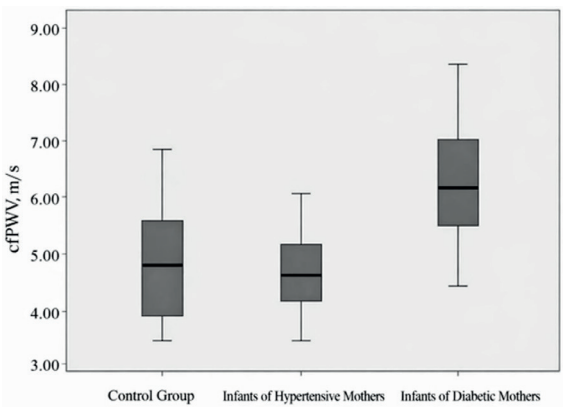

Fig. 2. Box plot of cfPWV values of infants of hypertensive mothers, diabetic mothers and control group.

cfPWV: carotid-femoral pulse wave velocity

Table III. Comparison results of the infants between the groups in terms of echocardiographic features.

	Control group (n=26)	Infants of hypertensive mothers (n=15)	Infants of diabetic mothers (n=26)	p
cfPWV, m/s	4.56±1.04	4.65±1.10	6.34±1.00	<0.001[b,c]
LV GLPS, %	-20.28±2.27	-20.40±1.51	-19.64±2.26	0.442
RV free wall strain longitudinal, %	-21.05±4.39	-25.55±6.85	-23.08±3.88	0.029[a]
RV global longitudinal peak strain, %	-18.96±3.01	-21.09±2.28	-20.46±2.80	0.057
LA reservoir strain, %	46.64±10.63	48.46±10.75	48.80±12.04	0.774
LA conduct strain, %	-30.04±10.70	-35.49±12.26	-30.26±8.33	0.230
LA contraction strain, %	-15.4 (-27.2 - -0.9)	-14.4 (-25.2 - -1)	-15.1 (-39.4 - -7.8)	0.749
IVSd, mm	4.32±0.59	4.84±0.53	4.94±1.03	0.014[a,b]
LVM, gram	11.41±2.65	11.23±2.05	11.54±2.84	0.932
LVMI, gr/m^2	45.54±9.33	48.25±7.18	48.27±10.32	0.510
RWT	0.42±0.06	0.44±0.08	0.49±0.12	0.015[b]

Continuous data showing normal distribution were expressed with arithmetic mean±SD; and continuous data that did not show normal distribution with median (min-max. Continuous data were compared with one way ANOVA test or Kruskal-wallis test.

[a]Significant difference between infant of control and hypertensive mother group, [b]Significant difference between infant of control and diabetic mother group, [c]Significant difference between infant of hypertensive mother and diabetic mother group.

cfPWV: carotid-femoral pulse wave velocity, IVSd: interventricular septum thickness, LA: left atrium, LV GLPS, left ventricular global longitudinal peak strain, LVM: Left ventricular mass, LVMI: Left ventricular mass index, RV: right ventricle, RWT: Relative wall thickness.

Table IV. Univariate and multivariate linear regression analysis for factors affecting cfPWV.

	Univariate linear regression analysis			Multivariate linear regression analysis		
	t	p	β (95% CI for β)	t	p	β (95% CI for β)
Age of mother	2.527	0.014	0.299 (0.014-0.117)	2.289	0.031	0.318 (0.006-0.122)
Maternal BMI	-1.868	0.066	-0.227 (-0.137-0.005)	-1.929	0.066	-0.268 (-0.164-0.006)
Parity	0.745	0.459	0.092 (-0.138-0.303)			
Method of birth (ref: NSVD)	1.790	0.078	0.217 (-0.070-1.291)	0.363	0.720	0.051 (-0.766-1.093)
Sex (ref: Male)	2.933	0.005	0.342 (0.293-1.541)	0.327	0.746	0.043 (-0.640-0.881)
Birth weight	0.851	0.398	0.105 (0.001-0.010)			
Maternal hemoglobin	-0.885	0.379	-0.110 (-0.317-0.122)			
IVF	0.815	0.418	0.101 (-0.566-1.346)			
HbA1c	1.476	0.149	0.242 (-0.263-1.668)	-0.228	0.822	-0.032 (-0.937-0.751)
Group (ref: Control Group)						
Maternal hypertension	0.263	0.794	0.042 (-0.605-0.786)			
Maternal diabetes	6.279	<0.001	0.664 (1.206-2.341)	4.418	<0.001	0.635 (1.046-2.880)

Multivariate linear regression; R=0.797, R^2=0.635, Adjusted R^2=0.543.

BMI: body mass index, IVF: in vitro fertilizasyon, NSVD: Normal spontaneous vaginal delivery, t: test statistic, β: standardized linear regression coefficient, CI: confidence interval.

level, and maternal hypertension were not significantly associated with the outcome. Variables with p<0.25 in the univariate linear regression analysis were included in the multivariate linear regression analysis.

In the multivariate linear regression model, maternal age (β=0.318, p=0.031) and maternal diabetes (β=0.635, p<0.001) remained independent predictors of the outcome variable. Maternal BMI (p=0.066), mode of delivery (p=0.720), neonatal sex (p=0.746), HbA1c level (p=0.822), parity, birth weight, maternal hemoglobin, IVF pregnancy, and maternal hypertension were not independently associated with the outcome.

The overall regression model demonstrated good explanatory capacity (R=0.797, R^2=0.635, adjusted R^2=0.543), indicating that approximately 63.5% of the variability in the outcome variable could be explained by the included predictors.

Discussion

Pulse wave velocity, a measure of arterial stiffness, predicts coronary heart disease, stroke, and cardiovascular mortality in adults.[20] This study found that infants born to mothers with gestational diabetes had higher pulse wave velocity values compared to controls or infants born to mothers with gestational hypertension. These findings suggest that maternal metabolic status influences neonatal arterial stiffness. The differences in PWV indicate a potential cardiovascular risk, suggesting that newborns' cardiovascular systems may undergo arterial stiffening due to maternal diabetes during the intrauterine period. The findings highlight the need to investigate prenatal diabetes exposure and examine the pathophysiological processes underlying vascular remodeling in newborns. Another important aspect was evaluating atrial and ventricular strain echocardiography, a technique not commonly used in neonates. Although the data showed no significant findings regarding early cardiac involvement, the assessment of atrial strain echocardiography for the first time in this population is noteworthy.

Increased PWV values have been documented in pediatric populations with conditions such as obesity, diabetes mellitus, and after heart transplantation procedures.[21] Although the data are conflicting, some perinatal factors may affect arterial stiffness later in life. Increased pulse wave velocity has been reported in adolescents with a history of preterm delivery, as well as in children born small for gestational age or whose mothers consumed alcohol during pregnancy.[22,23] Although there is limited research on pulse wave velocity in newborns, this remains an area that requires further exploration and clarification. In our study, the factors that may be associated with increased PWV in newborns were evaluated using the cfPWV method which is accepted as the gold standard.

Previous studies on pulse wave velocity in newborns report varying findings. One study measured aortic PWV of 30 newborns within 5 days and found an average of 4.6 m/s.[10] Another study by Alwan et al. examined 284 infants aged 14 to 42 days and found a mean brachial-femoral PWV of 6.7 m/s (brachial-ankle PWV measurements in adults are approx. 20% higher than cfPWV measurements).[24] A study using cardiac magnetic resonance imaging (MRI) on 15 newborns found PWV measurements from the thoracic arch to be 5.4 m/s in "time to peak" and 4.2 m/s in "time to foot" measurement.[25] The mean cfPWV value of our control group was 4.56 m/s, consistent with two other studies but differing from Alwan et al (likely due to differences in measurement technique). PWV values varied across studies due to factors like ambient temperature, measurement timing, and patient agitation.[26,27] Arterial stiffness can be assessed through various methods, with cfPWV recognized as the most effective non-invasive technique. While MRI provides superior measurements through three-dimensional imaging, its pediatric use is limited by sedation requirements, long examination time, high cost, and the need for specialized personnel. Echocardiographic assessment of cfPWV is the most reliable non-invasive indicator of aortic pulse wave velocity, though limited because the sternal notch to femoral artery distance doesn't represent true aortic

distance. Brachial-ankle and finger-toe pulse wave velocity measurements are less preferred as they don't reflect true values, despite their rapid measurement.[28] To standardize arterial stiffness assessment in newborns, examining large-scale cohort studies and the identification of influencing factors remains crucial.

The central finding of our study was that the cfPWV values were significantly elevated in infants born to mothers with gestational diabetes compared to both the infants of hypertensive mothers group and the healthy control group. No statistically significant difference was found between the infants of hypertensive mothers and the control group. Although there are very few studies in this area in newborns, PWV values were found to be increased in infants of diabetic mothers compared to the control group in the neonatal period[9] and to be similar to the control group in infants of hypertensive mothers in the Baby VIP study.[10] Subsequent studies on infants of diabetic mothers beyond the neonatal period have consistently reported elevated PWV values compared to the control group.[29,30] However, the lack of significant findings regarding arterial stiffness in infants born to hypertensive mothers in our study and a few others could be attributed to the small sample sizes. Since increased PWV detected in infants of diabetic mothers may constitute a risk factor for cardiovascular diseases and end-organ damage, studies including long-term follow-up should be conducted in this field and these patients should be monitored more closely for cardiovascular diseases.

The results of the multivariate linear regression analysis in our study indicate that increased maternal age and maternal diabetes mellitus were the key factors predicting cfPWV values ($p= 0.031$ and ≤ 0.001 respectively). The findings of our study are consistent with those of previous studies. Previous studies have shown that hyperglycemia can have detrimental effects on endothelial progenitor cells[31] and that advanced maternal age as well as gestational diabetes mellitus have been associated with impaired vascular development in newborns.[32,33] Factors such as maternal BMI, parity, mode of delivery, birth weight, maternal hemoglobin levels, and IVF pregnancy did not significantly influence cfPWV in our study population.

In our study, the mode of delivery was not found to be an independent determinant of the outcome. Cesarean section demonstrated a borderline association in the univariate analysis ($p=0.078$); however, this relationship disappeared after adjustment for confounding variables in the multivariate model ($p=0.720$). This finding suggests that the apparent association observed initially was likely related to underlying maternal characteristics rather than the delivery route itself. In particular, cesarean delivery is more frequently performed in pregnancies complicated by maternal conditions such as diabetes or advanced maternal age, which may account for the unadjusted association. Therefore, the route of delivery alone does not appear to influence the studied outcome.

The gestational age was significantly lower in infants born to both hypertensive and diabetic mothers compared to the control group. No significant difference in gestational age was found between infants of mothers with diabetes and infants of hypertensive mothers. The existing literature provides relevant insights. A comprehensive study by Metclafe et al. found that diabetic mothers delivered their infants earlier than the control group, consistent with the findings in our study.[34] Conversely, a cohort study by Palmsten et al. did not observe any difference in gestational age between hypertensive mothers and the control group.[35] However, a 2021 study by Bello et al., which included 137,000 pregnant women, reported that hypertensive mothers gave birth at earlier gestational ages.[36] Pregnancies complicated by hypertension and/or diabetes can result in metabolic and vascular abnormalities, as well as elevated risks of pregnancy-related complications. These factors may contribute to placental insufficiency, necessitating earlier delivery.[37] Additionally, the increased frequency of cesarean sections observed among

these patients in the present study may also be a factor in the earlier gestational age at birth.[36]

In this study, the mean IVSd in infants born to mothers with diabetes was significantly higher than in the control group. Studies on infants of diabetic mothers have reported elevated IVSd values compared to controls, attributed to increased insulin levels during pregnancy.[29,38] According to Breatnach et al., there was no significant difference in interventricular septal diameter between infants of hypertensive mothers and controls in echocardiographic examinations within 48 hours after birth.[39] Our findings corroborate earlier research, showing that infants of diabetic mothers have increased IVSd values compared to controls. However, we also observed that IVSd values in infants of hypertensive mothers were higher than in controls, contrary to existing literature. Previous studies have not reported similar findings regarding ventricular structures in infants of hypertensive mothers. Research by Vogg et al. showed that newborns exposed to maternal hypertensive disorders, particularly those born to preeclamptic mothers, exhibit increased thickness of left ventricular and septal walls compared to controls.[40] While the reasons for this increased thickness remain unclear, it may be attributed to fetal hypoxia from maternal hypertension and elevated catecholamine levels. Vogg et al. noted limited evidence for this relationship in infants of hypertensive mothers without preeclampsia.[40] Our study highlights the need for further investigations to evaluate these findings and elucidate potential pathophysiological associations.

The remodeling patterns of the left ventricle can be assessed through echocardiographic measurement of RWT and are categorized as normal or adverse. The adverse category is divided into eccentric or concentric remodeling. Research has shown that concentric remodeling, marked by high RWT, is associated with increased morbidity and mortality in hypertensive patients with hypertrophic cardiomyopathy.[23] The mean RWT of infants in our study was 0.45±0.10. An RWT value exceeding 0.41 suggests concentric remodeling or concentric hypertrophy; these cardiac alterations are distinguished by LVMI, with no established range for this parameter in newborns. In a study on preterm newborns weighing up to 2 kg, the mean RWT was 0.33, with an upper limit of 0.38, corresponding to the 80th percentile.[41] The lack of studies involving term newborns highlights the need for further research. In a study comparing a control group with infants born to diabetic mothers, both groups at 2 months of age, the RWT was 0.38 for controls and 0.5 for infants of diabetic mothers.[41] Consistent with literature, our study found that RWT of infants born to mothers with diabetes was significantly higher than in the control group.

Myocardial deformation, referred to as strain, encompasses the percentage change in length or thickness from the initial state. Strain is a physical concept describing the relative deformation of an elastic structure in response to an applied force. Strain echocardiography was utilized to evaluate the strength and contractile performance of the cardiac musculature.[42] The software developed for this method allows precise measurement of heart muscle motion in selected regions on 2D and 3D echocardiographic images. Strain echocardiography provides a more sensitive and quantitative assessment of myocardial function compared to traditional measures like ejection fraction, allowing for earlier detection of subtle abnormalities. It can detect changes in myocardial deformation that may not be apparent with conventional methods.[43] The limited literature presents a mixed picture regarding ventricular strain in infants of mothers with diabetes and/or hypertension. Some studies have reported lower left and right ventricular values in infants of diabetic mothers compared to the control group.[44] Other studies have found less negative left ventricular strain in infants of hypertensive mothers, but no difference in right ventricular strain.[39] Additionally, another study observed no divergence in left or right ventricular strain between infants of

hypertensive mothers and controls, though the right ventricular strain was less negative in infants of preeclamptic mothers relative to the control group.[45] We observed a statistically significant difference between the groups in terms of the RV free wall longitudinal strain ($p \leq 0.001$) in our study. The RV free wall strain longitudinal value of the infants of hypertensive mothers was significantly more negative than that of infants of the control group. There were no statistically significant differences in other strain parameters ($p>0.05$). Right ventricular strain parameters in neonates may be influenced by gestational age and postnatal cardiovascular adaptation, including transitional changes in pulmonary vascular resistance. The slightly lower gestational age in infants of hypertensive mothers may have contributed to the observed differences in RV strain parameters. However, these values remained within the normal range and were not considered clinically significant.[46] Traditional parameters indicate atrial function through instantaneous measurement at a single point in the cardiac cycle. However, the empty volume and fraction in the atrial phase can also be calculated to assess atrial function. These measurements however are sensitive to atrial load and indirectly reflect the atrial myocardial properties. Analyzing atrial myocardial mechanics with strain and strain rate imaging is very important as it allows direct measurement of atrial myocardial deterioration.[47] Atrial strain imaging in pediatric populations has been utilized to assess subtle atrial dysfunction, diastolic function, and remodeling in congenital heart disease, cardiomyopathies, and other conditions affecting cardiac function.[48] Although no studies have specifically evaluated left atrial strain in newborns of diabetic and hypertensive mothers, to the best of our knowledge, this is the first study in the literature to address this topic. Our study's left atrial reservoir strain of 47.89% and contraction strain of 15.04% were comparable to those reported in a study of healthy infants aged 0-24 months (52.8% and 14.2%, respectively).[49] It is important to note that in our study, there were no statistically significant differences in left atrial strain parameters between newborns of diabetic or hypertensive mothers and the control group, suggesting that, within our cohort, maternal diabetes and hypertension may not have a significant impact on neonatal left atrial function as assessed by strain echocardiography.

Limitations

Despite these findings, several limitations of the present study should be considered when interpreting the findings. First, the sample size was relatively small, particularly in the subgroup of infants of hypertensive mothers, which may have limited statistical power. Second, although maternal diagnoses were established according to standard clinical criteria during routine antenatal follow-up, subclinical metabolic alterations cannot be completely excluded. Finally, neonatal blood pressure was not systematically measured during echocardiographic assessment, although all infants were clinically stable at the time of examination and a substantial proportion were delivered and monitored at our institution.

Conclusion

The analysis of arterial stiffness in infants of diabetic mothers, infants of hypertensive mothers, and controls showed that advanced maternal age and maternal diabetes were particularly associated with increased cfPWV. Although increased cfPWV has been shown to be associated with cardiovascular events and end-organ damage, its effect in newborns is not clearly known. Echocardiographic assessment revealed an increased thickness of the interventricular septum in infants born to mothers with diabetes and hypertension, as compared to the control group. Additionally, RWT was observed to be higher in infants of diabetic mothers. This study highlights the potential influence of maternal metabolic status on neonatal cardiac morphology and vascular function. In contrast, atrial and ventricular strain parameters were not significantly affected in this patient group. The findings suggest that maternal metabolic status can influence

neonatal cardiac morphology and vascular function. Based on the data presented, further research is warranted to investigate whether the observed effects on arterial stiffness in infants of diabetic mothers persist into older ages and have long-term implications for the health of these patients.

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Ethical approval

This study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee on 20/09/2022 (Project No: GO 22/887, Decision No: 2022/18–34).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: UBM, HHA, ŞY, TK; data collection: UBM, HHA; analysis and interpretation of results: UBM, HHA; draft manuscript preparation: UBM, HHA, ŞY, 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

Electrical cardiometry and lung ultrasound in detection of volume overload in pediatric patients on hemodialysis

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ABSTRACT

Background. Assessment of volume overload and determination of dry weight are essential for children on hemodialysis (HD). This study aimed to compare the effectiveness of lung ultrasound (LUS)-derived B-lines and electrical cardiometry (EC)-derived thoracic fluid content (TFC) scores in detecting volume overload in pediatric patients undergoing maintenance HD.

Methods. This cross-sectional study was conducted on 50 patients aged 5 to 18 years, both sexes, with kidney failure on maintenance HD three times weekly. Dry weight was determined for each patient by a pediatric nephrologist based on a clinical assessment of hydration status (absence of edema, pulmonary rales, hypertension, intradialytic hypotension or cramps) and supported by bioimpedance spectroscopy values to estimate overhydration. Patients who did not reach dry weight at the end of the session were defined as the non-dry weight group (N=21) and those who did were defined as the dry weight (N=29) groups. Correlations of B-lines and TFC with clinical parameters and the diagnostic performance of these methods in predicting hypervolemia (ROC analysis) were analyzed.

Results. Before dialysis, TFC and B-line scores did not differ significantly between the dry-weight and non-dry-weight groups (P>0.05), but were significantly lower after the HD session in the dry weight group than in the non-dry weight group (P < 0.001). TFC and B-line scores could significantly predict hypervolemia (areas under the curve [AUC]: 0.750 and 0.801, respectively). In the same order the cut off values were >31 $kOhm^{-1}$ and >17, sensitivities were 76.19% and 80.95%, and specificities were 55.71% and 75.86%, respectively. TFC was comparable to the B-line score in the prediction of hypervolemia (P=0.585, difference between AUCs=0.050; 95% confidence interval: -0.132 to 0.234).

Conclusions. Both LUS and EC are valuable bedside methods for assessing volume overload in pediatric HD patients. However, EC is not as dependent on operator skills and may be a valuable tool in clinical practice, especially in settings where LUS might be challenging to perform.

Key words: lung ultrasound, electrical cardiometry, extravascular lung water, hemodialysis, pediatric.

Determining the ideal weight goal based on optimum fluid levels is challenging in children undergoing hemodialysis (HD).[1] Fluid overload stands as a distinct cardiovascular risk factor in pediatric HD patients.[2] Chronic excess fluid in the body is linked to heart-related health issues and death. However, excessive removal of fluid during HD may lead to cardiac stunning,

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hypotension, and earlier loss of residual kidney function.[3,4]

Optimizing the target weight for children undergoing HD is difficult due to multiple factors.[1] Pediatric dry weight fluctuates due to growth and might decrease dramatically during illnesses. Dry weight is mainly established by clinical evaluation, in which fluid assessment is subjective and inaccurate. Dry weight represents a clinically determined lowest post-dialysis body weight that the patient can tolerate without symptoms of hypovolemia.[5]

In recent years, various non-invasive objective techniques have been developed for monitoring hemodynamics and assessing fluid status.[6] Lung ultrasound (LUS) detects extravascular lung water (EVLW) as an indicator of systemic fluid overload in adults receiving HD and peritoneal dialysis.[7] EVLW may be detected with sonography by observing linear artifacts from enlarged interlobular septa and other subpleural structures.[8] The increase in lung density is due to transudate, which can cause reflection of the ultrasound (US) beam, resulting in bright, vertical lines called B-lines along the pleural line. The number of B-lines can be quantified using LUS and has been found to correspond to the amount of EVLW in adult patients.[1] In euvolemic patients, B-lines are typically absent. They may appear before clinical symptoms or signs of fluid excess.[9]

Electrical cardiometry (EC) measures cardiac output, thoracic fluid content (TFC), and additional hemodynamic parameters. It derives cardiac output from thoracic electrical bioimpedance (TEB) measurements.[10] TEB refers to the impedance encountered by high-frequency, low-amplitude electrical current passing through the upper and lower thorax electrodes. This measured impedance inversely correlates with the volume of thoracic fluids, meaning that higher thoracic fluid levels lead to reduced TEB values.[11]

TFC is the combined volume of fluids in the chest cavity, including intravascular and extravascular fluid. Alterations in TFC may indicate changes in total fluid status. Therefore, EC values are essential for monitoring thoracic blood volume changes during HD sessions.[12]

Although the effectiveness of LUS and EC in detecting volume overload has been compared in intensive care units, especially for predicting weaning[13], studies involving pediatric patients undergoing maintenance HD are limited.

Thus, this study aimed to compare the effectiveness of EC and LUS in detecting volume overload in pediatric patients undergoing maintenance HD, using clinically determined dry weight as the reference standard.

Materials and Methods

This cross-sectional study was carried out on 50 patients, of both sexes, aged 5 to 18 years, with kidney failure on maintenance HD three times weekly. The research was conducted from May 2023 to March 2024 after approval from the Ethics Committee (approval code: 36264PR187/4/23 , date: 15/04/2023). Informed written consent was obtained from the patients' guardians.

Coexisting interstitial lung disease, atelectasis, lung fibrosis, heart failure, and implantable cardiac pacemakers or defibrillators were deemed exclusion criteria.

All patients underwent medical history taking and physical examination. Pre- and postdialysis weights were recorded, and their systolic and diastolic blood pressure (SBP and DBP) values were measured and then presented as percentiles.[14] In this study, the patients did not have residual urine output, and only hypervolemic patients before dialysis were included.

Interdialytic weight gain (IDWG) was defined as the increase in body weight between two consecutive hemodialysis sessions and was calculated as the difference between predialysis weight and the postdialysis weight of the previous session.[15]

Interdialytic weight gain percentage (IDWG %) was calculated as follows: [(predialysis weight − previous postdialysis weight) / dry weight] × 100.[16]

Dry weight was defined as the postdialysis weight at which the child is clinically euvolemic, with no signs of fluid overload or dehydration.[17]

Delta weight was defined as the difference between postdialysis weight and dry weight.[17] Delta weight percentage (Delta weight %) was calculated as [(postdialysis weight − dry weight) / dry weight] × 100.

Dry weight was determined for each patient by a single pediatric nephrologist before starting the study[5], based on a comprehensive clinical evaluation of the patients' hydration status and bioimpedance spectroscopy (BIS). The clinically proper dry weight was defined as the lowest post-dialysis weight a patient could tolerate without exhibiting signs or symptoms of either overhydration or dehydration during or after dialysis. This determination involved assessing the patient's clinical condition, including the presence or absence of peripheral or generalized edema, chest discomfort, pleural effusion, or pulmonary edema. Intradialytic symptoms such as muscle cramps, dizziness, and hypotension were also reviewed through medical records.

The nephrologist's judgment was further supported by reference to dry weight estimated using BIS (TANITA MC-980MA-N Plus II, Japan, 2018), calculated as the pre-dialysis body weight minus the overhydration value measured by BIS. The final clinically proper dry weight combined clinical insights with BIS data, ensuring that the determined weight minimized symptoms associated with fluid imbalance.

Hypervolemia was defined as present when the patients' weight was higher than the determined dry weight. Patients who reached the clinically determined dry weight after dialysis were classified as the dry weight group, and those who remained hypervolemic were classified as the non-dry weight group. To minimize potential measurement bias, LUS and EC evaluations were conducted by independent investigators who were blinded to the clinical volume status and BIS measurements. All patients in this study were anuric. All patients were hypervolemic before the dialysis session during which the study interventions were performed.

Lung ultrasound evaluation

A physician with expertise in bedside US examinations using a SonoScape® system (A6, Shenzhen, China) equipped with a Linear Probe (6-13 MHz). The thorax was divided into 12 zones (six on each side: anterior-upper (U) R1, anterior-lower (L) R2; lateral-U R3, lateral-L R4; posterior-U R5, posterior-L R6; and similar zones on the left side: front U-L1, front-L L2; lateral-U L3, lateral-L L4; rear-U L5, rear-L L6) to check for the presence of A-lines (normal transverse shadows) or B-lines. B-lines were defined as vertical, hyperechoic artifacts that arise from the pleural line and extend to the bottom of the screen without fading. The B-line score was determined by summing the number of B-lines in the 12 lung zones. A higher B-line score indicates increased EVLW.[18]

Electrical cardiometry evaluation

An EC monitor (ICON®, Cardiotronics, Inc., La Jolla, CA, USA; Osypka Medical GmbH, Berlin, Germany) was utilized. The patients' data were entered. The device measured several hemodynamic parameters, such as TFC, cardiac index, and systemic vascular resistance. The ICON device was linked to 4 electrocardiogram electrodes that were applied to the patients' skin after alcohol cleansing. Two electrodes were positioned at the left mid-axillary line, specifically at the level of the xiphoid process, and another 5 cm below this point, one below the left ear in the neck, and one just above the left clavicular midpoint.

B-lines of LUS and EC parameters were assessed 30 minutes before and 30 minutes after a single mid-week dialysis session. Both approaches

were evaluated in terms of their specificity and sensitivity.

The patients underwent intermittent HD sessions using the Fresenius 4008 B HD machine (Germany) with blood flow rate of 5 mL/kg/min. The HD sessions utilized polysulphane hollow fiber dialyzers appropriate for the patients' surface area (Fresenius F3 = 0.4 m^2, F4 = 0.7 m^2, F5 = 1.0 m^2, and F6 = 1.2 m^2). Bicarbonate HD solutions were utilized, and patients were given supportive therapy, including erythropoietin injections, oral calcium supplements, one alpha agonist, folic acid, and antihypertensive medications such as angiotensin-converting enzyme (ACE) inhibitors and beta blockers for those with hypertension.

The study's primary outcome was the evaluation of volume status in pediatric patients on maintenance HD by LUS and EC. The secondary outcome was the comparison of the specificity and sensitivity of each method.

Sample size calculation

The sample size calculation was performed using G*Power 3.1.9.2 (Universität Kiel, Germany). According to a previous study[19], the mean ± SD of the B-line score before HD was 59.6 ± 42.8, and the B-line score after HD was 32.7 ± 27.9. The sample size was determined based on the following considerations: a 0.74 effect size, a 95% confidence interval (CI), and a study power of 95%. Two cases were added to each group to compensate for potential dropouts. Therefore, a total of 50 patients were recruited.

Statistical analysis

The statistical analysis was performed using SPSS version 27 (IBM©, Armonk, NY, USA). The Shapiro-Wilks test and histograms were used to determine whether the data distribution was normal. To evaluate quantitative parametric data, expressed as mean ± standard deviation (SD), the unpaired Student's t-test was used. Fisher's exact test or the chi-square test was used to evaluate qualitative variables expressed as percentages or frequencies. Pearson's correlation analysis was used to determine the correlation between quantitative variables. Post-dialysis values for SBP percentile, TFC, and B-lines were used for the correlation analysis. ROC curve analysis was used to determine the overall diagnostic performance. Statistical significance was defined as two-tailed p values less than 0.05.

Results

Eligibility was determined for 61 patients in this study. Seven failed to meet the requirements, and four refused to participate. The remaining 50 patients were included in the statistical analysis and assigned to the non-dry weight group (N = 21) and the dry weight group (N = 29) (Fig. 1).

Comparison of dry weight and non-dry weight groups

Age, sex, and duration of HD were comparable between the two groups. Dry weight, pre-dialysis weight, post-dialysis weight, and interdialytic weight gain (IDWG)% (pre-dialysis weight - previous post-dialysis weight) were similar between the dry and non-dry weight groups. Ultrafiltration was higher in the dry weight group with a non-significant difference (p=0.075). After dialysis, delta weight (post-

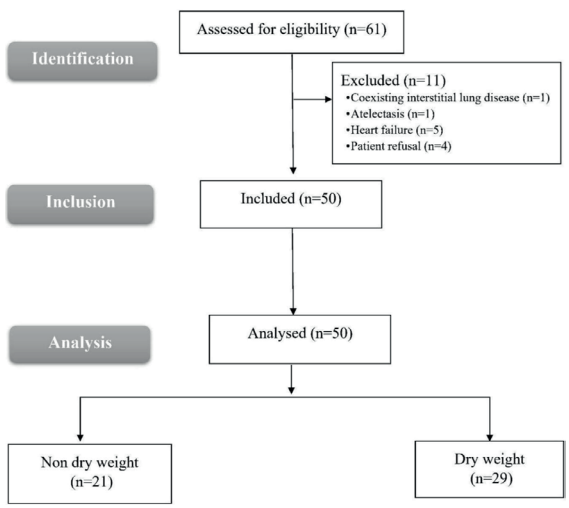

Fig. 1. STROBE flowchart of the enrolled patients.

dialysis weight - dry weight) was significantly lower in the dry weight group (p <0.001; Table I).

Before dialysis, SBP percentile did not differ significantly. After dialysis, SBP drop was higher in the dry weight group but the difference was not significant (p=0.06). Before or after-dialysis DBP percentiles did not differ significantly between groups (Table II).

TFC and B-line scores did not differ significantly before dialysis between the two groups. They were significantly lower after dialysis in the dry weight group than in the non-dry weight group (p < 0.001). TFC and B-line score changes were significantly greater in the dry weight group than in the non-dry weight group (p <0.05; Table II, Fig. 2).

Correlation of after dialysis TFC and B-line scores with clinical parameters

The correlations of post-dialysis TFC and B-line scores with clinical parameters (delta weight and after dialysis SBP percentile) among the 50 patients are given in Table III. TFC and B-line scores were positively correlated with delta weight (%) (r=0.415, p=0.002 and r=0.475, p<0.001; respectively). The B-line score was positively correlated with after dialysis SBP percentile (r = 0.439, p = 0.001), and TFC was also positively correlated with after dialysis SBP percentile (r = 0.286, p = 0.043; Table III).

Diagnostic performance of TFC and B-line scores in predicting hypervolemia

TFC significantly predicted hypervolemia (p <0.001 and area under the curve [AUC] = 0.750) with 76.19% sensitivity, 55.71% specificity, 55.2% positive predictive value (PPV), and 76.2% negative predictive value (NPV) at a cut-off>31 $kOhm^{-1}$ with a 95% CI of 0.608-0.862. The B-line score significantly predicted hypervolemia (P <0.001 and AUC = 0.801) with 80.95% sensitivity, 75.86% specificity, 70.8% PPV, and 84.6% NPV at a cut-off>17 (95% CI: 0.664-0.901). TFC was comparable to the B-line score in the prediction of hypervolemia (p=0.585, difference between AUCs=0.050, 95% CI: -0.132 to 0.234; Fig. 3).

Table I. Demographic data, weight, overload percentage pre dialysis and post dialysis of the study groups.

		Non-dry weight (n=21)	Dry weight (n=29)	P value
Age (years)		11.19 ± 3.67	10.86 ± 3.79	0.760
Sex	Male	11 (52.38%)	16 (55.17%)	0.845
	Female	10 (47.62%)	13 (44.83%)	
Duration of HD (years)		4 (2 - 6)	4 (3 - 6)	0.850
Dry weight (kg)		37.7 (28 - 56.5)	37.6 (26 - 47.2)	0.602
Pre-dialysis weight (kg)		39 (29.7 - 58)	38.45 (27 - 48.9)	0.609
Post-dialysis weight (kg)		38.25 (29.3 - 57.1)	37.6 (26.15 - 47.2)	0.473
Ultrafiltration (kg)		1.24 ± 0.21	1.44 ± 0.47	0.075
Delta weight (kg)		1.1 (0.7 - 1.4)	0.1 (0.1 - 0.15)	<0.001*
IDWG (%)		3.66 (3.13 - 6.38)	4.42 (3.08 - 5.21)	0.768
Delta weight (%)		2.65 (2.03 - 5.24)	0.29 (0.2 - 0.4)	<0.001*

Data is presented as mean ± standard deviation, or median (interquartile range) or frequency (%).
*Significant with p ≤0.05.
HD: hemodialysis
Delta weight= post-dialysis weight - dry weight.
IDWG (interdialytic weight gain) (%)=(Pre-dialysis weight - dry weight)/dry weight)*100.
Delta weight (%): ((Post - dialysis weight – dry weight)/dry weight) *100.

Table II. Systolic and diastolic blood pressure, TFC and B-line score of the studied groups

	Non-dry weight group (n=21)	Dry weight group (n=29)	p value
Patients using antihypertensive drugs	9 (42.85%)	11 (37.93%)	0.725
Systolic blood pressure (percentiles)			
Before	88.24±9.01	86.28±11.44	0.517
After	71.43±15.18	63.17±17.08	0.084
Change	-16.81±11.73	-23.1±11.14	0.060
Diastolic blood pressure (percentiles)			
Before	83.29±11.37	76.52±17.02	0.120
After	62.14±18.68	53.45±21.88	0.147
Change	-21.14±10.05	-23.07±13.72	0.588
TFC (kOhm-1)			
Before	44.29±3.91	43.52±4.02	0.503
After	35.38±4.15	31.86±3.54	0.002*
Change	-8.9±5.06	-11.66±4.07	0.038*
B-line score			
Before	61.9±37.24	58.83±25.29	0.729
After	47.95±30.63	17.34±15.69	<0.001*
Change	-13.95±19.94	-41.48±15.98	<0.001*

Data are presented as mean ± standard deviation. TFC: Thoracic fluid content.
*Significant with p ≤0.05.

Table III. Correlation of post-dialysis TFC and B-line scores with clinical parameters

		TFC (kOhm-1) (n=50)	B-line score (n=50)
Delta weight (%)	r	0.415	0.475
	p value	0.002*	<0.001*
SBP percentiles	r	0.286	0.439
	p value	0.043*	0.001*

Post-dialysis values for SBP percentile, TFC and B-lines were used for the correlation analysis.
*Significant with p ≤0.05.
r: Pearson correlation coefficient, SBP: systolic blood pressure, TFC: Thoracic fluid content.

Discussion

In this cross-sectional study, we assessed the role of different thoracic fluid status measurement methods (the LUS-derived B-lines and EC-derived TFC scores) to evaluate fluid overload in pediatric maintenance HD patients. Both methods were well correlated with clinical parameters of hypervolemia including post-dialysis residual hypervolemia (delta weight) and post-dialysis SBP. The predictive sensitivity and specificity of B-lines were 81% and 76%, whereas for TFC they were 76% and 55%, respectively.

The occurrence of both hypovolemia and hypervolemia can negatively impact quality of life and contribute to the development of chronic cardiovascular disease. Therefore, careful adjustment of the prescribed target weight in children undergoing HD is crucial to minimize the risks of fluid retention.[10]

Similarly, Paglialonga et al. noted that interdialytic BP fluctuations in pediatric cases undergoing chronic HD showed significant variability. Moreover, BP changes were significantly correlated with corresponding variations in body weight.[20]

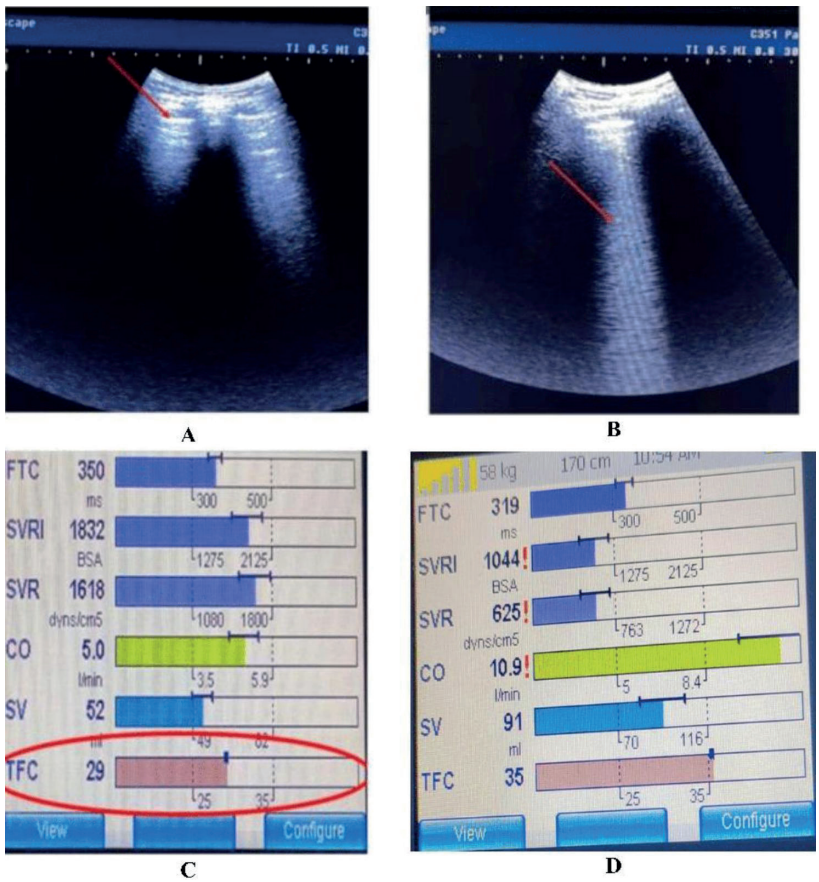

Fig. 2. Upper panel: Lung ultrasound showing **A)** normal A-lines (arrow) with no B-lines in a case in the dry weight group, and **B)** B-lines (arrow) in a case in the non-dry weight group. Lower panel: Cardiometry of a case in C) the dry weight group and **D)** the non-dry weight group.

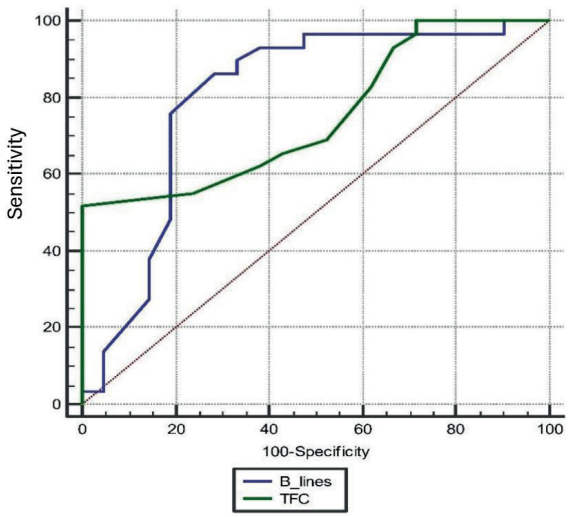

Fig. 3. ROC curves for thoracic fluid content and B-line score in the diagnostic evaluation of hypervolemia.
TFC: Thoracic fluid content.

In our study, B-line scores were significantly lower after dialysis in the dry weight group compared to the non-dry weight group, and both modalities showed good predictive ability for detecting hypervolemia, confirming the utility of LUS in assessing fluid status. Our results regarding B-lines are consistent with previous observations. Arthur et al.[21] stated that B-line scores were significantly lower after dialysis than before dialysis. The B-line number decreased by 1.69 between the pre-dialysis assessment and the midpoint of the HD session and by 0.58 between the midpoint and the end of the session. Additionally, there was a correlation between fluid loss and B-line reduction, with each 1 mL/kg of fluid loss corresponding to a decline of 0.079 in the initial B-line count. Based on these findings, the

researchers concluded that LUS can effectively evaluate fluid volume status, as demonstrated by the correlation between B-line changes and the amount of fluid removed per body weight.

Similarly, Sweed et al.[19] found no difference in B-line scores between the two groups (the non-dry and dry weights) before dialysis. However, after dialysis, the dry weight group had significantly lower B-line scores than the non-dry weight group. Additionally, there was a positive correlation between the total number of B-lines before dialysis and interdialytic weight gain, pre-dialytic BP, and clinical fluid score. Weight loss was correlated with the decline in B-line scores.

Additionally, Fu et al.[22] stated that the mean B-line scores diminished from before HD to after HD (23.5 vs. 8.5) in the dry Weight group and from before HD to after HD (56.5 vs. 32) in the non-dry weight group.

Our study also demonstrated the clinical value of TFC as an indicator of fluid status. Within our pediatric HD cohort, TFC was significantly lower after HD in those who achieved dry weight compared to the non-dry weight group. This supports the utility of TFC in assessing hypervolemia and monitoring fluid removal.

In line with our findings, Wilken et al.[23] studied the effect of HD on EC parameters in pediatric patients with kidney failure on HD. They found that TFC was significantly lower after dialysis than before the dialysis session. They concluded that TFC could be used as an additional parameter to assess the patients' fluid status. Bioimpedance (comparable to the EC parameter TFC) has been studied with other devices in the HD setting.[24,25]

However, it is important to note that EC-derived TFC is an indirect measure of thoracic fluid and may be influenced by factors other than net fluid removal. Transcellular fluid shifts, changes in plasma osmolarity, hemoconcentration, electrolyte variations, and redistribution between intravascular, interstitial, and intracellular compartments during HD can alter electrical conductivity and affect TFC readings independently of actual fluid volume. Consequently, TFC values should be interpreted with caution, particularly in pediatric HD patients, whose fluid and electrolyte shifts may be more volatile. Combining EC with other direct or imaging-based assessments may improve accuracy and reduce misclassification of volume status.[23]

TFC serves as an indicator for both extravascular and intravascular thoracic fluid. Nevertheless, TFC exhibited a strong correlation with the US in estimating EVLW.[26] Consequently, a high TFC value may serve as an indirect indicator of hypervolemia. Prior studies in which TFC successfully monitored the hemodynamic impact of diuretics substantiate this hypothesis, as well as its role in assessing thoracic edema in heart failure patients.[27] Additionally, TFC has been shown to monitor the patients' body weight change and the volume of ultrafiltrate extracted during HD.[28] TFC and fluid balance during cardiac surgery have exhibited a strong correlation.[29]

In line with these findings, Yoon et al. found that TFC correlated well with LUS in estimating EVLW in neonates with transient tachypnea, which is characterized by pulmonary edema resulting from delayed resorption and clearance of fetal alveolar fluid.[30]

Another study conducted by El-Fattah et al. compared the effectiveness of EC-derived TFC and LUS in diagnosing and monitoring transient tachypnea of newborns (TTN) in late preterm and term infants. The researchers demonstrated that both TFC, measured by EC and LUS, offer valuable bedside tools for diagnosing and managing TTN. Furthermore, they found a strong correlation between TFC, the LUS score, and the degree of respiratory distress characterized by EVLW.[31]

Despite these strengths, EC has limitations. Although EC is considered operator-independent, its accuracy may be affected by factors like skin resistance, electrode placement,

and patient movement, which can compromise signal quality. Additionally, TFC measured by EC is an indirect marker of fluid status and does not specifically quantify EVLW. Therefore, TFC values should be interpreted cautiously, particularly in patients with conditions that may influence thoracic conductivity.

Although the ROC analysis revealed that TFC measured by EC and the B-line score assessed via LUS had similar diagnostic performance in detecting hypervolemia (p=0.585), their clinical utility and feasibility in routine practice differ in important ways. Both methods demonstrated moderate to high sensitivity and specificity, suggesting that either can be useful in evaluating fluid status in pediatric HD patients. However, EC offers certain advantages due to its operator-independence, rapid application, and real-time monitoring capabilities. It may be particularly useful in settings where trained sonographers are not readily available or when continuous hemodynamic monitoring is required. Conversely, LUS provides direct visualization of pulmonary congestion but requires operator expertise and may be limited in cases with poor acoustic windows (e.g., obesity, subcutaneous emphysema).

Thus, while EC and LUS are diagnostically comparable, their strengths differ: EC is better suited for automated, bedside monitoring, whereas LUS remains a valuable imaging tool when performed by trained personnel. Integrating both methods, when feasible, may provide complementary data, improving diagnostic confidence and patient management.

One drawback of LUS is its limited specificity for B-lines, which makes it challenging to distinguish between fibrotic B-lines (associated with intralobular or subpleural septal thickening) and edematous B-lines (indicating intralobular or interlobular septal thickening).[32] Furthermore, EVLW accumulation caused by respiratory disease or cardiac failure is challenging to distinguish from one another.[33] Additionally, cases of morbid obesity, subcutaneous emphysema, pneumectomy, or pleurisy in patients may lead to reduced precision when employing this technique.[34] Despite its popularity as a valuable instrument for lung assessment, the requirement for an expert operator restricts the application of LUS. Good inter-observer agreement has been reported for LUS.[35] Nevertheless, it continues to be regarded as a subjective and operator-dependent method.

EC can be used to measure EVLW non-invasively.[36] By monitoring alterations in TEB throughout the cardiac cycle, it is possible to continuously track the progression of lung edema and the reduction in lung water content as the condition improves. Without radiation exposure, this method can quantify disease severity and treatment response.[37]

Within the cohort of pediatric HD patients, our study confirmed that TFC was significantly lower after HD in those who achieved dry weight compared to the non-dry weight group, supporting its utility in assessing fluid status and hypervolemia.

The current study was subject to several limitations, including a limited sample size and its completion at a single location, which may hinder the generalizability of the findings. Future research involving larger, multi-center studies with control groups is recommended. Additionally, comparisons with other techniques, such as echocardiography and BIS, would provide valuable insights. While LUS offers direct visualization of pulmonary congestion, it is operator-dependent and may be limited in patients with poor acoustic windows, such as those with obesity or subcutaneous emphysema.

Conclusions

While the predictive strengths of EC and LUS are comparable, EC is not as dependent on operator skills and can detect hypervolemia with similar accuracy. EC is a feasible alternative to LUS for assessing hypervolemia in pediatric HD patients. Given its objectivity and reduced

reliance on skilled operators, EC may be a valuable tool in clinical practice, especially in settings where LUS might be challenging to perform.

Ethical approval

The study was approved by Ethical Committee Tanta University Hospitals, Egypt (approval code: 36264PR187/4/23, date: 15/04/2023) and registration of clinicaltrials.gov (ID: NCT05943717).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: SME, HIH; data collection: HAB, SAM; analysis and interpretation of results: MSE, YGHE; draft manuscript preparation: SME. 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

Comprehensive phenotypic characterization of *Pseudomonas aeruginosa* isolates from cystic fibrosis patients: antimicrobial susceptibility, tolerance, hypermutation, biofilm formation, and antibiofilm activity

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ABSTRACT

Background. *Pseudomonas aeruginosa* is an opportunistic pathogen that plays a critical role in chronic lung infections in patients with cystic fibrosis (CF), primarily due to its ability to form biofilms and develop antibiotic resistance. This study aimed to evaluate the biofilm-forming ability and antibiotic resistance profiles of *P. aeruginosa* isolates obtained from patients with CF, and to investigate the relationship between biofilm production and antimicrobial resistance.

Methods. 151 *P. aeruginosa* isolates were collected from patients with CF attending a university hospital. Antibiotic susceptibility testing was performed using both broth microdilution and gradient diffusion methods. Phenotypic determination of virulence factors was performed using standard plate assays. Biofilm production was quantified using the crystal violet microtiter plate assay and Minimum Biofilm Eradication Concentration (MBEC) assay. Statistical analysis was performed to evaluate the association between biofilm formation and antibiotic resistance.

Results. The median age of patients with CF was 11.5 years, with 51.7% being female. Although resistance to certain antibiotics was observed, overall resistance rates remained relatively low, with the highest rate being 11%. A total of 30 (19.9%) *P. aeruginosa* isolates, showing intra-zone growth, were positive for antibiotic tolerance, while 10 (6.6%) of the 151 isolates exhibited hypermutator phenotypes based on the phenotypic hypermutation test. Biofilm evaluation showed that 14% of isolates were strong biofilm producers, 35.8% moderate, and 21.9% weak. 75 *P. aeruginosa* isolates were assessed for antibiofilm activity using the MBEC assay. Diallyl disulfide alone showed no significant effect. Combined with ciprofloxacin, it reduced minimum biofilm inhibitory concentration (MBIC) in 16% of isolates, while 28% showed increased MBIC, suggesting antagonism. With tobramycin, 22.3% of isolates showed enhanced antibiofilm activity, indicated by a decrease in MBIC.

Conclusion. In our study, while a high level of biofilm production was observed among *P. aeruginosa* isolates from patients with CF, antibiotic resistance rates were found to be low. These results highlight the need for therapeutic strategies targeting biofilms to improve treatment outcomes in CF-related *P. aeruginosa* infections. Additionally, our data indicate that low ceftazidime resistance in this cohort supports the use of beta-lactam–based empirical strategies and carbapenem-sparing approaches, while recognizing that these findings may not be directly generalizable beyond the local context.

Key words: biofilm, crystal violet, cystic fibrosis, MBEC assay, *P. aeruginosa*, virulence.

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Cystic fibrosis (CF) is the most common life-limiting autosomal recessive genetic disorder with an estimated birth incidence of approximately 1 in 3200.[1] CF arises from mutations in both alleles of the cystic fibrosis transmembrane conductance regulator *(CFTR)* gene, located on the long arm of chromosome 7.[2] The defective CFTR protein, which functions as a chloride channel, leads to recurrent and chronic sinus and pulmonary infections in patients with CF.[3] Impaired CFTR function in the respiratory tract results in thickened mucus that cannot be effectively cleared by the mucociliary system. Consequently, this promotes chronic infections and triggers persistent inflammation. The accumulation of inflammatory cytokines and secreted products contributes to lung damage and the development of bronchiectasis.[4] Throughout their lives, patients with CF experience recurrent respiratory infections, with the spectrum of pathogens evolving over time and with age.[5] *Staphylococcus aureus* is most frequently detected in young children whereas *Pseudomonas aeruginosa*, *Achromobacter* spp., *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* complex (Bcc) species are more commonly isolated in children and adults. While these bacteria are traditionally considered classical CF pathogens, there is growing recognition of the significance and pathogenic potential of mycobacteria, fungi, and viruses in CF respiratory infections.[6]

The respiratory tract of patients with CF is particularly prone to colonization by *P. aeruginosa* which is the most significant and prevalent gram-negative pathogen in this population *P. aeruginosa* is a rod shaped bacterium belonging to the family *Pseudomonadaceae*. As an opportunistic pathogen it rarely causes disease in healthy individuals but proliferates easily in immunocompromised patients.[7] Metabolically, *P. aeruginosa* is oxidase positive and does not ferment lactose. However, under anaerobic conditions, such as those present in the CF lung, it can utilize nitrite or nitrate as terminal electron acceptors. In the early stages of infection, *P. aeruginosa* typically exists as a nonmucoid strain that can either be cleared by the host's immune system or eradicated through antibiotic therapy.[8,9] Over time, however, *P. aeruginosa* undergoes a phenotypic switch, producing alginate and forming robust biofilms.[10] Once biofilms are established, they present a significant challenge to standard antibiotic treatments due to their protective matrix. Therefore, strategies are available to eliminate early infection by using inhaled antibiotics with or without oral quinolones. Consequently, therapeutic strategies have been developed to target early infections, including the use of inhaled antibiotics with or without oral quinolones[8]. Additionally, the biofilm environment facilitates the emergence of multidrug-tolerant persistent cells which are implicated in the persistence of chronic and recurrent infections in patients with CF.[11]

A biofilm is a structured community of microorganisms that attaches to both living and nonliving surfaces, encased within a self-produced matrix of extracellular polymeric substances. This matrix is composed of exopolysaccharides, proteins, metabolites, and extracellular DNA. Microbial cells within biofilms exhibit significantly reduced susceptibility to antimicrobial agents and host immune defenses compared to their planktonic counterparts, which grow in liquid suspension.[12] In patients with CF, *P. aeruginosa* is a major cause of chronic lung infections, forming resilient biofilms on lung epithelial cell surfaces. This process involves the secretion of DNA, proteins, and exopolysaccharides, which contribute to the protective nature of the biofilm and the persistence of the infection.[13]

The aim of this study was to evaluate the antibiotic susceptibility, biofilm-forming capacity, and antibiofilm activity (tobramycin, ciprofloxacin, and garlic extract) of *P. aeruginosa* isolates obtained from respiratory tract samples (throat swab, sputum, and bronchoalveolar lavage) of patients with CF during routine hospital visits, as well as to identify hypermutator and antibiotic-tolerant phenotypes among the isolates and to assess their associations with relevant clinical parameters.

Materials and Methods

This study was approved by Hacettepe University Health Sciences Research Ethics Committee (Date: March 30, 2021, Decision No: 2021/07-11).

Patient population

Demographic characteristics of patients and clinical samples (age, gender, follow-up period of patients, body mass index, sample type) and potential risk factors (diagnosis of concomitant infection, diagnosis of other concomitant disease (diabetes, etc.), antibiotic use (frequency of antibiotic use within the past year), number of acute pulmonary exacerbations in a year and history of hospitalization, date of application to CF outpatient clinic) at the time of the first *P. aeruginosa* isolation were prospectively recorded for each patient using a standardized patient information form. Pediatric patients with CF who had either an initial *P. aeruginosa* isolation or established *P. aeruginosa* colonization were included in the study.

Definition and referencing of clinical severity

In this study, we used the definition for Pulmonary Exacerbation based on signs and symptoms characterized as major criteria or minor criteria, those who required hospitalization and intravenous (IV) antibiotic and/or oxygen/respiratory support treatment were considered to have severe and those treated at home with oral antibiotics were defined as mild exacerbations.[14]

Imaging methods and bronchiectasis ascertainment

Thorax high-resolution computed tomography (HRCT) is the gold standard for the detection and characterization of bronchiectasis and atelectasis in patients with CF. In this study, HRCT examinations were routinely performed between January 2021 and May 2023 and interpreted by two experienced pediatric radiologists.

Bacterial isolates

This prospective study included 151 patients with CF and *P. aeruginosa* (n=151) isolates grown in respiratory tract samples (throat swab, sputum) taken during both disease episodes and routine hospital visits in patients who were followed up at the Department of Pediatric Pulmonology at Hacettepe University Children's Hospital between January 2021 and May 2023. Species identification of *P. aeruginosa* was performed with the matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS/ Phoenix/ (Bruker, Germany)) system. Species identification in all isolates was confirmed with conventional methods (Gram staining, oxidase test and inoculation in triple sugar iron agar). Following species identification and confirmation of *P. aeruginosa* isolates, all isolates were stored in tryptic soy broth supplemented with glycerol and stored at -20 °C for the duration of the study.

Antibiotic susceptibility testing

Antibiotic susceptibility testing was performed using both broth microdilution and gradient diffusion methods. Mueller-Hinton broth (MHB) (Sigma Aldrich, USA) and Mueller-Hinton agar (MHA) (BD, USA) media were used for antimicrobial susceptibility testing of all isolates. For the broth microdilution method, the following antibiotic powders were utilized: tobramycin (minimum inhibitory concentration [MIC] range = 0.016-256 mg/L, Thermo scientific-USA), meropenem (MIC range: 0.002-32 mg/L, Thermo scientific-USA), ceftazidime (MIC range: 0.016-256 mg/L, Thermo scientific-USA), levofloxacin (MIC range = 0.002-32 mg/L, Cayman-USA) and colistin sulfate (MIC range = 0.125-256 mg/L, Cayman-USA). For gradient diffusion testing, piperacillin-tazobactam (Oxoid, UK) gradient strips were used, and *P. aeruginosa* ATCC 25853 served as the quality control strain.

Phenotypic determination of virulence

Determination of antibiotic-tolerant phenotypes in P. aeruginosa isolates from CF patients (TD test)

All isolates included in the study (n=151) were adjusted to a bacterial suspension of 10^6-10^7 CFU/mL. The suspensions were then inoculated onto Luria-Bertani (LB) agar plates, following a procedure similar to the disk diffusion method. A tobramycin antibiotic disk was placed at the center of each plate and the plates were incubated at 37 °C overnight. After 24 hours, the antibiotic disk was removed and a disk containing 2 mg of glucose was placed in the same position, followed by an additional overnight incubation. The absence of intra-zone bacterial growth following the first incubation and the appearance of intra-zone regrowth after the second incubation were interpreted as the presence of tolerant/persistent cells.[15]

Determination of hypermutator phenotypes among P. aeruginosa isolates in CF patients

Bacterial isolates were subcultured on blood agar and incubated at 37 °C for 24 hours. Following incubation, bacterial suspensions were prepared and serially diluted from 10^{-1}-10^{-8}. The undiluted, 10^{-1} and 10^{-2} bacterial suspensions were inoculated onto MHA containing 300 μg/mL rifampicin, while the 10^{-7} and 10^{-8} dilutions were inoculated onto MHA without antibiotics. All plates were incubated at 37 °C for 24 hours and colony counts were performed. The hypermutation frequency was calculated as the ratio of the total number of colonies on rifampicin-containing plates to the total number of colonies on antibiotic-free plates.[16]

Assessment of biofilm formation using the crystal violet assay

Biofilm formation was assessed using the standard crystal violet microtiter plate assay, as previously described. Briefly, bacterial suspensions were inoculated into 96-well microplates and incubated to allow biofilm formation. After washing to remove non-adherent cells, biofilms were stained with crystal violet, and the optical density was measured at 590 nm to quantify biofilm production. The optical density cutoff value (ODc) was calculated as three standard deviations (SD) above the mean OD value of the negative control. ODc= mean OD of the negative control + (3 x SD negative control). Based on this threshold, biofilm production was categorized as follows: strong biofilm formation (4 x ODc <OD), moderate biofilm formation (2 x ODc <OD≤4 x ODc); weak biofilm formation (ODc <OD≤2 x ODc); and non-biofilm (OD≤ODc) according to their optical densities.[17]

Evaluation of antibiofilm efficacy using calgary biofilm device

A total of 75 *P. aeruginosa* isolates, previously categorized based on crystal violet staining as strong, moderate or weak biofilm producers, along with tobramycin-resistant non-biofilm-forming isolates, were selected for assessment of antibiofilm activity against various agents using the Minimum Biofilm Eradication Concentration Assay™ (MBEC Assay) (Physiology and Genetics, P&G, Innovotech Inc., Edmonton, AB, Canada). Initially, all isolates were grown overnight in Tryptic soy broth (TSB) medium at 37 °C. The following day, overnight cultures were adjusted to an optical density at 600 nm (OD600) of 0.1 (10^5 CFU/mL) using TSB medium and subsequently subjected to a 1:1000 dilution in TSB medium. A volume of 150 μL of the diluted bacterial suspension was added to the wells of sterile 96-well microtiter plates, each fitted with a polystyrene microtiter peg lid (MBEC Assay). Plates were incubated at 37 °C with shaking at 110 rpm for 24 hours to allow biofilm formation on the pegs. After incubation, the peg lids were removed and washed three times in 150 μL sterile distilled water to eliminate planktonic bacteria. The peg lids were transferred to new

96-well microtiter plates (antibiotic challenge plates) containing 200 μL per well of different concentrations of ciprofloxacin, colistin or diallyl disulfide. In columns 1 to 11, the tested concentration ranges of ciprofloxacin, colistin and diallyl disulfide were 128 mg/L, 128 mg/L and 512 mg/L, respectively. Antibiotic containing plates with peg lids were incubated overnight at 37 °C with shaking at 110 rpm. Following antibiotic exposure, the peg lids were again washed three times in microtiter plates containing 150 μL sterile distilled water and transferred to fresh 96-well plates containing 200 μL TSB medium in each well. Biofilms were dislodged from the pegs via sonication for 30 minutes and plates were sealed with regular flat lids and incubated at 37°C for another 24 hours under the same shaking conditions at 110 rpm (recovery plates). Biofilm regrowth was quantified by measuring optical density at 650 nm (OD650) using a microplate reader enzyme-linked immunosorbent assay (ELISA). Minimum biofilm inhibitory concentration (MBIC) was defined as the lowest concentration of a compound that inhibits biofilm formation.

Statistical analyses

Statistical analyses were performed using the SPSS version 25.0 software package (IBM, SPSS, Chicago, IL, USA). The normality of data distribution was assessed both analytically (Kolmogorov–Smirnov and Shapiro–Wilk tests) and visually (via histograms and probability plots). Categorical variables were presented as absolute and relative frequencies. Continuous variables were expressed as mean ± standard deviation (SD) if normally distributed, or as median and interquartile range (IQR) if not. Changes in forced expiratory volume in 1 second (FEV_1; initial and final values) were evaluated using the Wilcoxon signed-rank test, as the data were not normally distributed. The chi-square test was applied to assess the association between antibiotic resistance and biofilm production. A p-value of <0.05 was considered statistically significant.

Results

Patients and demographic characteristics

The demographic and clinical characteristics of the pediatric patients with CF are summarized in Table I. Briefly, the cohort consisted of both male and female patients with a median age in childhood and a median body mass index within the expected range for CF. Approximately one-third of the patients experienced at least one acute pulmonary exacerbation during follow-up, most of which were mild. *P. aeruginosa* was isolated predominantly from sputum samples, and chronic infection was more frequent than initial isolation. No significant difference was observed between initial and final FEV_1 values during the follow-up period ($p = 0.2$). Eradication regimens used in patients with initial *P. aeruginosa* isolation were summarized in Fig. 1. Inhaled tobramycin, either alone or in combination with oral ciprofloxacin, was the most frequently preferred treatment, while alternative IV and inhaled regimens were used in a smaller proportion of patients. No eradication therapy was initiated in a limited number of cases due to unavailable follow-up data. The distribution of comorbid systemic manifestations among the patients is shown in Fig. 2. Exocrine pancreatic insufficiency (EPI) and bronchiectasis were the most frequently observed conditions, while malnutrition and other systemic comorbidities were detected at lower frequencies.

Antibiotic susceptibility testing results

The MIC range, MIC_{50} and MIC_{90} values and resistance rates of *P. aeruginosa* isolates against tobramycin, meropenem, ceftazidime, levofloxacin, colistin sulfate and piperacillin-tazobactam (PIP+TAZ) are given in Table II.

Detection of antibiotic-tolerant and hypermutator phenotypes in P. aeruginosa isolates

According to the tolerance test results; it was determined that there was intra-zone growth

Table I. Demographic and clinical characteristics of patients with cystic fibrosis and *Pseudomonas aeruginosa* infection (N=151).

Gender, n (%)	
Male	73 (48.3%)
Female	78 (51.7%)
Age, years, (SD: 4.8)	17.1
Acute pulmonary exacerbation, n (%)	50 (32.4%)
Mild	33 (67.3%)
Severe	17 (32.7%)
Specimen type, n (%)	
Oropharyngeal swab	33 (21.8%)
Sputum	118 (78.2%)
Initial vs. chronic infection	
Initial infection, n (%)	59 (39.1%)
Chronic infection, n (%)	92 (60.9%)
Colonization time, months, median (IQR)	38 (23-84)
FEV_1	
Initial FEV_1 between 60% and 95% of predicted, n (%)	125 (82%)
Final FEV_1 between 60% and 100% of predicted, n (%)	118 (78%)

FEV_1: forced expiratory volume in 1 second, IQR: interquartile range, SD: standard deviation.

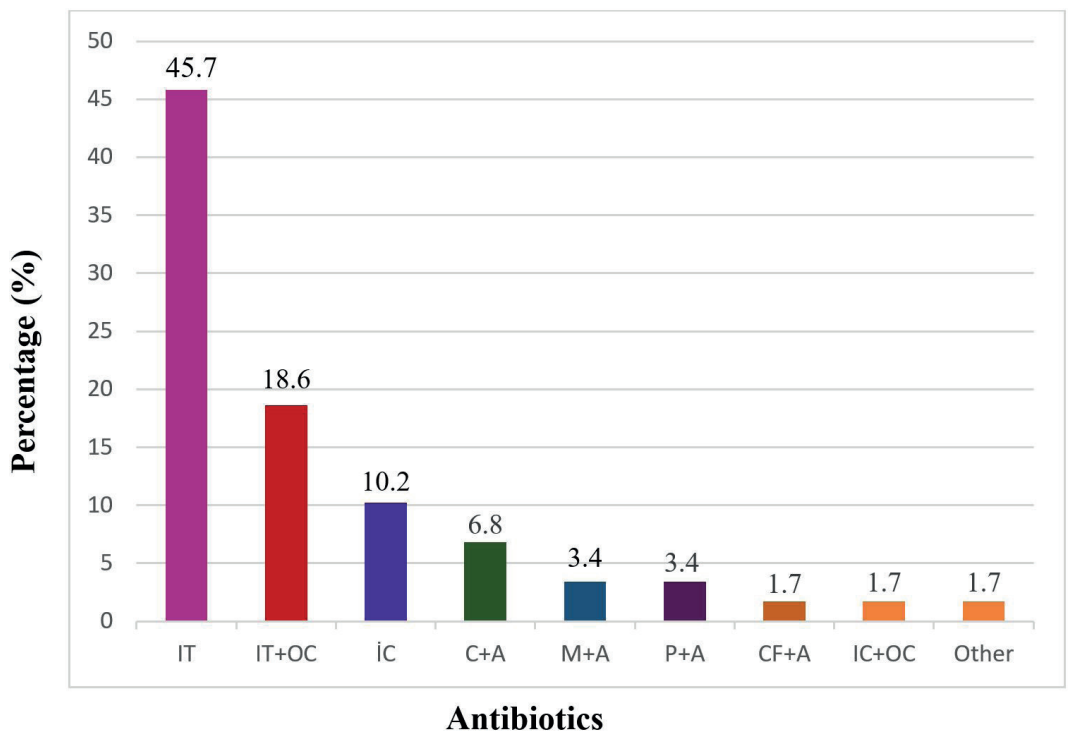

Fig. 1. Preferred eradication treatments in 59 patients with initial *P. aeruginosa* isolation.

IT: inhaled tobramycin, IT+OC: inhaled tobramycin and oral ciprofloxacin, IC: inhaled colistin, C+A: ceftazidime and amikacin, M+A: meropenem and amikacin, P+A: piperacillin and amikacin, CF+A: cefixime and amikacin, IC+OC: inhaled colistin and oral ciprofloxacin.

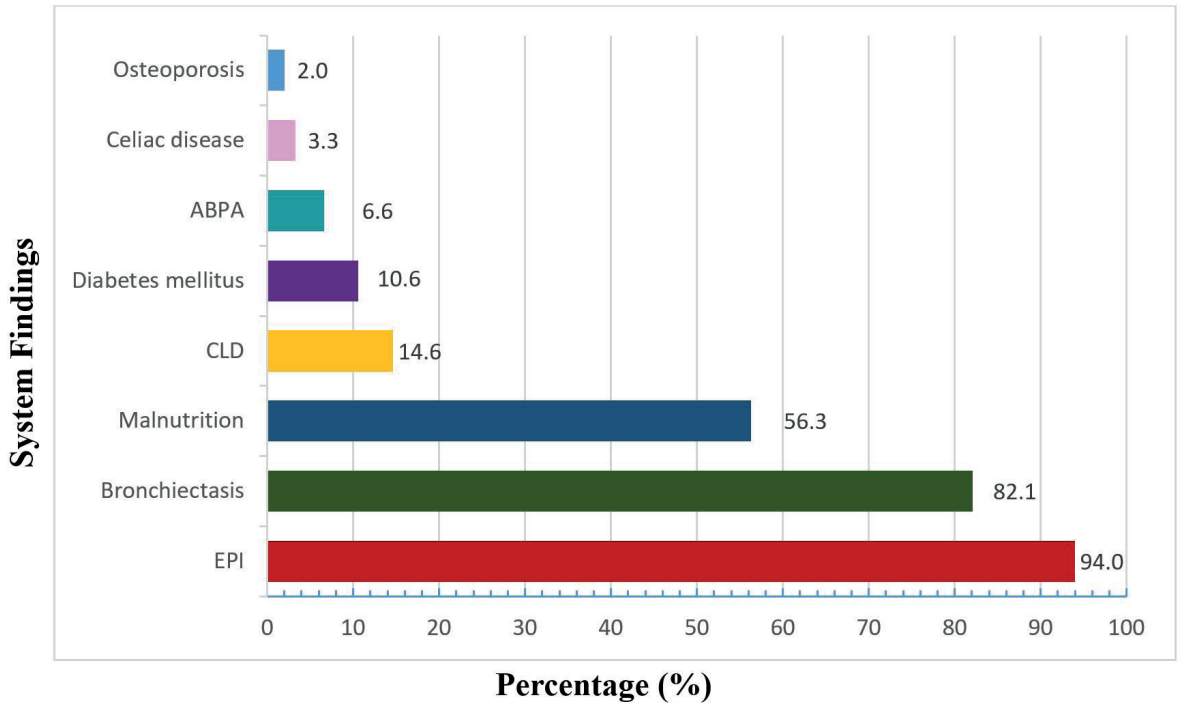

Fig. 2. Percentage distribution of accompanying system findings detected in cystic fibrosis patients included in the study (n=151).

ABPA: allergic bronchopulmonary aspergillosis, CLD: chronic liver disease, EPI: exocrine pancreatic insufficiency.

Table II. MIC50, MIC90 values, MIC distribution and resistance rate of the isolates obtained from antibiotic susceptibility testing (N = 151).

Antimicrobial drug	MIC50 (μg/mL)	MIC90 (μg/mL)	MIC Range (μg/mL)	Resistance (%)
Tobramycin	0.5	1	0.125–64	11.2
Ceftazidime	2	4	0.001–8	6.6
Levofloxacin	0.5	1	0.001–8	5.3
Colistin sulfate	1	2	0.06–64	3.3
PIP+TAZ	2	4	0.0125–256	1.9
Meropenem	0.25	0.5	0.06–64	1.9

MIC: minimum inhibitory concentration, MIC50: the lowest antibiotic concentration that inhibits 50% of the tested isolates, MIC90: the lowest antibiotic concentration that inhibits 90% of the tested isolates, PIP+TAZ: piperacillin-tazobactam.

in 30 isolates out of 151 when the tobramycin antibiotic disk was removed and a disk containing 2μg glucose was placed. It was determined that 30 (19.9%) *P. aeruginosa* isolates showing intra-zone growth had positive tolerance test. Based on the results of the phenotypic hypermutation test, 10 (6.6%) out of 151 isolates were identified as hypermutator phenotypes.

Biofilm production

Among the 151 isolates, the biofilm formation was quantitatively detected in 108 isolates based on comparisons with the negative control. Specifically, 21 (14%) isolates exhibited strong biofilm production, 54 (35.8%) were moderate and 33 (21.9%) were weak biofilm producers. The remaining 43 (28.3%) *P. aeruginosa* isolates were classified as non-biofilm forming (Fig. 3).

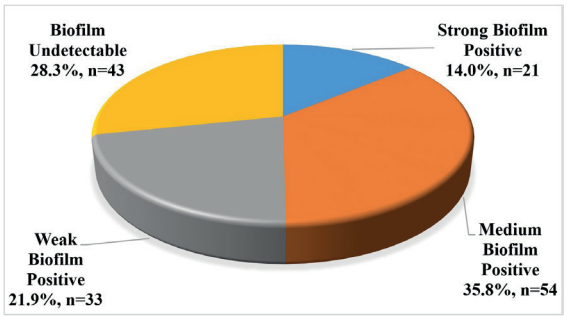

Fig. 3. The rates of biofilm formation by *P. aeruginosa* isolates in the patients with cystic fibrosis.

No statistically significant difference was observed in biofilm formation according to FEV_1 values in either the initial infection or chronic colonization groups, (p>0.05).

Similarly, no significant association was found between FEV_1 category (<80% vs. ≥80%) and antibiotic resistance patterns for any of the tested agents. In the chronic colonization group, strong biofilm formation was detected in 31.8% of isolates from patients with FEV_1 < 80% and in 43.7% of those with FEV_1 ≥ 80%. Overall, resistance rates were low, with the highest frequencies observed for tobramycin and colistin; however, these differences did not reach statistical significance. No statistically significant difference was found in antibiotic resistance rates between strong and weak biofilm-producing *P. aeruginosa* isolates (p>0.05).

Antibiofilm activity

A total of 75 *P. aeruginosa* isolates were selected for antibiofilm evaluation using the MBEC assay. These included 21 strong, 40 moderate, and four weak biofilm-producing isolates as determined by the crystal violet staining method, along with 10 non-biofilm-forming isolates that were resistant to tobramycin. The biofilm-forming capacity and susceptibility to diallyl disulfide alone and in combination with antibiotics were assessed.

Diallyl disulfide alone did not demonstrate significant antibiofilm activity against any of the tested *P. aeruginosa* isolates.

In combination with ciprofloxacin: No change in MBIC values was observed in 42 isolates (56%); an increase in MBIC values was detected in 21 isolates (28%), indicating potential antagonistic interaction; and a decrease in MBIC values, suggestive of synergistic or additive effects, was observed in 12 isolates (16%). Thus, the diallyl disulfide–ciprofloxacin combination was effective in reducing MBIC values in 16% of the tested isolates.

In combination with tobramycin: No change in MBIC values was observed in 36 isolates (48%), an increase in MBIC values was found in 17 isolates (22.6%), and a decrease in MBIC values was observed in 23 isolates (29.3%). Accordingly, the diallyl disulfide–tobramycin combination exhibited an enhanced antibiofilm effect in 22.3% of the total isolates.

Discussion

P. aeruginosa undergoes a characteristic evolutionary adaptation during chronic CF lung infection. Infection of patients with CF occurs via initial colonization of the airway, with accumulation of adaptive mutations in the bacterial genome associated with increased fitness in the lung environment, leading to chronicity. Adaptation of *P. aeruginosa* to the airway is an important aspect in the progression of CF lung disease.[18]

P. aeruginosa infection is quite common in patients with CF and this bacteria frequently causes acute pulmonary exacerbations. The rate of acute exacerbations caused by *P. aeruginosa* may vary depending on the age of the patients, the chronicity of the infection, and the geographical region. It is known that the risk of acute exacerbations is increased especially in patients with chronic *P. aeruginosa* infection.[19]

In our study, all patients were followed for a period exceeding one year, during which acute pulmonary exacerbations were identified in 50 individuals (32.5%). Among these patients, 33 experienced mild and 17 exhibited severe pulmonary exacerbations. To date, there are

limited studies categorizing acute pulmonary exacerbations. In conclusion, *P. aeruginosa* infections are highly prevalent among patients with CF and significantly contribute to the risk of acute pulmonary exacerbations, particularly in the case of chronic colonization. These results underscore the necessity of vigilant monitoring and the implementation of targeted therapeutic strategies to effectively manage *P. aeruginosa* infections. Timely and appropriate interventions are essential to improving both the quality of life and clinical outcomes in patients with CF.

Antibiotic strategies for eradication of *P. aeruginosa* in patients with CF have been demonstrated in different studies revealing that early eradication therapy led to significantly higher rates of microbiological clearance compared to no anti-pseudomonal treatment after two years of follow-up.[19] According to a review published in 2023, early treatment with inhaled tobramycin in patients with CF with initial *P. aeruginosa* infection was associated with successful microbiological eradication of the microorganism from the respiratory tract samples of the patients. The same review compared oral ciprofloxacin and inhaled colistin with standard treatment revealing that early eradication therapy led to significantly higher rates of microbiological clearance of the microorganism.[20]

The eradication guidelines of the CF Foundation also recommend inhaled tobramycin as the first line agent for *P. aeruginosa* eradication. Inhaled colistin can serve as an alternative regimen while oral ciprofloxacin is recommended in addition to inhaled therapies. In cases where the patient exhibits severe symptoms or fails to respond to inhaled and oral treatments, IV antibiotic therapy should be considered. In such cases, a combination of a beta-lactam antibiotic (e.g., ceftazidime) and an aminoglycoside (e.g., tobramycin) is recommended.[21]

According to the hospital patient record system data, among 59 patients in whom *P. aeruginosa* was isolated for the first time, the preferred eradication treatments were included inhaled tobramycin alone in 27 patients, inhaled tobramycin and oral ciprofloxacin in 11 patients, inhaled colistin in six patients, ceftazidime and amikacin in four patients, meropenem and amikacin in two patients, piperacillin and amikacin in two patients, cefixime and amikacin in one patient, inhaled colistin and oral ciprofloxacin in one patient, and other treatments in one patient. Four patients did not receive treatment due to a lack of follow-up. Given the complexity and variability in clinical presentation and treatment response, the treatment strategies must be evaluated individually for each patient. Therefore, the management of pediatric patients with CF should be managed by an experienced multidisciplinary team to ensure optimal therapeutic outcomes.

The system manifestations accompanying the disease generally depend on the progression of the disease and the underlying genetic variants. EPI, a gastrointestinal system disorder, is particularly common among patients with CF. A review published in 2023 reported that 85% of children with CF have pancreatic insufficiency, while emphasizing that this rate is similarly high in adults (85-90%).[22] In our study, EPI was identified in 142 of the 151 patients, confirming its high prevalence. EPI in CF is typically managed with pancreatic enzyme replacement therapy.

Bronchiectasis is another significant clinical feature observed in patients with CF. Studies have reported a high prevalence of bronchiectasis in patients with CF. For example, a study conducted in Taiwan found radiological evidence of bronchiectasis in 80-90% of patients with CF.[23] Consistent with this, bronchiectasis was detected in 124 out of 151 patients in our study.

Malnutrition is also a common concern in pediatric patients with CF and its prevalence in pediatric patients with CF varies depending on age, severity of the disease, and the evaluation criteria used. According to the results of a study

conducted in 2014, 22.1% of patients with CF were found to have malnutrition and 13.2% were found to have overweight or obesity.[24] In our study, malnutrition was identified in a total of 85 (56.3%) of our patients, highlighting the importance of nutritional monitoring and intervention in CF care.

According to a study conducted in 2014, malnutrition was observed in 22.1% of patients with cystic fibrosis, whereas 13.2% were overweight or obese.[24] In our study, malnutrition was detected in 85 patients (56.3%), highlighting the need for careful nutritional assessment and intervention in CF management.

Jarzynka et al. reported that in adult patients with CF, a moderate correlation was found between β-lactam resistance of *P. aeruginosa* isolates and lung function decline, while biofilm formation per se did not correlate significantly with decreased FEV_1. This heterogeneity in bacterial phenotypes, as documented by Jarzynka et al., reinforces our observation that reduced FEV_1 may not uniformly associate with strong biofilm or elevated resistance patterns in *P. aeruginosa* isolates.[25] Our findings suggest that reduced lung function is not directly associated with biofilm strength or antibiotic resistance among *P. aeruginosa* isolates from patients with CF.

P. aeruginosa complicates treatment due to its adaptability and biofilm formation ability. A review published in 2023 revealed that *P. aeruginosa* isolates obtained from patients with CF were particularly resistant to beta-lactams, and resistance rates to antibiotics such as meropenem, aztreonam, and ceftazidime ranged between 30–40%.[26] In another study resistance to ceftazidime was observed in 30–50% of *P. aeruginosa* isolates.[27] In contrast, in our study, ceftazidime resistance was identified in only ten isolates. According to another study, resistance rates to tobramycin among *P. aeruginosa* isolates in patients with CF ranged from 20% to 40%. This resistance is often attributed to chronic infections and prolonged antibiotic use, making treatment strategies difficult. Therefore, this may necessitate alternative treatment or combination therapies.[28] Notably, our findings revealed a low rate of tobramycin resistance, with only 17 isolates exhibiting resistance. In our cohort, ceftazidime resistance was low, suggesting that empirical regimens incorporating ceftazidime or other beta-lactam agents may remain effective in most cases. These findings support the feasibility of carbapenem-sparing strategies, which could help preserve broader-spectrum agents and align with local antimicrobial stewardship goals. However, these results are derived from a single-center cohort, and caution should be exercised according to the patients antimicrobial susceptible testing.

A meta-analysis published in October 2024 evaluating *P. aeruginosa* colistin resistance rates for 32 countries found the highest resistance rates in Egypt (15%) and Pakistan (13%). Subgroup meta-analyses based on the year of publication indicated that resistance colistin increased modestly from 2% to 3% in 2009.[29] In our study, colistin resistance was found to be low, with a MIC rate of 3.3%. In conclusion, this persistent resistance in patients with chronic infections complicates the treatment process and highlights the critical need for early detection, appropriate antimicrobial stewardship and aggressive treatment strategies to improve clinical outcomes in patients with CF.

Researchers investigating antibiotic tolerance have used the TDtest method, which we also applied in our study, to detect antibiotic tolerance in clinical isolates. In a study, TDtest was applied to 20 clinical *Escherichia coli* isolates specifically and the antibiotic tolerance profiles of these isolates were determined. The results showed that the isolates had varying levels of tolerance to different antibiotics. This study demonstrates that TDtest is a reliable method for detecting antibiotic tolerance in clinical isolates[15]. In our study, TDtest was performed on 151 *P. aeruginosa* isolates. Following removal of the tobramycin antibiotic disk and placement of a disk containing 2 μg glucose, intra-zone bacterial regrowth was observed in 30 isolates. These findings indicate that 30 (19.9%) of *P.*

aeruginosa isolates were positive for antibiotic tolerance. The TDtest may serve as a valuable tool for the routine detection of antibiotic tolerance in clinical microbiology laboratories and may contribute to the establishment of more effective and individualized antibiotic treatment regimens for pathogenic bacteria.

Detection of hypermutator phenotype using a rifampicin containing medium is a widely applied phenotypic method, particularly in the evaluation of hypermutator phenotype in *P. aeruginosa*. A study published in 2016 addresses the detection of hypermutator phenotypes in *P. aeruginosa* in a selective medium containing rifampicin. In this study, it was observed that the mutant colony formation of hypermutator strains was 100 times more frequent than that of normal strains.[30] As a result of the study, examining the hypermutator phenotypes among *P. aeruginosa* strains obtained from patients with CF in Australia in 2019, a total of 59 *P. aeruginosa* isolates were examined and 22% of them were detected as hypermutators. In our study, phenotypic hypermutation testing identified 10 (6.6%) out of the 151 isolates as phenotypic hypermutators. The findings emphasize the importance of detecting and monitoring hypermutator phenotypes, as such strains have an increased tendency to develop antibiotic resistance. Early identification of hypermutators in patients with CF may contribute to more effective treatment strategies and the prevention of multidrug resistance.

In the study conducted by Winstanley et al., it was reported that 80% of *P. aeruginosa* isolates in patients with CF had the ability to form biofilm.[31] Similarly in a study conducted in Tehran in 2021, it was found that 76% of *P. aeruginosa* isolates in CF patients had the ability to form biofilm.[32] In our study, using the CV method, biofilm formation was quantitatively demonstrated in 108 (71.5%) of 151 isolates, while 43 (28.3%) *P. aeruginosa* isolates did not form biofilm. Studies show that bacterial resistance is enhanced in biofilm-forming bacteria, especially in the lungs of patients with CF. Biofilms facilitate prolonged bacterial persistence and increased resistance to antimicrobial treatments.

The Calgary Biofilm Device (CBD) is widely used for the evaluation of antibiofilm susceptibility in patients with CF. This device helps determine antibiotic resistance profiles in biofilm-producing bacterial populations. According to a study conducted at the Biofilm Center in Canada, elevated MIC values were detected for tobramycin and its antibiofilm activity was found to be quite high, indicating that tobramycin alone can prevent biofilm development at certain concentrations.[33] In another study published by Chen et al. in 2020, CBD was used to evaluate the effect of tobramycin on 24-hour *P. aeruginosa* biofilms. It was observed that the bactericidal activity of tobramycin was concentration-dependent rather than time-independent with increased efficacy observed after 72 hours.[34]

Garlic, recognized for its natural antimicrobial properties, has been shown to be effective against bacteria. In a 2005 study investigating the antibiofilm activity of 1% garlic extract in combination with tobramycin, the combination was effective against most biofilm-forming isolates, while tobramycin alone had minimal effect. Moreover, garlic extract alone showed no significant effect on biofilm viability.[35] In another study examining the effect of garlic extract on both biofilm activity, the active compounds in garlic, such as allicin, were found to inhibit *P. aeruginosa* by disrupting quorum sensing mechanisms. In another study, the active compounds in garlic, particularly allicin, were found to inhibit *P. aeruginosa* by disrupting quorum sensing mechanisms. Garlic extract reduced bacterial infectivity, impaired biofilm structure formed by *P. aeruginosa* in the lungs and contributed to biofilm dispersal.[36]

In our study, the antibiofilm activity of ciprofloxacin alone was found to be effective in 16% of the total *P. aeruginosa* isolates. Similarly, the combination of garlic extract (diallyl disulfide) with ciprofloxacin was also effective indicating no difference between the

combination treatment and the ciprofloxacin alone. However, tobramycin alone showed antibiofilm activity in 29.3% of the isolates, whereas the combination of garlic extract and tobramycin was effective in 22.3% of our total isolates. Furthermore, garlic extract alone demonstrated no detectable effect on biofilm viability but tobramycin alone was more effective. These results highlight the limited synergistic potential of garlic extract in combination therapies and underscore the importance of optimizing antibiotic use for the treatment of chronic biofilm-associated infections. The antibiofilm activity of diallyl disulfide- garlic extract was assessed using *in vitro* MBEC assays. These results reflect laboratory conditions and do not represent clinical outcomes. Currently, our center does not use any garlic-derived products clinically. Interestingly, 28% of isolates showed increased MBIC values when treated with a combination of ciprofloxacin and diallyl disulfide, suggesting a potential antagonistic interaction. These findings should not be directly extrapolated to clinical practice and are instead considered hypothesis-generating, providing a basis for future preclinical and clinical studies.

Among *P. aeruginosa* isolates from all patients with CF, 17 (81%) of the strong biofilm producers and 44 (81.5%) of the moderate biofilm producers were found to be susceptible to all antibiotics. These findings suggest that biofilm strength alone may not be an independent predictor of resistance. Eleven (52.4%) of the strong biofilm producers and 24 of the moderate biofilm producers were from patients exhibiting colonization. Examination of the eradication regimens administered to these patients revealed that 25 (71.4%) received inhaled tobramycin therapy. Based on these findings, it was concluded that inhaled tobramycin alone may be an appropriate option for the eradication of *P. aeruginosa* colonization in patients with CF.

Although no statistically significant correlations were identified between FEV_1 values, biofilm formation, and antibiotic resistance, these findings emphasize the complexity of host–pathogen interactions in CF. In line with this, no significant difference was found in antibiotic resistance rates between strong and weak biofilm-producing *P. aeruginosa* isolates ($p > 0.05$). Although biofilm formation is recognized as a key virulence factor contributing to antimicrobial tolerance, our results suggest that biofilm strength alone may not be a decisive predictor of antibiotic resistance or pulmonary function decline in CF isolates. These observations highlight that bacterial phenotypic adaptation, including biofilm production and resistance development, likely depends on local microenvironmental and immunological factors rather than solely on lung function status, underscoring the need for future multi-omic studies to clarify how biofilm phenotypes interact with resistance gene expression and clinical outcomes.

Conclusion

In conclusion, this study provides a comprehensive phenotypic characterization of *P. aeruginosa* isolates obtained from pediatric patients with CF, demonstrating a high prevalence of biofilm formation alongside generally low antimicrobial resistance rates. Although antibiotic resistance, including resistance to colistin and ceftazidime, remained limited in this cohort, the frequent detection of antibiotic-tolerant and hypermutator phenotypes highlights the complexity of managing chronic *P. aeruginosa* infections in CF. Importantly, no significant associations were identified between biofilm strength, lung function parameters, or antimicrobial resistance, suggesting that biofilm formation alone may not be a reliable predictor of clinical severity or resistance patterns. The observed antibiofilm effects of selected agents under in vitro conditions warrant further investigation but should be interpreted cautiously given the single-center design and limited sample size. Future multicenter and longitudinal studies integrating clinical, microbiological, and molecular data are needed to better define the

clinical relevance of these phenotypic traits and to optimize therapeutic strategies for CF–associated *P. aeruginosa* infections.

Ethical approval

The study was approved by Non-Interventional Ethics Committee of Hacettepe University (date: March 30, 2021, number: 2021/07-11).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: ÖGT, ÖKE, DK, BÖ, EEY, NE, DDE, UÖ; data collection: ÖGT, ÖKE; analysis and interpretation of results: ÖGT, ÖKE, DK, BÖ; draft manuscript preparation: ÖGT, ÖKE. 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

Pediatric pulmonologists' current practices and variations in flexible bronchoscopy: a national survey study from Türkiye

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ABSTRACT

Background. Flexible bronchoscopy (FB) is a critical diagnostic and therapeutic tool in respiratory diseases, enabling airway assessment, sample collection, and therapeutic interventions. Despite international guidelines, practices vary widely across centers. This study aimed to assess current FB practices and to identify variations among pediatric pulmonologists in Türkiye.

Methods. A descriptive cross-sectional survey was distributed via email to clinical directors of 19 centers performing FB in March 2023. The survey comprised 80 questions across seven domains: demographics, patient preparation, bronchoscopy procedure, sedation/anesthesia, discharge, bronchoscope cleaning, and respondent comments. Participants were asked to provide accurate and objective data on FB practices at their centers.

Results. All 19 centers participated in the survey, achieving a 100% response rate. The median FB experience was 12.5 years (IQR: 1-30), with a median 210 procedures per year per center (min-max: 30-500; IQR: 80-250). The most frequently reported indications were atelectasis (84.2%), bronchiectasis (78.9%), suspected foreign body aspiration (52.6%), and to obtain bronchoalveolar lavage (BAL) in patients with immunodeficiency (52.6%).

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Nine centers (47.4%) indicated performing advanced bronchoscopic procedures, including endobronchial biopsy (31.6%), bronchoscopic intubations (26.3%), and tracheal/bronchial stent insertion (10.5%). General anesthesia (84.2%) was the predominant sedation method, and propofol (89.5%) the most frequently used agent. Premedication was used in 13 centers (68.4%), with midazolam being the most commonly used agent (76.9%). Twelve centers (63.2%) also used topical lidocaine for local anesthesia. Respondents reported the need for developing interventional procedures and increasing the number of trained bronchoscopy teams.

Conclusions. This first comprehensive national survey of pediatric FB practices in Türkiye, encompassing all relevant centers, revealed significant heterogeneity in procedural approaches, particularly regarding sedation protocols, BAL techniques, and interventional capabilities. The findings underscore the importance of developing interventional procedures and enhancing the training of pediatric pulmonologists and interdisciplinary teams practicing pediatric bronchoscopy to improve patient outcomes and procedural consistency.

Key words: flexible bronchoscopy, pediatric, survey.

Flexible bronchoscopy (FB) is an essential endoscopic technique in pediatric pulmonology since its introduction in the late 20th century.[1] It allows for direct visualization of the anatomical and functional aspects of the airway for diagnostic and therapeutic purposes, including sample collection for cytological and microbiological studies, and therapeutic interventions.[1-3] With the improvement of bronchoscopy equipment and technology, FB has gradually been applied to neonates and high-risk patients, including those undergoing lung transplantation and extracorporeal membrane oxygenation in intensive care units (ICU).[4,5] Moreover, anesthesia management lacks standardization, with different methods chosen based on the indications for bronchoscopy.[1,6,7] The growing need for an interdisciplinary approach to FB emphasizes the importance of establishing national standards and practice policies. Although international and national guidelines on FB indications, management, and techniques exist[1-3,6,7], recent European Respiratory Society Task Force statements and survey studies highlight significant inconsistencies in clinical practice.[3,8-13]

Survey studies offer a cost-effective and efficient way to collect large-scale data, identify best practices, and highlight challenges, ultimately aiding in the development of evidence-based national guidelines.[14] In Türkiye, pediatric FB has been increasingly adopted in both tertiary and secondary centers. However, a comprehensive understanding of current practices, including adherence to international standards, technical preferences, and procedural safety, is lacking. While a limited number of surveys have assessed pediatric FB practices[8-11], no such data are currently available from Türkiye. To address this gap, we conducted a nationwide survey among pediatric pulmonologists in Türkiye to evaluate the current approaches to FB, identify areas of variability, and highlight opportunities for standardization and improvement in clinical practice. This survey may also serve as a reference for new bronchoscopy units and help clinicians refer patients to centers with established FB programs.

Materials and Methods

Study design

This descriptive cross-sectional study was conducted using an online questionnaire created via Google Forms. The survey was developed based on existing bronchoscopy guidelines and previous pediatric bronchoscopy surveys.[1-3,8-10] It consisted of 80 questions divided into seven categories: demographics, patient preparation and preprocedural tests, bronchoscopy procedure, sedation/anesthesia, discharge process, bronchoscope cleaning, and comments. Participants responded using yes/no options, multiple-choice answers, or free-text (e.g., indications) responses where applicable. They could also provide comments and suggestions at the end of the questionnaire. No patient data

were collected. The study was approved by the Ege University Faculty of Medicine Ethics Committee (Approval No: 23-5T/40, Date: 05.11.2023).

Since pediatric pulmonology is a relatively new subspecialty in Türkiye and the number of specialists performing flexible bronchoscopy is limited, we invited all 19 pediatric pulmonology centers known to perform the procedure to participate. The survey link, information sheet, and an electronic informed consent form were emailed to the clinical directors of these centers in March 2023. Access to the questionnaire was enabled only after the consent box was checked. Completion of the questionnaire indicated voluntary participation and constituted informed consent. Participants were asked to provide accurate and objective data on FB practices at their centers.

Only the city of each medical center was disclosed, while the center names remained confidential. Participation was voluntary, with no incentives offered. To improve the response rate, a follow-up email was sent four weeks after the initial request. Data collection lasted three months, and all participants approved participation in the study.

Statistical analysis

The answers extracted from Microsoft Excel spreadsheets were processed, and analyzed using Statistical Package for Social Sciences (SPSS for Windows Version 26) software. Descriptive data are given as numbers (n) and the percentage values (%). Values for continuous variables were given as either mean ± standard deviation (SD) or as median (interquartile range [IQR]), based on the normality of their distribution.

Results

Clinical directors from 19 pediatric pulmonology departments performing FB participated in the study. The median number of clinicians per center was nine (IQR: 1-13), with 76% female. Twelve centers (63.2%) were located in Türkiye's three most populous metropolitan

Fig. 1. Location of participating centers in seven geographical regions of Türkiye. A total of 19 centers performing pediatric flexible bronchoscopy from five geographical regions participated in the study. The figure shows the number of centers located in 10 provinces out of 81.

cities (Fig. 1). The median FB experience was 12.5 years (IQR: 1-30). Three centers (15.8%) had less than three years of FB experience, four (21.1%) had 6-10 years, six (31.6%) had 11-15 years, five (26.3%) had 16–20 years, and one (5.3%) had 30 years of experience.

A total of 3,118 FB procedures were performed in the previous year. Annual pediatric FBs per center had a median of 210 (min-max: 30-500; IQR: 80-250).

Indications

Parameters related to bronchoscopy are shown in Table I. The most frequently reported indications were atelectasis (16 centers, 84.2%), bronchiectasis (15 centers, 78.9%), suspected foreign body aspiration (10 centers, 52.6%), and obtaining BAL in patients with immune deficiency (10 centers, 52.6%) (Fig. 2).

Interventional bronchoscopy

Based on participant reports, therapeutic FB constituted a median 35% (range 2–80%) of all FB procedures, indicating that diagnostic FB was performed approximately twice as often as therapeutic FB. Moreover, of the nine centers (47.4%) indicating that they can perform advanced bronchoscopic procedures, endobronchial and mucosal biopsy was reported by six centers (31.6%), bronchoscopic intubations by five centers (26.3%), foreign body removal by three centers (15.8%), and tracheal/bronchial stent insertion by two centers (10.5%). Detailed information on bronchoscopic interventions is presented in Table I.

Equipment and personnel

Sixteen centers (84.2%) used video-assisted flexible bronchoscopes. Every center had at least two bronchoscopes with different outer diameters (ODs). Seven centers (36.8%) had three different ODs available, while one center (5.3%) had four. The three commonly reported bronchoscope ODs were 4.9 mm (12 centers, 63.2%), 3.6 mm (6 centers, 31.6%), and 2.8 mm (5 centers, 26.3%).

When the availability of experienced, dedicated staff for pediatric FB (nurses, anesthesiologists, and anesthesia technicians) was assessed across 19 centers, three (15.8%) reported having none, four (21.1%) had a nurse only, one (5.3%) had an anesthesiologist only, one (5.3%) had an anesthesia technician only, three (15.8%) had a nurse and an anesthesiologist, and seven (36.8%) had all three dedicated staff members.

Twelve centers (63.2%) reported that bronchoscopies were mainly performed in operating rooms; in four centers (21.1%) bronchoscopies were carried out in bronchoscopy suites, and one center (5.3%) used an airway endoscopy suite. In two centers, more than one site was available. Additionally, nine centers (47.4%) performed FB for critically ill patients in the ICU.

Preprocedural evaluations

Routine preprocedural testing was conducted in 18 centers (94.7%): complete blood count was obtained in 16 centers (84.2%), coagulation parameters in 14 centers (73.7%), chest X-ray in 12 centers (63.2%), pulmonary function tests in four centers (21.1%), and serologic testing for hepatitis viruses, syphilis, and Human immunodeficiency virus (HIV) antibodies in four centers (21.1%). All respondents confirmed obtaining written informed consent from caregivers before FB. Additionally, 13 centers (68.4%) required notifying the bronchoscopy team or operating room personnel at least one day before the procedure.

Bronchoalveolar lavage

During FB, the most commonly used personal protective equipment included sterile gloves (89.5%), N95 masks (52.6%), and safety glasses (36.8%). Additionally, 63.2% of respondents reported performing the procedure while positioned behind the patient's head—near the airway—facing the bronchoscopy monitor. The remaining respondents reported standing at the patient's side during the procedure.

Table I. Data about bronchoscopy and BAL method.

Variables	n	%
Frequency of bronchoscopy sessions		
Once a week	11	57.9
2-3 times a week	7	36.8
Every day	1	5.3
Type of bronchoscopes*		
Fiberoptic bronchoscope	2	10.5
Video bronchoscope	1	5.3
Video- assisted fiberoptic bronchoscope	16	84.2
Diagnostic procedures**		
Evaluation of upper and lower airway	19	100
BAL	19	100
Endobronchial biopsy	6	31.6
Mucosal biopsy	6	31.6
Transbronchial biopsy	2	10.5
Therapeutic interventions		
Removal of mucus plug	18	94.7
Partial lung lavage	13	68.4
Whole lung lavage	10	52.6
Bronchoscopic intubation	5	26.3
Foreign body removal	3	15.8
Tracheal/bronchial stent insertion	2	10.5
Balloon dilatation	1	5.3
Dominant hand holding the bronchoscope		
Right	11	57.9
Left	5	26.3
Either	3	15.8
Route of bronchoscope insertion		
Via the laryngeal mask airway	13	68.4
Via the nasal route	5	26.3
Via the oral route without an airway device	1	5.3
Routes of oxygen supplementation		
Via nasal cannula	2	10.5
Via mechanic ventilation	17	89.5
Quantity of saline used for BAL in each aliquot		
10 mL	1	5.3
10-20 mL	1	5.3
1 mL/kg, max 10 mL	5	26.3
1 mL/kg, max 20 mL	12	63.2
Routine BAL segments in non-focal disease		
Right middle lobe and lingula	12	63.2
Right middle lobe	7	36.8
Instruments used to aspirate BAL fluid		
Electric portable machine	9	47.4
Wall mounted	7	36.8
50 mL syringe	3	15.8
Availability and routine use of BAL fluid analyses	n_a; n_r***	$\%_a$; $\%_r$***
Bacterial culture	19; 19	100; 100
Cytology	19; 11	100; 57.9
Cultures for tuberculosis	19; 13	100; 68.4
Fungal culture	18; 9	94.7; 50
Lipid-laden alveolar macrophages	18; 9	94.7; 50
Lymphocyte panel (immunology)	17; 2	89.5; 11.8
Differential cell counts	17; 13	89.5; 76.5
Histopathology	16; 8	84.2; 50
Virology	15; 2	78.9; 13.3
Hemosiderin-laden macrophages	1; 0	5.3; 0

Percentages are based on 19 centers unless otherwise specified.
*"Fiberoptic bronchoscope" refers to traditional scopes using optical fiber bundles for illumination and image transmission, "video bronchoscope" denotes scopes with a built-in digital camera and processor, and "video-assisted fiberoptic bronchoscope" describes a fiberoptic model connected to an external camera for monitor viewing.
** "Endobronchial biopsy" refers to sampling that includes the bronchial wall and submucosa for structural/pathologic evaluation, whereas "mucosal biopsy" denotes a superficial epithelial sampling primarily for histopathologic or inflammatory assessment.
*** n_a (available) = the test could be performed at the center when clinically indicated; n_r (routine) = the test was regularly performed in all BAL samples as part of standard diagnostic practice. $\%_a$ represents the proportion of centers with test availability among all 19 centers ($\%_a = n_a/19$). $\%_r$ represents the proportion of centers performing the test routinely among those in which the test was available ($\%_r = n_r/n_a$).
BAL: Bronchoalveolar lavage

The aliquot counts for microbiological and cytological examinations were two (8 centers, 42.1%), three (5 centers, 26.3%), six (3 centers, 15.8%), one (2 centers, 10.5%), and four (1 center, 5.3%). Table I illustrates the variations in BAL techniques, and BAL fluid analysis. Cytology and tuberculosis tests were available in all centers; however, they were performed routinely in 11 centers (57.9%) and 13 centers (68.4%), respectively.

Cleaning and disinfection of bronchoscopes

For bronchoscope reprocessing, automated cleaning was reported by nine centers (47.4%), automated disinfection by 10 centers (52.6%), and manual drying by nine centers (47.4%) (Table II). Moreover, 15 centers (78.9%) sterilized the bronchoscopes and 14 centers (73.7%) sent random bacterial surveillance culture samples to reference laboratories.

Premedication and sedation

Thirteen centers (68.4%) implemented premedication, with considerable variability in drug selection, procedural approaches, and patient monitoring methods, as shown in Table III. Three centers (15.8%) routinely administered inhaled bronchodilators as preprocedural medication, while one center (5.3%) additionally used intranasal adrenergic drops, and another center (5.3%) used intravenous antihistamines in addition to bronchodilators. Pre-oxygenation was routinely performed prior to general anesthesia (GA). Among the three centers using moderate conscious sedation, two reported performing pre-oxygenation.

Anesthesiologists evaluated patients the day before the procedure in 16 centers (84.2%), and on the same day in three centers (15.8%). FB was predominantly performed under GA combined with local anesthesia (9 centers, 47.4%). However, three centers (15.8%) opted for moderate conscious sedation combined with lidocaine spray for local anesthesia. Of the 16 centers (84.2%) utilizing GA, nine (47.4%) also administered local anesthesia. Lidocaine was the sole agent used for local anesthesia, though the instillation sites varied (Table III).

Patient discharge

The discharge protocols for elective outpatient FB showed that four centers (21.1%) discharged patients the following day, whereas the remaining 15 (78.9%) performed same-day discharge—seven centers (36.8%) within 1–3 hours and eight centers (42.1%) within 6–12 hours post-procedure. None of the centers prescribed routine medications at discharge; however, five centers (26.3%) routinely performed a post-procedural chest X-ray.

Respondent feedback

Five respondents (26.3%) emphasized the need to enhance interventional procedures and increase the number of trained anesthesiologists and nurses. Additionally, three respondents (15.8%) advocated for the immediate development of national pediatric FB guidelines to standardize procedural approaches.

Discussion

This study presents the first nationwide epidemiologic overview of pediatric FB practices among pediatric pulmonologists in Türkiye. As all centers performing pediatric FB participated, our findings provide a realistic representation of current national practices. The survey revealed substantial heterogeneity in procedural approaches, highlighting the need for national standards to improve consistency, training, and patient outcomes.

Flexible bronchoscopy has been performed by pediatric pulmonologists in Türkiye for nearly three decades. However, the median number of procedures per center per year (210 in 19 centers) is markedly higher than that reported from Europe (35 in 198 centers), China (158 in 47 centers), and India (75 in 24 centers).[2,8,9] A detailed comparison with international survey data is provided in Table IV. Despite the high

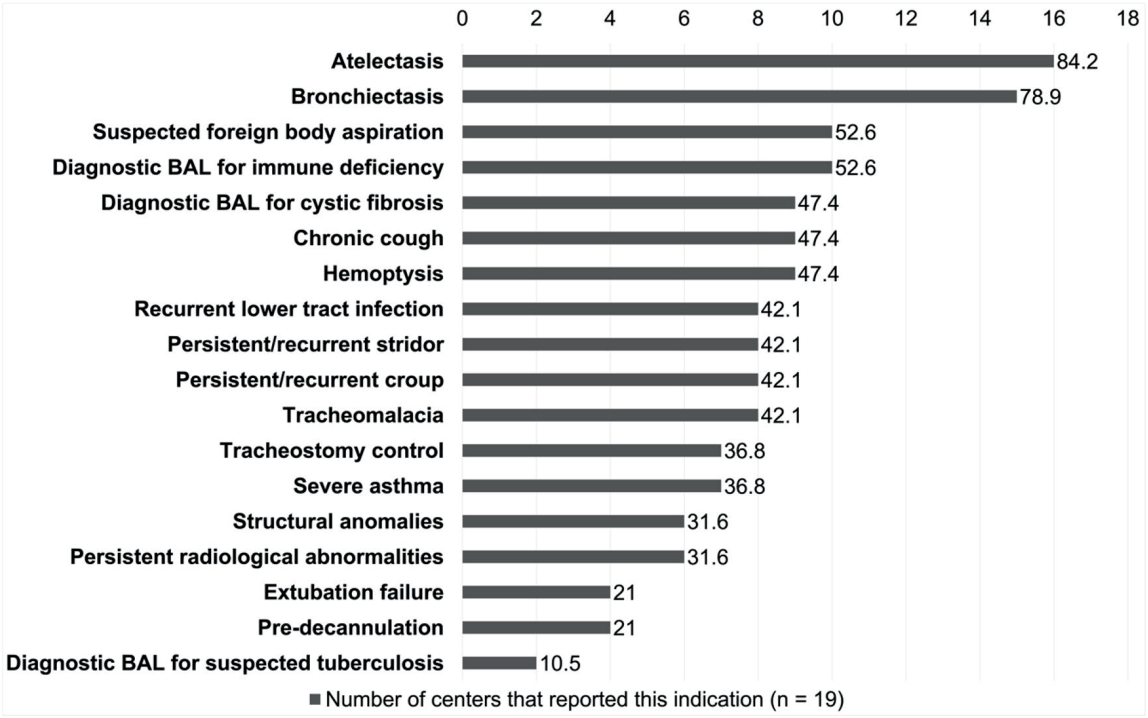

Fig. 2. Indications for pediatric flexible bronchoscopy. The x-axis shows the number of centers that reported each indication. The numeric values displayed at the end of each bar represent the percentage (%) of centers reporting that indication.

Table II. Cleaning, disinfection and storage of bronchoscopes.

Variables	n	%
Cleaning methods of bronchoscopes		
Manual	3	15.8
Automated	9	47.4
Both	7	36.8
Disinfection methods of bronchoscopes		
Manual	3	15.8
Automated	10	52.6
Both	6	31.6
Methods of drying bronchoscopes		
Manual	9	47.4
Compressed air	5	26.3
Bronchoscope drying cabinet	3	15.8
70% alcohol solution	2	10.5
Storage containers for bronchoscopes		
Storage cabinet	10	52.6
Bronchoscope suitcase	8	42.1
Sterile surgical drape	1	5.3
Disinfectant solutions used for manual disinfection of bronchoscopes (n = 9)		
Peracetic acid and hydrogen peroxide	5	55.6
2% glutaraldehyde solution	3	33.3
Peracetic acid	1	11.1

Percentages are based on 19 centers, unless otherwise specified.

Table III. Methods of premedication and sedation.

Variables	n	%
Premedication given by (n = 13)		
Anesthesiologist	7	53.8
Nurse	3	23.1
Anesthesia technician	2	15.4
Pediatric pulmonologist	1	7.7
Drugs used for premedication (n = 13)*		
Midazolam	10	76.9
Lidocaine	5	38.5
Methylprednisolone (as needed) **	4	30.8
Fentanyl	3	23.1
Ketamine	1	7.7
Routinely used medications before procedure		
None	14	73.7
Inhaled bronchodilators	3	15.8
Inhaled bronchodilators + Intranasal adrenergic drops	1	5.3
Inhaled bronchodilators + Intravenous antihistamines	1	5.3
Methods of sedation		
Moderate conscious sedation combined with local anesthesia	3	15.8
General anesthesia	7	36.8
General anesthesia combined with local anesthesia	9	47.4
Drugs used for induction of anesthesia		
Propofol	17	89.5
Midazolam	11	57.9
Fentanyl	6	31.6
Remifentanil	3	15.8
Ketamine	3	15.8
Atropine	3	15.8
Lidocaine	2	10.5
Rocuronium	1	5.3
Drugs used for maintenance of anesthesia		
Sevoflurane alone	6	31.6
Propofol infusion alone	4	21.1
Propofol infusion + sevoflurane	8	42.1
Propofol infusion + remifentanil infusion	1	5.3

Percentages are based on 19 centers unless otherwise specified.
*Some centers use more than one drug for premedication.
** Used in selected patients (e.g., with asthma or airway hyperreactivity).
*** Sedation adequacy was self-reported. "Always sufficient" = clinically acceptable depth without escalation in nearly all cases; "Often sufficient" = clinically acceptable depth without escalation in most cases.
ECG; electrocardiography, $EtCO_2$; end-tidal CO_2, NIBP; non-invasive blood pressure, SPO_2; oxygen saturation measured using pulse oxymetry.

Table III. Continued.

Variables	n	%
Topical lidocaine applications (n = 12)		
Pharyngeal	1	8.3
Intratracheal	4	33.3
Pharyngeal plus intratracheal	5	41.7
Combined used intranasal + pharyngeal + intratracheal	2	16.7
Endotracheal lidocaine injection sites (n = 11)		
Epiglottis	11	100
Carina	11	100
Routinely used medications after procedure		
None	11	57.9
Nebulization with bronchodilator	6	31.6
Intravenous methylprednisolone	5	26.3
Nebulization with adrenalin	3	15.8
Cool mist	1	5.3
Parameters monitored during procedure		
SpO_2, ECG, $EtCO_2$, NIBP	7	36.8
SpO_2, ECG, $EtCO_2$	4	21.1
SpO_2	4	21.1
SpO_2, ECG, NIBP	3	15.8
SpO_2, ECG	1	5.3
Adequacy of sedation provided during the procedure***		
Always sufficient	16	84.2
Often sufficient	3	15.8

Percentages are based on 19 centers unless otherwise specified.
*Some centers use more than one drug for premedication.
** Used in selected patients (e.g., with asthma or airway hyperreactivity).
*** Sedation adequacy was self-reported. "Always sufficient" = clinically acceptable depth without escalation in nearly all cases; "Often sufficient" = clinically acceptable depth without escalation in most cases.
ECG; electrocardiography, $EtCO_2$; end-tidal CO_2, NIBP; non-invasive blood pressure, SPO_2; oxygen saturation measured using pulse oxymetry.

number of procedures per center, only 10 out of 81 provinces offer FB, meaning each center serves about eight provinces. These findings indicate challenges in referral pathways and raise concerns about service capacity. Whether this high number of procedures in a few centers results from serving a large population or reflects advanced expertise will become clearer through future comparative studies.

In our survey, atelectasis, bronchiectasis, suspected foreign body aspiration, and immune deficiency (to obtain BAL for microbiological evaluation) were the most common indications for FB. Compared with European data, FB for immunodeficient patients was more frequently reported in Türkiye.[2] This finding may be explained by the higher prevalence of primary immunodeficiencies in regions with increased consanguinity.[12,13] A recent study in Türkiye assessed the diagnostic value of FB and BAL in immunosuppressed children, revealing that microscopic examination of BAL specimens identified pathogens in 65.1% of cases despite prior antimicrobial therapy.[14] Diagnostic complexity due to pathogen diversity underscores the importance of FB in immunosuppressed children with respiratory symptoms.[10,15-20]

Table IV. Comparison of pediatric flexible bronchoscopy (FB) practices: Türkiye vs. international multicenter surveys.

Parameter	Schramm et al., 2017[2]	Lin et al., 2020[9]	Jat et al., 2022[8]	Present study, 2026
Study year and country	2015 and European countries	2018 and Western China	2019 and India	2023 and Türkiye
Total centers and response rate	198 centers in 33 countries Response rate 75% (33/44)	47 centers in 32 cities Response rate 87% (47/54)	24 centers in 14 cities Response rate 5.2% (24/455)	19 centers in 10 cities Response rate 100% (19/19)
Performed FBs per center per year (median)	96	158	75	210
Main indication for FB	-Aspiration (72.7%) -Infection (48.5%) -Radiographic abnormalities (48.5%)	Pooled rate; -Atelectasis/lobar pneumonia (95% CI, 25-30%), -Persistent/recurrent wheeze (95% CI, 17-20%) -Chronic cough (95% CI, 11-15%)	-Suspected tuberculosis (87.5%) -Atelectasis (87.5%) -Suspected airway malacia (83.3%) -Infection other than tuberculosis (83.3%) -Persistent/recurrent pneumonia (83.3%)	-Atelectasis (84.2%) -Bronchiectasis (78.9%) -Immune deficiency (52.6%) -Suspected foreign body aspiration (52.6%)
Advanced bronchoscopic procedures	-Endobronchial biopsy (73.2%) -Transbronchial biopsy (37.8%) -Balloon dilatation (21.2%) -Stent placement (9.5%)	-Cryoablation (23.4%) -Balloon dilatation (21.2%) -Thermal ablation (17%) -Stent placement (0%)	-Endobronchial biopsy (37.5%) - Transbronchial biopsy (12.5%) -Mucosal biopsy (16.6%) -Balloon dilatation (0%) -Stent placement (0%) -Bronchoscopic intubation (45.8%) -Foreign body removal (41%)	-Endobronchial biopsy (31.6%) - Transbronchial biopsy (10.5%) -Mucosal biopsy (31.6%) -Balloon dilatation (5.3%) -Stent placement (10.5%) -Bronchoscopic intubation (26.3%) -Foreign body removal (15.8%)
Bronchoscope types and OD	OD 4.9 mm and 3.6 mm were most common; counts/ percentages not reported. Bronchoscope types not reported.	Not reported	OD not reported. -Video bronchoscope (41%) -Fiberoptic bronchoscope (33%) - Video- assisted fiberoptic bronchoscope (21%)	OD 4.9 mm (63.2%), 3.6 mm (31.6%), and 2.8 mm (26.3%) were most common. - Video- assisted fiberoptic bronchoscope (84.2%) -Fiberoptic bronchoscope (10.5%) - Video bronchoscope (5.3 %)

BAL; bronchoalveolar lavage, CBC; complete blood count, CXR; chest X-ray, ECG; electrocardiography, GA; general anesthesia, ICU; intensive care units, IQR; interquartile range, LA; local anesthesia, LLAM; lipid-laden alveolar macrophages, OD; outer diameter, PFT; pulmonary function test, SpO_2; oxygen saturation.

Table IV. Continued.

Parameter	Schramm et al., 2017[2]	Lin et al., 2020[9]	Jat et al., 2022[8]	Present study, 2026
Dedicated staff for pediatric FB	"Most of the centers reported three qualified bronchoscopists and two dedicated nurses." (counts/ percentages not reported).	-47 centers (100%) had median 4 (IQR; 1-19) dedicated nurses. -24 centers (51.1%) had median 1 (IQR; 0–5) anesthesiologists.	"Healthcare personnel involved in the procedure included a trained pediatric pulmonologist, trained nurse, pediatric resident, pediatric pulmonology fellow, laboratory technician, or anesthetist." (counts/percentages not reported).	-Nurse (21.1%) -Anesthesiologist (5.3%) -Anesthesia technician (5.3%) -Nurse and anesthesiologist (15.8%) - Nurse, anesthesiologist, and anesthesia technician (36.8%) -None (15.8%)
Site of bronchoscopy	-Bronchoscopy suite (87.3%) -Operating room (74.7%) -ICU (62.1%)	-ICU (66%) -Endoscopy suite (61.7%) -Bronchoscopy suite (4%) -More than one site (79.2%)	-Bronchoscopy suite (58.3%) -Operating room (25%) -ICU (12.5%) -Endoscopy suite (4.2%)	-Operating room (63.2%) -ICU (47.4%) -Bronchoscopy suite (21.1%) -Endoscopy suite (5.3%) -more than one site (10.5%)
Routine pre-procedure tests	Not reported	-CBC (100%) -CXR (97.9%) -Coagulation function (97.9%) -PFT (40%) -Serologic testing for hepatitis viruses, syphilis, and HIV antibodies (100%)	Not reported	-None (5.3%) -CBC (84.2%) -Coagulation function (73.7%) -CXR (63.2%) -PFT (21.1%) -Serologic testing for hepatitis viruses, syphilis, and HIV antibodies 21.1%
Routine preprocedural medication	Not reported	Not reported	-Atropine (16.7%) -Nasal adrenergic drops (54.2%)	-Bronchodilator (26.3%) -Nasal adrenergic drops (5.3%) -Intravenous antihistamines (5.3%)
Methods of anesthesia	"Usually performed under GA or moderate sedation/ analgesia." (counts/ percentages not reported).	-Conscious sedation combined with LA (63.8%) -GA with tracheal intubation (42.6%) -GA with LMA (44.7%) -GA with HFV (2.1%)	-Conscious sedation (79%) -GA (8.4%) -Conscious sedation or GA (12.5%)	-GA combined with LA (47.4%) -GA (36.8%) -Conscious sedation combined with LA (15.8%)

BAL; bronchoalveolar lavage, CBC; complete blood count, CXR; chest X-ray, ECG; electrocardiography, GA; general anesthesia, ICU; intensive care units, IQR; interquartile range, LA; local anesthesia, LLAM; lipid-laden alveolar macrophages, OD; outer diameter, PFT; pulmonary function test, SpO_2; oxygen saturation.

Table IV. Continued.

Parameter	Schramm et al., 2017[2]	Lin et al., 2020[9]	Jat et al., 2022[8]	Present study, 2026
GA medication	"The main intravenous anesthetic was propofol, the main inhalation anesthetic was sevoflurane." (counts/percentages not reported).	-Midazolam (95.8%) -Propofol (31.9%) -Fentanyl (44.7%)	-Midazolam + fentanyl (37.5%) -Midazolam + propofol (20.8%)	-Propofol (89.5%) -Sevoflurane (73.7%) -Midazolam (57.9%) -Fentanyl (31.6%)
Local anesthesia	"Local anesthesia during GA was most often provided by lidocaine." (counts/percentages not reported).	-Lidocaine 77.1% (sites did not reported)	-Spray as go lignocaine (71%) -Both nebulized and spray as go lignocaine (25%) -Nebulized lignocaine (4.2%)	12 centers (63.2%) used lidocaine for LA; -Pharyngeal + intratracheal (41.7%) -Intratracheal (33.3%) -Intranasal + pharyngeal + intratracheal (16.7%)
Routine monitoring	Not reported	-SpO_2 100% -ECG 100%	-SpO_2 100% -Blood pressure 21% -ECG 33.3%	-SpO_2 100% -Blood pressure 52.6% -ECG 78.9% -EtCO2 57.9%
Availability or routine of BAL	Availability; -Microbiology (93.9%) -Cytology (82.8%) -Virology (73.7%) -Immunology (70.7%) -Differential cell count (82.8%) -LLAM (54.5%)	Routine; -Bacterial culture (95.7%) -Cytology (80.9%) -PCR (61.7%) -Histopathological examination for bronchial mucosa (55.3%)	Not reported	Availability and routine; -Bacterial culture (100% and 100%) -Cytology (100%, and 57.9%) -Virology (78.9% and 13.3%) -Immunology (89.5% and 11.8%) - Differential cell count (89.5% and 76.5%) -LLAM (94.7% and 50%)
BAL aliquots	Not reported	Not reported	3–4: 8 (33.3%) 2–3: 5 (20.8%)	Median 2 (range 1–6)

BAL; bronchoalveolar lavage, CBC; complete blood count, CXR; chest X-ray, ECG; electrocardiography, GA; general anesthesia, ICU; intensive care units, IQR; interquartile range, LA; local anesthesia, LLAM; lipid-laden alveolar macrophages, OD; outer diameter, PFT; pulmonary function test, SpO_2; oxygen saturation.

Advanced interventional procedures were performed less frequently than in European centers, particularly bronchoscopic intubation and transbronchial biopsy.[2] While pediatric airway anatomy presents unique challenges, international recommendations emphasize that such procedures should be performed by experienced pediatric bronchoscopists.[3] As pediatric pulmonology continues to evolve in Türkiye, the frequency of these procedures is expected to rise with an increasing number of pediatric pulmonologists, well-trained bronchoscopy teams, and the development of national pediatric FB guidelines.[2,21]

There is no consensus on the optimal sedation method for pediatric FB.[1,6-8,10] Mild sedation with topical anesthetics may be sufficient[22]; however, deeper sedation is often required to suppress cough during FB.[23] Although the use of GA has increased with advances in anesthetic techniques[6], it may mask dynamic airway abnormalities such as tracheomalacia and bronchomalacia. Our survey found that GA combined with local anesthesia is the most preferred approach. The benefit of combining topical local anesthesia with GA during FB remains controversial, as available evidence shows no clear efficacy in cough suppression and suggests a potential increase in perioperative respiratory adverse events.[24,25] Given the frequent use of GA in our country, a multi-center randomized study could assess the efficacy of local anesthesia in FB.

In our study, propofol was the most frequently used agent for both induction and maintenance of anesthesia, consistent with its established safety and efficacy in pediatric FB.[23,26] Among 13 centers using propofol for maintenance, eight combined it with sevoflurane, and only one used it with remifentanil. However, evidence remains inconclusive regarding its optimal use alone or in combination[27,28], Sedation methods and agent preferences varied widely across centers and international studies.[2,8,9] This study highlights differences in anesthesia practices due to varying experiences among bronchoscopists and anesthesiologists. We believe that our findings may contribute to individualized sedation strategies and support efforts toward standardizing FB practices.

Premedication was routinely used in most centers, with midazolam being the preferred agent. Although there is no consensus on premedication use in pediatric FB[1,6-8,10], previous studies have examined the effects of premedication agents on cough, anxiety, and recovery time.[26-34] Midazolam has been shown to improve procedural tolerance and reduce the incidence and severity of the cough reflex.[26,31,35] In addition, combining midazolam with propofol has been shown to decrease propofol's induction dose, reducing its cardiovascular and respiratory side effects.[36,37] Minimizing discomfort before FB improves both child and parental satisfaction, making premedication particularly beneficial in anxious or uncooperative children.

The optimal number of aliquots, saline volume per aliquot, and sampling sites for BAL remain unclear in the literature.[1,6,10] Our findings align with general recommendations, suggesting 1 mL/kg per aliquot (maximum 20 mL) and favoring the right middle lobe and lingula for sampling.[1,38] Routine cytological and microbiological analyses were inconsistently performed despite guideline recommendations.[1,7] Therefore, a national FB guideline is needed to standardize BAL fluid practices and improve diagnostic yield.

Bronchoscope reprocessing methods also differed, with both manual and automated approaches in use. While most centers performed microbiological surveillance cultures, evidence supporting their routine use remains limited.[1,39] Alcohol flushing, which was rarely used, is known to reduce positive culture rates.[40] Since bacterial surveillance cultures are time-consuming and costly, alcohol flushing may offer a practical alternative to reduce contamination and drying time.

This study has several limitations. First, self-reported responses introduce potential bias due to differences in interpretation, recall, and reporting. Although we captured anesthesia practices at a center level, the survey did not ask GA-using centers how they modify their approach when dynamic airway disease is suspected, such as preserving spontaneous breathing or opting for minimal sedation. Additionally, the questionnaire did not include details on suction pressures or fluid retrieval percentages during BAL, both of which are essential for diagnostic accuracy. The lack of clarity regarding sample handling—whether initial or subsequent samples were analyzed according to recommended standards—may also impact diagnostic reliability.

In conclusion, current pediatric FB practices in Türkiye demonstrate significant variability across centers, particularly in sedation protocols, interventional procedures, BAL techniques, and reprocessing methods. Moreover, comparison with survey results from other countries allowed us to observe both similarities and differences in procedural approaches. These findings highlight the need for standardized national guidelines, expanded training programs, and multidisciplinary collaboration to improve procedural quality and patient safety.

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Ethical approval

The study was approved by Ege University Faculty of Medicine Ethics Committee (date: November 5, 2023, number: 23-5T/40).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: EO, FG; data collection: EB, EÇ, NÇ, PE, SEP, SG, GKÖ, AAK, MK, FÜ, AÖ, BÖ, SP, VŞ, TŞE, ZSU, EY, and HY; analysis and interpretation of the results: EÇ, NÇ, SG, EY; draft manuscript preparation: EO, FG, GKÖ. 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

Nasal polyps in childhood: insights from a pediatric pulmonology cohort

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ABSTRACT

Introduction. Nasal polyps (NP) are benign inflammatory growths originating from the nasal/paranasal sinus mucosa. NPs can occur independently or signify underlying respiratory conditions. This study aimed to evaluate the demographic and clinical characteristics of NPs in children at a pediatric pulmonology department.

Method. This cross-sectional study included children aged 0-18 years diagnosed with NP at the pediatric pulmonology department from 2007 to 2025. Patients were categorized into four groups: cystic fibrosis (CF), primary ciliary dyskinesia (PCD), asthma/allergic rhinitis (AR), and undefined etiology. Demographic and clinical data were compared across these groups.

Results. A total of 47 (40.4% female) patients were included in the study. The median age of NP diagnosis was 11 years (4.6-17.8). The most common presenting symptoms were nasal obstruction (47, 100%) and mouth breathing during sleep (37, 78.7%). The etiological causes of NPs were PCD (13, 27.7%), CF (9, 19.1%), asthma/AR (11, 23.4%), and an undefined etiology (14, 29.8%). Bilateral NPs were present in 32 (68.1%) cases. In 27 (57.4%) patients, NP was the first presentation, with no other symptoms. Among all PCD patients, NP was the first presentation in 7 (53.8%) of cases. NP recurrence was documented in 14 patients (29.8%). No significant differences were observed among the groups in sex, growth z-scores, or age at NP diagnosis ($p>0.05$). Bilateral NPs were more common in the PCD group (92.3%) than in the CF (66.7%), asthma/AR (36.3%), and undefined groups (71.4%) ($p=0.034$). NP recurrence was more frequent in the CF group (66.7%) compared with the PCD (38.5%) and undefined groups (13.6%), while no recurrence was observed in the asthma/AR group ($p=0.021$).

Conclusion. This study highlights the heterogeneity of pediatric NP in causes, presentation, and course. Patients with PCD often present bilaterally, while CF patients have the highest recurrence rate. In PCD, NP was the initial sign in over half of cases, suggesting isolated NP should prompt suspicion of PCD.

Key words: nasal polyp, cystic fibrosis, primary ciliary dyskinesia, asthma, allergic rhinitis.

Nasal polyps (NP) originate from any part of the mucosa of the nose or paranasal sinuses. NPs are benign inflammatory growths that range in color from grayish-pink to yellow. They may appear as solitary or multiple masses and are usually easily movable during examination. NPs can occur as an isolated condition, but they may also be a sign of various underlying respiratory disorders. These include cystic fibrosis (CF), primary ciliary dyskinesia (PCD), asthma, allergic rhinitis (AR), and immunodeficiency, among others. Moreover, in

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some cases, NP may be the first manifestation of a severe underlying disease. When identified, clinicians should raise suspicion for potential underlying conditions.[1,2]

NPs are relatively rare in the general pediatric population, with an estimated incidence of approximately 0.1%.[1] However, their prevalence is higher with certain chronic respiratory diseases. The literature reports that the incidence of NPs in children with CF varies from 6% to 48%.[2,3] Similarly, studies report a prevalence ranging between 15%-30% in patients with PCD, likely due to impaired mucociliary clearance leading to persistent sinonasal congestion and infection.[4] In pediatric asthma populations, NPs are less frequent but still noteworthy, with reported rates around 7%, particularly in those with coexisting AR. In addition to causing persistent nasal obstruction, NPs can impair children's quality of life by disrupting breathing, sleep, and daily activities. They are linked to chronic upper airway colonization, serving as a reservoir for pathogens. This colonization may increase pulmonary exacerbations in children with chronic respiratory conditions like CF and PCD.[2-7]

This study aimed to evaluate the demographic and clinical features of NPs in children who were followed up at a pediatric pulmonology department, and to examine their distribution across primary underlying conditions, thereby improving the understanding of disease patterns.

Methods

This was a cross-sectional study. All procedures involving human participants in the study adhered to the ethical standards established by the institutional research committee (Gazi University Ethics Committee, date: September 24, 2024, meeting: 15, reference number: 2024-1502), as well as the Declaration of Helsinki and its subsequent amendments or similar ethical guidelines. All children aged 0 to 18 years who were followed up with a diagnosis of NP at the pediatric pulmonology department between 2007 and 2025 were included in the study. The study population consisted of patients referred to the pediatric pulmonology department because NP was identified at their initial visit, as well as those who developed NP during follow-up for underlying conditions such as CF or PCD. Only patients with a confirmed NP diagnosis and complete medical records were included, while those with an uncertain diagnosis or missing data were excluded.

The medical data of the patients were retrospectively collected from their medical records. Demographic and clinical information, including sex, symptoms, growth parameter z-scores, etiological causes of NP, history of polypectomy, and age at polypectomy, were recorded, along with whether patients had pulmonary function test (PFT) and home sleep study (HSS) results documented.

Pulmonary function tests were performed according to the American Thoracic Society/ European Respiratory Society (ATS/ERS) guidelines, using acceptable criteria for children. Measurements included forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), peak expiratory flow (PEF), and forced expiratory flow from 25% to 75% (FEF25–75%), all recorded as percentages. Additionally, the FEV1/FVC ratio was documented and assessed based on age, sex, and height. PFTs are generally conducted for individuals aged six and older.[8] PFT values obtained at the time of NP diagnosis were recorded.

A home sleep study (Type 3 polygraphy, ApneaLink(ResMed)) was used to diagnose sleep-disordered breathing (SDB) when in-laboratory polysomnography is not available. It was performed when obstructive sleep apnea (OSA) was suspected in patients who reported nighttime symptoms such as snoring or witnessed apneas. During the study period, access to HSS testing was sometimes restricted or temporarily unavailable.[9] The apnea-hypopnea index (AHI) was defined as follows: AHI < 1 is normal, 1 ≤ AHI < 5 is classified as

mild OSA, 5 ≤ AHI < 10 is classified as moderate OSA, and AHI ≥ 10 is classified as severe OSA. The term "apnea" refers to parent-reported or witnessed breathing pauses during sleep.

Medical records of patients who had NP were evaluated, and their clinical and diagnostic findings were recorded. The assessment included a detailed medical history, physical examination, PFT, allergy testing (including serum IgE levels and skin prick tests), sweat chloride testing when clinically indicated, and, when clinically indicated, high-speed video microscopy (HSVM) and/or genetic testing. CF diagnosis was established according to the European Cystic Fibrosis Society guidelines. Sweat testing was performed using the chloride titration method, with sweat chloride values >59 mmol/L considered diagnostic for CF, values <30 mmol/L considered normal, and values between 30 and 59 mmol/L requiring repeat testing. Accordingly, CF was diagnosed based on either two sweat chloride measurements >59 mmol/L, or one sweat chloride measurement >59 mmol/L together with the identification of two CF-causing mutations by DNA analysis, or the identification of two CF-causing mutations in the presence of typical clinical features of CF.[10]

Diagnosis of PCD was based on a compatible clinical presentation, characteristic radiological findings, HSVM results showing abnormal ciliary beat patterns consistent with PCD (including stiff-beating and immotile cilia patterns), and/or genetic testing in accordance with ERS/ATS diagnostic guidelines.[11] Among genotyped patients, for patients carrying apparently heterozygous variants, parental segregation analysis was performed, demonstrating compound heterozygosity, with each parent carrying one variant.

Asthma diagnosis was determined through pediatric allergy consultation, clinical history, spirometry, and adherence to the Global Initiative for Asthma guidelines.[12] The diagnosis of AR was established based on clinical symptoms, physical examination, and a positive skin prick test and/or serum-specific IgE results.[13]

Patients were divided into four diagnostic subgroups based on etiology: CF, PCD, asthma/AR, and undefined etiology. Demographic and clinical data were compared across groups.

Diagnosis of NP

The diagnosis of NP was made by otolaryngologists using one or more of these methods: direct inspection, anterior rhinoscopic examination, nasal endoscopy, or sinonasal imaging, including paranasal sinus computed tomography or magnetic resonance imaging. NP was confirmed when polypoid lesions were found in the nasal or paranasal cavity with any of these techniques.

Definition of NP regression

Regression of NPs was defined as a ≥25% reduction in polyp size or complete resolution, as documented by nasal endoscopic and clinical examination findings following medical and/or surgical treatment. Regression was determined by the attending physician's assessment, based on a visible reduction in obstruction or the disappearance of polyps.[14,15]

Definition of recurrent NP

Recurrent NP were defined as the reappearance of polypoid lesions after prior medical and/or surgical treatment, confirmed by clinical examination, endoscopic evaluation, and/or sinonasal imaging.

Treatment of NP

At our institution, children with NP are initially treated with intranasal corticosteroids and saline irrigation. Systemic corticosteroids are rarely used and are reserved for selected cases with severe obstruction or inadequate response to topical therapy. Surgical intervention is considered for patients who do not respond to medical treatment or who experience

recurrence, taking into account the underlying primary disease. The final decision to proceed with surgery is made after evaluation by an otolaryngologist, with the indication mainly based on the severity of nasal obstruction and symptom burden.

Medical treatment consisted mainly of intranasal corticosteroid sprays (such as mometasone furoate, triamcinolone acetonide, and fluticasone furoate) in combination with regular nasal saline irrigation. Intranasal corticosteroids were administered once or twice daily for at least one month (≥4 weeks) or longer depending on clinical response. Antihistamines and short courses of oral corticosteroids were used only in selected cases, taking into account the underlying disease.

Statistical analysis

IBM SPSS Statistics version 22.0 (IBM, Armonk, NY, USA) was used for the statistical analyses. In the descriptive statistics section, categorical variables are presented as counts and percentages, while continuous variables are shown with means ± standard deviations, and medians (minimum–maximum values). The Pearson chi-square test and Fisher's exact test were used to evaluate categorical variables. The Mann–Whitney U-test was employed for comparing two independent variables in data that did not meet normal distribution assumptions, and the independent sample t-test was used for data that followed a normal distribution. When comparing three or more variables, one-way analysis of variance (ANOVA) was performed under conditions suitable for parametric tests, and the Kruskal–Wallis H test was used when parametric conditions were not met. The relationship between non-normally distributed data was assessed using Spearman's correlation test, while Pearson's correlation test was used for data that conformed to a normal distribution. P-values less than 0.05 were considered statistically significant.

The required sample size was calculated using G*Power 3.1.9.7. Assuming a large effect size (Cohen's w = 0.50) for the chi-square test comparing NP rates across four etiological groups, with a power of 80% and a two-sided alpha of 0.05, a minimum of 44 patients was estimated. Since this retrospective study included all eligible cases (n= 47), the required sample size was achieved.

Results

The demographic and clinical data for all patients, along with comparisons between groups, are shown in Table I. A total of 47 patients were included in the study. Nineteen (40.4%) were female and 28 (59.6%) were male. The median age at NP diagnosis was 11 (4.6-17.8) years. The median weight z-score was -0.41 (-2.33- 4.87), height z-score was -0.32 (-2.69-9.62), and BMI z-score was 0.0 (-3.93-2.49) at the time of diagnosis of NP. The most common presenting symptoms were nasal obstruction 47 (100%), mouth breathing during sleep 37 (78.7%), and snoring 25 (53.2%). NPs were unilateral in 15 (31.9%) cases and bilateral in 32 (68.1%) cases.

In 27 (57.4%) patients, NP were the first presentation, with no other symptoms. Among these patients, one had a diagnosis of CF, seven had a diagnosis of PCD, one had a diagnosis of asthma, and four had a diagnosis of AR. Among the 13 confirmed PCD patients included in the study with NP, NP were the first presenting feature in 7 (53.8%) of them.

Intranasal corticosteroids combined with nasal saline irrigation were the most commonly used medical treatments (40 patients, 85.1%). Antihistamines were prescribed in 4 (8.5%) and short courses of oral corticosteroids were prescribed in 2 (4.2%) patients, respectively.

Thirty (63.8%) patients had a history of polypectomy, with a mean age at surgery of 12.7 years (range: 5–25 years). Regression of NP was

Table I. Demographic and clinical data of the CF, PCD, and Asthma-AR and Unknown etiology groups .

	CF n (%) (Total: 9 patients)	PCD n (%) (Total: 13 patients)	Asthma/AR n (%) (Total: 11 patients)	Unknown etiology n (%) (Total: 14 patients)	p
The age of diagnosis of NP (year) ‡	10.8 (5.8-17.8)	11.9 (5.1-15.6)	10 (5.1-16)	12.6 (4.6-17.4)	0.659
Female	4 (44.4)	9 (69.3)	2 (18.2)	4 (28.6)	0.055
Male	5 (55.5)	4 (30.7)	9 (81.8)	10 (71.4)	
Weight z-score ‡	-0.66 (-1.80-4.74)	-0.49 (-2.33-2.18)	0.82 (-1.81-4.87)	-0.28 (-1.64-2.42)	0.367
Height z-score ‡	0.13 (-1.47-7.0)	-0.40 (-1.37-2.31)	-0.49 (-1.84-9.62)	-0.30 (-2.69-1.96)	0.915
BMI z-score ‡	-0.4 (-3.93-1.91)	-0.39 (-2.25-1.44)	0.39 (-1.58-2.01)	-0.11(-2.31-2.49)	0.117
Symptoms					
Nasal obstruction	9 (100)	13 (100)	11 (100)	14 (100)	-
Mouth breathing during sleep	7 (77.8)	12 (92.3)	9 (81.8)	9 (64.2)	-
Snoring	3 (33.3)	6 (46.2)	6 (54.5)	10 (71.4)	-
**Apnea*	2 (22.2)	-	1 (9.1)	1 (7.1)	-
Morning headache	1 (11.1)	1 (7.6)	1 (9.1)	1 (7.1)	-
Daytime sleepiness	-	1 (7.6)	1 (9.1)	2 (14.2)	-
Spirometry	n=8	n=12	n= 4	n=6	
FEV1% ‡	91 (58-128)	94 (48-114)	96 (78-135)	103 (71-127)	0.361
FVC% ‡	90 (58-124)	90 (52-116)	97 (79-122)	105 (65-112)	0.667
FEV1/FCV ‡	103 (62-110)	99 (75-108)	106 (84-116)	103 (86-116)	0.574
FEF_{25-75}% ‡	87 (24-133)	90 (37-115)	110 (47-160)	84 (60-143)	0.591
HSS	n=3	n=1	n=2	n=1	
Mild OSA	2 (22.2)	1 (7.7)	2 (18.2)	-	
Moderate OSA	-	-	-	1 (7.1)	-
Severe OSA	1 (11.1)	-	-	-	
NP presentation					
Unilateral	3 (33.3)	1 (7.7)	7 (63.7)	4 (28.6)	0.034
Bilateral	6 (66.7)	12 (92.3)	4 (36.3)	10 (71.4)	
Presenting with NP as the first manifestation	1 (11.1)	7 (53.8)	5 (45.5)	14 (100)	-
Medical treatments					
Intranasal steroids& nasal lavage	6 (66.6)	12 (92.3)	9 (81.8)	13 (92.8)	-
Antihistamines	1 (11.1)	1 (7.7)	1 (9.1)	1 (7.1)	
Oral steroid	-	2 (15.4)	-	-	
History of polypectomy	6 (66.7)	10 (76.9)	5 (45.5)	9 (64.3)	0.442
The age of polypectomy (year) ‡	11.5 (9.6-25)	13.2 (7.2-20.6)	11 (6-18.5)	13 (5-21.3)	0.988
Regression of NP	3 (33.3)	8 (61.5)	11 (100)	11 (78.5)	0.021
Recurrence of NP	6 (66.7)	5 (38.5)	-	3 (13.6)	0.021
Follow-up duration (months)	148 (21–201)	31 (1–146)	4.5 (1–76)	1 (1–15)	<0.001

AR: Allergic Rhinitis, BMI: Body mass index, CF: Cystic Fibrosis, HSS: Home Sleep Study, NP: Nasal Polyp, OSA: Obstructive Sleep Apnea, PCD: Primary Ciliary Dyskinesia

‡:[median (min-max)]

* The term "apnea" indicates parent-reported or witnessed breathing pauses during sleep.

observed in 33 (70.2%) patients. NP recurrence was documented in 14 patients (29.8%).

Spirometry data were available for 30 patients. The median FEV1 was 95% (range: 48–135%), FVC was 91% (52–124%), the FEV1/FVC ratio was 101% (62–116%), and the mean FEF_{25-75} was 91% (24–160%).

Aspirin provocation testing was performed in two patients suspected of NSAID hypersensitivity, and neither met the criteria for aspirin-exacerbated respiratory disease. The other children with NP had no history of suspected NSAID hypersensitivity. HSS was performed in seven patients, all of whom were diagnosed with OSA; five had mild OSA, one had moderate OSA, and one had severe OSA.

Among the 47 patients, 33 (70.2%) had an identifiable underlying disease, including PCD (13, 27.7%), CF (9, 19.1%), asthma (5, 10.6%), and AR (6, 12.8%). Fourteen (29.8%) patients had no defined etiology. In our pediatric pulmonology clinic, 57 patients were followed up with a diagnosis of CF, and 24 with PCD. Among these, NPs were detected in 9 (15.8%) patients with CF and in 13 (54.2%) patients with PCD.

Demographic and clinical characteristics of patients with NP were compared across four etiological groups: CF (n = 9), PCD (n = 13), asthma/AR (n = 11), and unknown etiology (n = 14). No statistically significant differences were observed regarding sex (p = 0.055), current age (p = 0.345), weight z-score (p = 0.367), height z-score (p = 0.915), BMI z-score (p = 0.117), or age at NP diagnosis (p = 0.659) among the groups.

Regarding NP laterality, bilateral presentation was significantly more common in the PCD group (92.3%) than in the other groups (p = 0.034).

The history of polypectomy was reported in 66.7% of CF patients, 76.9% of PCD patients, 45.5% of asthma/AR patients, and 64.3% of patients with unknown etiology (p = 0.442), with no significant difference in the age at polypectomy across the groups (p = 0.988). Notably, NP recurrence was significantly more frequent in the CF group (66.7%) (p = 0.021).

Spirometry was available for subsets of each group (n=8 for CF, n=12 for PCD, n=4 for asthma/AR, and n=6 for the unknown etiology group). No significant differences were found in median values of FEV1, FVC, FEV1/FVC ratio, or FEF_{25-75} among the groups (respectively, p= 0.361, p= 0.667, p= 0.574, p= 0.591).

Among patients, the median follow-up durations were 148 (21–201) months for the CF group, 31 (1–146) months for the PCD group, 4.5 (1–76) months for the asthma/AR group, and 1 (1–15) months for the unknown etiology group (p < 0.001).

In the CF group, five CF patients received CFTR modulator therapy during the study. Four patients were treated with elexacaftor/tezacaftor/ivacaftor for a median of 11 months (range: 5–18 months), and one patient received on ivacaftor for 18 months. When considering all CFTR modulator–treated CF patients together, the median treatment duration was 17 months (range: 5–18 months). Three of them had a history of polypectomy and recurrence of NP.

Because of the retrospective design and the historical period of patient evaluation, genetic analysis was available for only 8 of the 13 patients diagnosed with PCD. Five patients with PCD were lost to follow-up. In the remaining five patients, the genetic analysis results were unavailable. The results of the genetic analysis for the CF and PCD patients are presented in Table II.

Discussion

This study is among the few pediatric pulmonology cohorts examining NPs across various etiologic groups rather than focusing on a single disease. Including children with CF, PCD, Asthma–AR, and unknown causes provides a broader clinical perspective. It emphasizes disease-specific patterns, such as

Table II. The genetic analysis reports of the CF and PCD patients.

CF	Patient 1. *CFTR*: 3199del6 /3199del6
	Patient 2. *CFTR*: R1070Q / G178R / S466X (TAA)
	Patient 3. *CFTR*: E831X / E831X
	Patient 4. *CFTR*: G85E / G85E
	Patient 5. *CFTR*: 1677delTA/ F508del
	Patient 6. *CFTR*: R1162X/ 2789+5G>A
	Patient 7. *CFTR*: F508del / F508del
	Patient 8. *CFTR*: R334W / N1303K
	Patient 9. *CFTR*: F508del / N1303K
PCD	Patient 1. *TTC12*: c.1480G>A, *DNAAF4*: c.791A>G, *DNAAF3*: c.1445C>A, *DNAH1*: c.7809C>T
	Patient 2. *KIF9*: c.1515-1G>A, c.1960G>A, *DNAH7:* c.16-6A>G / c.8945+652G>A, *DNAH1*: c.7759G>T, *DRC1*: c.26C>T
	Patient 3. *DNAJB13*: c.721-37C>G, c.607-314dup, *CFAP74*: c.2241+34G>A, c.3012-56G>A, *CCDC40*: c.2445A>G, *DNAL1*: c.306C>T
	Patient 4. *DNAAF1*: c.455G>A, *DNAI1*: c.1286G>A, c.7975A>G, c.11788-29G>A, *DNAH9:* c.2427C>T
	Patient 5. *DNAH5*: c.6037C>T / c.6037C>T
	Patient 6. *CCDC151*: c.1291C>T / c.1291C>T
	Patient 7. *DNAH5:* c.12596G>A / c.12596G>A
	Patient 8. *DNAH5:* c.5563dupA / c.2511dupC

CF: Cystic Fibrosis, PCD: Primary Ciliary Dyskinesia .

increased recurrence in CF and predominantly bilateral presentation in PCD. In PCD, NP was the initial presentation in over half of the cases, highlighting that isolated NP should prompt suspicion of an underlying PCD diagnosis. Underlying genetic mucociliary disorders predispose patients to more pronounced and recurrent NP.

Nasal polyps in children often are related to chronic sinonasal inflammation and may signal underlying genetic, allergic, or inflammatory conditions. In our group, PCD and CF were primary causes, seen in 27.7% and 19.1% of patients, respectively, with fewer cases of AR and asthma. These findings are consistent with evidence that impaired mucociliary clearance and ongoing inflammation contribute to NP.[16,17] Notably, 70.2% of patients had underlying diseases, emphasizing that NP often indicates broader systemic or respiratory issues. In some cases, NP may be the first sign of systemic diseases like CF or PCD, especially in children without initial pulmonary symptoms. In our cohort, 57.4% presented with NP first, and 13 were diagnosed with an underlying disease. However, 29.8% had no identifiable cause, highlighting diagnostic challenges. Therefore, children presenting with NPs should undergo a structured initial evaluation, including assessments for CF, PCD, and allergic airway diseases. Additional genetic, immunologic, or radiologic tests should be reserved for cases in which initial findings suggest an underlying systemic or chronic condition. This highlights the need for a multidisciplinary approach to NP in children for proper management and early detection of serious conditions. Long-term follow-up is recommended. Assessing children with isolated NP may help detect systemic diseases early. The high initial NP rate in our study may be due to increased awareness and routine evaluations by pulmonologists.

Nasal polyps are considered the final stage of chronic mucosal inflammation caused by

ongoing inflammatory exposure in the upper airways. The prevalence of NP has been shown to increase with age, with studies reporting higher occurrence in older children and adolescents.[18-20] Additionally, previous research has indicated an age range from early childhood to adolescence. Supporting this, our study also included a notably broad age spectrum. In our cohort, the age at diagnosis varied widely from 4.6 to 17.8 years, suggesting that, besides cumulative inflammatory burden, other factors such as genetic susceptibility, host response, and underlying comorbidities may also significantly influence the timing of presentation.

In CF, the reported prevalence of NP in pediatric groups varies widely across studies, ranging from 6% to 86%.[21,22] In our cohort, NP was present in 15.8% of children with CF, a rate lower than that reported in other studies. This variability between studies may be influenced by multiple factors, including genetic background, differences in study design, patient age distributions, diagnostic methods for NP, and clinical follow-up practices across centers. In PCD, the prevalence of NP has been reported to range from 15% to 30% across most studies.[4] In our cohort, NP was detected in 54.2% of patients with PCD, a rate notably higher than in most previous reports. This difference may be due to our tertiary referral setting, where patients generally have more advanced or symptomatic disease, as well as our systematic ENT assessments, which enable more comprehensive detection of NP throughout the disease course.

Previous studies have shown that highly effective CFTR modulator therapies are associated with decreased sinonasal symptoms, improved endoscopic and radiologic findings, and regression of NPs in some patients with CF. In our study, nine CF patients were included in the NP subgroup, of whom five received highly effective *CFTR* modulator therapy during follow-up. Among those patients, three had a history of nasal polypectomy and experienced NP recurrence. However, due to the small number of CF patients, the limited number receiving therapy, and differences in follow-up duration and therapy length, we could not perform a statistical analysis of the impact of CFTR modulators on NP regression or recurrence. As a result, our data do not establish a direct link between *CFTR* modulator therapy and the clinical progression of NP. Nonetheless, based on existing research, *CFTR* modulator therapies represent a significant advance in treating CF-related sinonasal disease, and larger, prospective studies are needed to better understand their effects on NP.[23]

Nasal obstruction is an independent contributor to SDB.[24] In our cohort, it was the most common symptom, present in all patients, followed by mouth breathing during sleep and snoring. These findings support the known effect of NP in increasing upper airway resistance, especially in children with smaller anatomies, making them more vulnerable to airflow restriction. Mouth breathing and snoring, often seen as harmless, are linked to SDB and can lead to poor sleep, neurocognitive issues, and fatigue. Less common symptoms include apnea, headache, and daytime sleepiness. Apnea in children with NP may indicate undiagnosed OSA. All seven patients assessed with HSS had OSA, emphasizing the role of NP in pediatric SDB. Chronic sinonasal inflammation may also contribute to headaches and fatigue through cytokines and systemic responses. This diversity of symptoms highlights the importance of a thorough clinical assessment in children with nasal obstruction or mouth breathing, as these may signal more serious upper airway conditions beyond simple rhinitis.

Differences in NP characteristics across disease groups reflect different mechanisms. Bilateral NP was more common in PCD, likely due to mucociliary impairment causing extensive sinonasal inflammation and bilateral NP formation. An international study of 345 PCD patients found NP in 14%, with 47% bilateral.[4] In our study, NP recurrence was most common in CF, likely due to persistent inflammation from thick secretions and infections, leading to ongoing sinonasal issues and regrowth after

surgery. The asthma/AR group showed the highest rate of unilateral NP and no recurrence, indicating a milder pattern. Although pediatric studies on AR-associated NP are limited, evidence from atopy-related NP suggests a less aggressive course. Steehler et al.[25] identified central atopic disease as an NP phenotype associated with inhalant allergy, with lower recurrence and revision rates than those of other CRS subtypes. These findings support the idea that NP in atopic conditions may be more localized and milder than in CF or PCD, which involve more severe airway pathology.[4,17,24-29] These insights highlight that clinical features such as NP can inform different management strategies depending on the disorder, underscoring the importance of disease-specific surveillance in pediatric NP.

Spirometric parameters were similar across disease groups, including CF, PCD, and asthma/AR. In children, nasal disease and NP mainly reflect upper-airway issues and are only weakly related to spirometric indices.[30-32] CF and PCD pulmonary impairment mainly result from lower-airway disease, while in asthma, airflow limitation depends on control. Our data showed similar spirometric profiles across groups. A recent meta-analysis found no significant postoperative improvements in FEV1, FVC, or FEV1/FVC after sinus surgery in CF, suggesting that sinonasal disease affects morbidity but not pulmonary decline.[25] Adult studies link NP and chronic rhinosinusitis with more severe asthma, but limited pediatric data show no spirometric decline related to NP.[33] Our findings support the idea that NP primarily causes sinonasal issues, not directly affecting lung function.

This study has some limitations. The retrospective design introduces potential risks of missing data and selection bias. Heterogeneity within subgroups and relatively small sample sizes may have limited the ability to detect subtle differences, which is a common challenge in rare disease cohorts. Not all patients had an HSS, which is another limitation. Additionally, systematic screening for NSAID hypersensitivity was not available for all patients. Since this was a cross-sectional study, follow-up duration and visit frequency varied among patients, which could have impacted the accuracy of recurrence rate assessment and limited the evaluation of long-term disease progression and causal relationships.

In conclusion, our findings highlight the variability of pediatric NP in terms of underlying causes, presentation, and clinical progression. Patients with PCD were more likely to present with bilateral NP, whereas those with CF exhibited the highest recurrence rates. Identifying underlying chronic diseases in many children with NP emphasizes the importance of comprehensive evaluation in this group. Additionally, when NP is diagnosed, it should be evaluated for underlying conditions. Specifically, disorders like CF and PCD, which involve genetically impaired mucociliary clearance, are associated with a higher burden and recurrence of NPs and should be considered during follow-up. Variations in NP features across different underlying causes indicate that detailed characterization of these features could help evaluate disease progression and guide follow-up care. These findings underscore the importance of routine upper airway monitoring in high-risk populations.

Ethical approval

The study was approved by Gazi University Ethics Committee (date: September 24, 2024, number: 2024-1502).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: HK, TSE, ATA; data collection: ABÇ, NK; analysis and interpretation of results: FB; draft manuscript preparation: HK, TSE, ATA. 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

Impact of rheumatologic diseases on pediatric inflammatory bowel disease

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ABSTRACT

Background. The coexistence of rheumatologic diseases (RD) and inflammatory bowel disease (IBD) in children remains underexplored. This study aimed to assess the frequency of RD and its clinical impact in pediatric IBD patients.

Methods. This retrospective cohort study included pediatric IBD patients followed at the Department of Pediatric Gastroenterology, Hepatology and Nutrition at Hacettepe University, Ankara, Türkiye between November 2008 and December 2020. Demographic characteristics, disease activity scores, inflammatory markers, and treatment modalities were compared between patients with and without concomitant RD; an additional analysis was performed in the familial Mediterranean fever (FMF) subgroup.

Results. A total of 88 patients (35 females, 53 males; median age 14.6 years) were analyzed. RD was identified in 28 patients (31.8%), with FMF being the most frequent (19/28, 67.9%; overall 21.6%). Although patients with RD had lower disease activity at diagnosis ($p = 0.010$), they required more frequent biologic therapy during follow-up (35.7% vs. 16.7%, $p = 0.047$). In the FMF subgroup, disease activity scores were significantly lower at diagnosis and higher at the last follow-up compared with patients without RD. There were no significant differences in inflammatory markers between the groups at diagnosis and last follow-up.

Conclusions. RD, particularly FMF, is commonly observed in pediatric IBD, with a prevalence of 31.8% for RD and 21.6% for FMF. The presence of RD is associated with an increased need for biologic therapy despite lower initial disease activity. Children with IBD should be systematically evaluated for RD, especially in regions with high *MEFV* mutation prevalence, to support more personalized management strategies.

Key words: biologic therapy, familial Mediterranean fever, inflammatory bowel disease, rheumatologic diseases.

Inflammatory bowel disease (IBD), including Crohn's disease (CD), ulcerative colitis (UC), and unclassified inflammatory bowel disease (IBDU), represents a chronic inflammatory condition affecting the gastrointestinal tract.[1] Pediatric IBD is frequently associated with extraintestinal manifestations, particularly rheumatologic diseases (RD), such as familial

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Mediterranean fever (FMF) and enthesitis-related arthritis (ERA) among the juvenile idiopathic arthritis (JIA) subgroups.[2]

FMF is an inherited autoinflammatory disorder, especially common in populations from the Mediterranean region, and is characterized by recurrent febrile episodes, serositis, and systemic inflammation.[3] Recent studies have reported a higher prevalence of *MEFV* gene mutations among pediatric IBD patients, suggesting a genetic predisposition that may influence disease phenotype and severity.[4-7] In a Japanese cohort, *MEFV*-mutated pediatric IBDU patients demonstrated distinct mucosal phenotypes and responded favorably to colchicine, implying that *MEFV*-related autoinflammation may shape intestinal immune responses.[8] In another cohort from Armenia, pediatric UC patients with coexisting FMF were reported to require earlier initiation of biologic therapy compared to those without FMF.[9]

Despite growing evidence, the clinical implications of FMF in pediatric IBD have not been fully elucidated. Whether the coexistence of FMF alters the disease course or affects treatment responsiveness remains unclear.

Therefore, this study aims to assess the frequency of FMF among pediatric IBD patients and to evaluate its impact on disease activity, inflammatory markers, and the need for biologic therapy. We hypothesize that the presence of FMF may be associated with an altered disease course and increased likelihood of biologic therapy.

Materials and Methods

This retrospective cohort study was conducted in the Department of Pediatric Gastroenterology, Hepatology and Nutrition at Hacettepe University, encompassing cases from November 2008 to December 2020. Pediatric patients diagnosed with IBD (CD, UC and IBDU) were included. IBD diagnosis was established based on clinical presentation, laboratory parameters, endoscopic appearance, histopathologic features, and radiologic findings, in accordance with the revised European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) Porto criteria.[10]

Patients were categorized into two groups based on the presence or absence of coexisting RD, including FMF and JIA (including the ERA subtype), or other RD such as chronic recurrent multifocal osteomyelitis (CRMO), IgG4-related disease, or IgA vasculitis. The diagnosis of FMF was established according to the Eurofever/PRINTO criteria.[11] JIA and ERA were identified using the International League of Associations for Rheumatology (ILAR) classification criteria[12], while CRMO was diagnosed based on the Jansson criteria.[13] IgA vasculitis was defined according to the EULAR/PRINTO/PRES Ankara 2008 criteria.[14] The diagnosis of IgG4-related disease was based on the 2020 Revised Comprehensive Criteria for IgG4-RD.[15]

Data included demographic variables, clinical features, disease activity scores (Pediatric Crohn's Disease Activity Index [PCDAI] and Pediatric Ulcerative Colitis Activity Index [PUCAI]), inflammatory markers (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], albumin, platelet count, fecal calprotectin), and treatment history, including biologic therapy.

Indications for initiating biologic therapy followed standard pediatric IBD practice consistent with ESPGHAN recommendations, including steroid-refractory or steroid-dependent disease, moderate-to-severe activity, fistulizing disease, or inadequate response to immunomodulators.

Statistical analyses were conducted using SPSS for Windows, version 22.0. Continuous variables were presented as median (Q1-Q3) or mean ± standard deviation based on data distribution, while categorical variables were expressed as counts and percentages. Between-group comparisons were performed using the Mann-Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical

variables. A two-tailed p-value of <0.05 was considered statistically significant.

Given the retrospective and exploratory nature of the study, no a priori sample size or power calculation was performed. Due to variable data completeness, a formal post-hoc power analysis could not be applied to all parameters, and the results should therefore be interpreted with caution.

The study received approval from the Hacettepe University Institutional Review Board and was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. A waiver of informed consent was granted by the Board owing to the retrospective nature of the study.

Results

Patient demographics and clinical features

A total of 88 pediatric patients diagnosed with IBD were included, comprising 35 females (39.8%) and 53 males (60.2%) with a median age of 14.6 years (10.7-17.9 years). Disease subtypes included CD in 46 patients (52.3%), UC in 37 (42%), and IBDU in 5 (5.7%).

A family history of IBD was noted in 10 patients (11.4%), FMF in 3 (3.4%), and both diseases in 3 (3.4%). Parental consanguinity was present in 34 patients (38.6%), with no significant difference observed between the RD and non-RD groups (p = 0.93).

A comprehensive comparison of demographic features, disease subtype, baseline disease activity, inflammatory markers at diagnosis, time to biologic therapy, and treatment outcomes between patients with RD and those without RD is presented in Table I. A separate comparison between patients with FMF and those without RD is shown in Table II. The proportion of patients with CD was significantly higher in the RD group compared with patients without RD (71.4% vs. 43.3%, p = 0.024). Within the FMF subgroup, CD was also more frequent than in patients without RD (63.1% vs. 43.3%); however, this difference did not reach statistical significance (p = 0.101). Regarding disease activity, scores at diagnosis were significantly lower both in patients with RD compared with those without RD (p = 0.010) and in the FMF subgroup compared with patients without RD (p = 0.011). However, at the last follow-up, disease activity scores were significantly higher in the FMF group than in patients without RD (p = 0.015).

Inflammatory markers

At diagnosis, the median CRP level was 3.1 mg/dL (0.9-7.6), and the median ESR was 42 mm/h (20-58). At final follow-up, these values decreased to a median CRP of 0.32 mg/dL (0.16-0.80) and ESR of 13 mm/h (7-23.5), indicating overall improvement in inflammatory burden. Fecal calprotectin levels were available in 47 patients at diagnosis, with a median value of 300 μg/g (300-682), and in 10 patients at the final follow-up, with a median of 87.9 μg/g (2.5-326), supporting a reduction in intestinal inflammation over time. There were no statistically significant differences in CRP, ESR, or fecal calprotectin levels between patients with and without RD at either diagnosis or final follow-up.

Rheumatologic disease distribution

RD were identified in 28 of the 88 patients (31.8%), while the remaining 60 patients (68.2%) had no RD. FMF was the most common RD, observed in 19 patients, representing 21.6% of the total cohort and 67.9% of those with RD. Of the 19 patients with FMF, 11 had already been diagnosed with FMF and were receiving colchicine at the time of IBD diagnosis, whereas the remaining 8 patients were diagnosed with FMF after IBD onset and started colchicine thereafter. Among the 19 patients with FMF, *MEFV* mutation analysis revealed a predominance of pathogenic biallelic genotypes (52.6%), with M694V/M694V being the most frequent genotype (47.3%), followed by M694V/M680I (5.3%). Heterozygous

Table I. Comparison of clinical and laboratory characteristics of pediatric inflammatory bowel disease patients with and without concomitant rheumatologic diseases

	IBD with RD (n=28)	IBD without RD (n=60)	p value
Age at IBD diagnosis, years*	9.8 (5.7-14.4)	8.3 (2.9-12.3)	0.299
Female sex, n (%)	14 (50%)	21 (35%)	0.181
Parental consanguinity, n (%)	11 (39.3%)	23 (38.3%)	0.932
IBD subtype, n (%)			0.024
Crohn's disease	20 (71.4%)	26 (43.3%)	
Ulcerative colitis	7 (25%)	30 (50%)	
Unclassified (IBDU)	1 (3.6%)	4 (6.7%)	
IBD activity at diagnosis*†	1 (1-2)	2 (1-3)	0.010
CRP at diagnosis, mg/dL*	3.4 (1.8-7.1)	2.9 (0.7-8.9)	0.633
ESR at diagnosis, mm/h*	40 (20-58)	43 (17-61)	0.986
Serum albumin at diagnosis, g/dL*	3.7 (2.9-4.2)	3.5 (2.9-3.9)	0.234
Platelet count at diagnosis, $\times 10^3/\mu L$*	476 (298-636)	491 (410-670)	0.285
Fecal calprotectin at diagnosis, μg/g*	300 (279-622)	300 (300-1037)	0.906
Biologic therapy for IBD, n (%)	10 (35.7%)	10 (16.7%)	0.047
IFX	3 (10.7%)	7 (11.7%)	
ADA	3 (10.7%)	1 (1.7%)	
IFX→ADA	2 (7.1%)	2 (3.3%)	
ADA→IFX	2 (7.1%)	0	
Time to use of biologics for IBD, months*	9.5 (3.5-17.0)	17.1 (12.2-36.6)	0.124
Outcome (IBD activity at last follow-up)* †	0 (0-1)	0 (0-1)	0.121

*Values are presented as median (Q1-Q3).
†0=Remission, 1=Mild, 2=Moderate, 3=Severe
Note: Some variables contain missing values; analyses reflect available cases.
ADA: adalimumab, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, IBD: inflammatory bowel disease, IBDU: unclassified IBD, IFX: infliximab, RD: rheumatologic disease.

pathogenic variants included M694V, M680I, and V726A. Variants of uncertain significance (VUS) included E148Q and A744S. The overall *MEFV* mutation spectrum is summarized in Table III, and individual patient-level genotypes are provided in Table IV.

FMF was diagnosed as an isolated condition in 14 patients (15.9%) and in combination with other RD in 5 patients (5.7%), including 4 with ERA and 1 with oligoarticular JIA. ERA was identified in 8 patients (9.1%), of whom 4 (4.5%) had isolated ERA and 4 (4.5%) had ERA coexisting with FMF. Other RDs included CRMO in 2 patients (2.3%), isolated oligoarticular JIA in 1 patient (1.1%), IgG4-related disease in 1 patient (1.1%), and IgA vasculitis in 1 patient (1.1%). The overlap between FMF, ERA, and oligoarticular JIA within the RD group is illustrated in Fig. 1.

Biologic therapy for IBD

Biologic therapy for IBD was administered to 20 patients (22.7%) in the cohort. Among them, 10 received infliximab (IFX), 4 received adalimumab (ADA), 4 were switched from IFX to ADA, and 2 from ADA to IFX. To avoid misclassification, only biologic agents initiated specifically for IBD were included in this analysis; biologic therapies prescribed solely for rheumatologic indications were recorded separately.

Among patients with CD, 5 received IFX, 2 received ADA, 2 were switched from IFX to

Table II. Subgroup analysis comparing patients with familial Mediterranean fever to patients without rheumatologic disease

	IBD with FMF (n=19)	IBD without RD (n=60)	p value
Age at IBD diagnosis, years*	9.2 (2.4-13.9)	8.3 (2.9-12.3)	0.872
Female sex, n (%)	9 (47.4%)	21 (35%)	0.333
Parental consanguinity, n (%)	10 (52.6%)	23 (38.3%)	0.271
IBD subtype, n (%)			0.101
Crohn's disease	12 (63.1%)	26 (43.3%)	
Ulcerative colitis	6 (31.6%)	30 (50%)	
Unclassified (IBDU)	1 (5.3%)	4 (6.7%)	
IBD activity at diagnosis*†	1 (1-2)	2 (1-3)	0.011
CRP at diagnosis, mg/dL*	3.4 (1.1-6.8)	2.9 (0.7-8.9)	0.937
ESR at diagnosis, mm/h*	39 (20.5-56)	43 (17-61)	0.784
Serum albumin at diagnosis, g/dL*	3.7 (2.9-4.5)	3.5 (2.9-3.9)	0.257
Platelet count at diagnosis, $\times 10^3/\mu L$*	506 (266-646)	491 (410-670)	0.482
Fecal calprotectin at diagnosis, μg/g*	300 (123-300)	300 (300-1037)	0.444
Biologic therapy for IBD, n (%)	6 (31.6%)	10 (16.7%)	0.194
IFX	2 (10.5%)	7 (11.7%)	
ADA	1 (5.3%)	1 (1.7%)	
IFX→ADA	2 (10.5%)	2 (3.3%)	
ADA→IFX	1 (5.3%)	0	
Time to use of biologics for IBD, months*	10 (3.5-17.0)	17.1 (12.2-36.6)	0.121
Outcome (IBD activity at last follow-up), median*†	1 (0-1.5)	0 (0-1)	0.015

*Values are presented as median (Q1-Q3).
†0=Remission, 1=Mild, 2=Moderate, 3=Severe
Note: Some variables contain missing values; analyses reflect available cases.
ADA: adalimumab, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, FMF: familial Mediterranean fever, IBD: inflammatory bowel disease, IBDU: unclassified IBD, IFX: infliximab, RD: rheumatologic disease.

Table III. *MEFV* mutation spectrum in familial Mediterranean fever patients

MEFV mutation	Patients with genotype, n (%)
Two pathogenic variants	10 (52.6%)
M694V/M694V	9 (47.3%)
M694V/M680I	1 (5.3%)
One pathogenic variant	6 (31.6%)
M694V/-	4 (21.0%)
M680I/-	1 (5.3%)
V726A/-	1 (5.3%)
One pathogenic variant / one VUS	
M694V/E148Q	1 (5.3%)
Two VUS	
E148Q/E148Q	1 (5.3%)
One VUS	
A744S/-	1 (5.3%)

VUS: variant(s) of uncertain significance.

Table IV. Individual *MEFV* genotypes of familial Mediterranean fever patients

	MEFV mutation 1	*MEFV* mutation 2
Patient 1	A744S	-
Patient 2	M694V	-
Patient 3	M680I	-
Patient 4	V726A	-
Patient 5	M694V	M694V
Patient 6	M694V	M694V
Patient 7	M694V	E148Q
Patient 8	M694V	M694V
Patient 9	M694V	M694V
Patient 10	M694V	M694V
Patient 11	M694V	M694V
Patient 12	M694V	-
Patient 13	M694V	-
Patient 14	M694V	M680I
Patient 15	M694V	M694V
Patient 16	M694V	M694V
Patient 17	M694V	M694V
Patient 18	E148Q	E148Q
Patient 19	M694V	-

ADA, and 2 from ADA to IFX. In patients with UC, 5 received IFX, 2 received ADA, and 2 received sequential IFX followed by ADA. Biologic agents were used more frequently in patients with RD (10/28, 35.7%) compared to those without RD (10/60, 16.7%) (p = 0.047). In the FMF subgroup, the frequency of biologic therapy use was higher, although not statistically significant, compared with patients without RD (p = 0.194). Notably, 3 patients received biologic therapy for both IBD and RD: 1 with CD, FMF, and ERA; 1 with CD and FMF; and 1 with CD and ERA.

Biologic therapy for rheumatologic disease

Biologic therapy specifically targeting RD was administered to 8 patients (28.6%) within the RD group. Among these, 3 also required biologic agents for concomitant IBD, as previously noted.

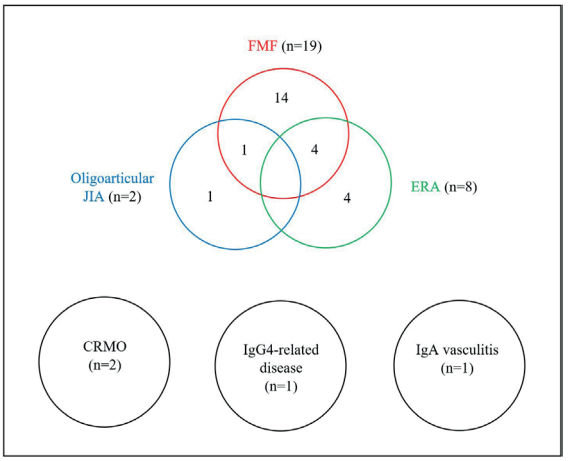

Fig. 1. Venn diagram showing the overlap between FMF, ERA, and oligoarticular JIA among pediatric inflammatory bowel disease patients with rheumatologic diseases.

FMF shows overlap with ERA (n=4) and oligoarticular JIA (n=1). CRMO (n=2), IgG4-related disease (n=1), and IgA vasculitis (n=1) occurred only as isolated conditions and are therefore shown as separate, non-overlapping sets in the diagram.

CRMO: chronic recurrent multifocal osteomyelitis, ERA: enthesitis-related arthritis, FMF: familial Mediterranean fever, JIA: juvenile idiopathic arthritis.

Canakinumab was used in 3 patients, 1 of whom had previously received anakinra. One patient was switched from anakinra to IFX, and another was treated with IFX without prior biologics. ADA was administered to 2 patients, 1 following prior etanercept therapy and the other without any prior biologic treatment. Anakinra was used as initial therapy in 1 patient.

The primary indications for biologic therapy were FMF in 4 patients (3 treated with canakinumab and 1 with anakinra), ERA in 3 patients (1 treated with IFX and 2 with ADA), and coexisting FMF and ERA in 1 patient treated with IFX.

Discussion

This study investigated the prevalence and clinical impact of RD, particularly FMF, in children with IBD. We found that RD was

present in approximately one-third of the cohort, with FMF being the most common, observed in 21.6% of all patients and 67.9% of those with concomitant RD. Although patients with RD had significantly lower disease activity scores at diagnosis, they were more likely to require biologic therapy during follow-up. Our findings align with previous studies reporting a high prevalence of FMF among pediatric IBD patients, particularly in populations with a high frequency of *MEFV* mutations, such as Turkey and Armenia.[6,9] For example, Uslu et al. reported that 21.2% of Turkish children with IBD had FMF[6], while Amaryan et al. observed an even higher prevalence in Armenian pediatric patients with UC.[9] These results support a regional and possibly genetic predisposition for FMF-IBD coexistence. In our cohort, CD was significantly more common in patients with RD than in those without RD. A similar trend was observed in the FMF subgroup; however, this difference did not reach statistical significance.

The coexistence of FMF and IBD has also raised questions about whether *MEFV* mutations could modify the course of pediatric IBD. Several studies have investigated the prevalence of *MEFV* variants in IBD patients and reported significantly higher rates than in the general population.[5,6] A multicenter Turkish study detected *MEFV* mutations in 41.9% of pediatric IBD patients, suggesting a possible genetic overlap or modifying effect.[5]

It has been proposed that *MEFV* mutations may influence the clinical course of IBD by enhancing innate immune activation, potentially contributing to treatment-refractory or atypical disease phenotypes.[5,16] However, results across studies remain inconsistent. In our cohort, patients with FMF did not exhibit more severe inflammatory markers at diagnosis, and although the frequency of biologic therapy use was higher, this difference did not reach statistical significance. CRP and ESR were also similar between groups, which should be interpreted cautiously, given the relatively small sample size. Notably, however, disease activity scores at the last follow-up were significantly higher in the FMF group, suggesting that disease control over time may be more difficult to achieve in these patients despite comparable baseline inflammatory markers.

Although some reports have suggested that *MEFV* mutations may underlie atypical colitis phenotypes categorized as IBDU[16], our study specifically included patients with confirmed FMF and identified different treatment patterns despite comparable baseline inflammatory markers. This observation is also consistent with a recent genetic study of our cohort, which identified *MEFV* mutations as the most frequent monogenic cause of early-onset IBD and highlighted their potential role in modifying disease phenotypes and possibly influencing treatment responses in children with IBD.[17]

In our cohort, patients with FMF presented with lower clinical disease activity scores at diagnosis compared with patients without RD. This finding may be partially explained by prior colchicine use, as 11 of the 19 FMF patients had been diagnosed with FMF before their IBD onset and were already receiving colchicine therapy. Colchicine, the cornerstone of FMF treatment, prevents attacks and suppresses subclinical inflammation through inhibition of microtubule polymerization, neutrophil activation, and downstream inflammatory pathways.[3] Its sustained anti-inflammatory effects may mask FMF-related systemic symptoms and attenuate inflammatory biomarkers (e.g., CRP, ESR), potentially leading to underestimation of IBD activity by standard indices such as PCDAI.

Indeed, several case reports have documented infantile or early-onset colitis and CD that responded dramatically to colchicine initiation, highlighting its capacity to modify gastrointestinal inflammatory phenotypes.[18-20] However, while colchicine may dampen clinical and laboratory signs, it does not necessarily prevent progressive intestinal inflammation, which may ultimately require escalation to biologic therapy.[21] Therefore, the anti-inflammatory effects of colchicine should be recognized as a potential confounding factor

that may obscure true disease activity and influence treatment decisions in patients with overlapping FMF and IBD.

The potential masking effect of colchicine complicates treatment decisions, especially in refractory cases. The management of patients with concomitant IBD and FMF can be challenging, particularly in those who respond inadequately to standard therapies. In our cohort, patients with RD had a higher likelihood of receiving biologic therapy for IBD, and several also required targeted treatment for FMF. IL-1 inhibitors such as anakinra and canakinumab were used in selected cases, particularly among patients with colchicine-resistant FMF. These findings align with previous reports supporting the effectiveness of IL-1 blockade in managing inflammation associated with both isolated FMF and FMF-IBD overlap syndromes.[4,7]

This study provides additional insight into the interplay between autoinflammatory conditions and pediatric IBD, suggesting that FMF may influence treatment decisions even in the absence of severe initial disease activity. Through a comprehensive analysis of clinical characteristics, inflammatory markers, and treatment patterns, we observed that FMF, as a frequent comorbidity, may be associated with certain differences in disease presentation and treatment approaches.

However, several limitations must be acknowledged. The relatively small cohort limits generalizability, particularly for less common rheumatologic conditions. Additionally, therapeutic decisions may have been influenced by clinician judgment and institutional protocols.

Despite these limitations, our findings highlight the importance of systematically screening for RD, particularly FMF, in pediatric IBD populations, especially in regions with a high prevalence of *MEFV* mutations. Conversely, clinicians should consider underlying IBD in children with known RD who present with chronic diarrhea, abdominal pain, or growth delay. Future prospective, multicenter studies incorporating genetic analyses and long-term outcome data are warranted to clarify the clinical and mechanistic impact of FMF-IBD overlap. Early recognition of FMF in this context may facilitate more personalized treatment strategies and ultimately improve disease management.

Ethical approval

The study was approved by Hacettepe University Ethics Committee (date: February 23, 2021, number: GO 21/75).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: DDG, HHG, HD, İNST, HÖ, SÖ; Data collection: DDG, HHG, ES, ZB; Analysis and interpretation of results: DDG, HHG, HÖ, HD, İNST, SÖ; Draft manuscript preparation: DDG, HHG. 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

Predictors of psychosocial adjustment in siblings of children with autism spectrum disorder: a structural equation modeling study

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ABSTRACT

Background. Siblings of children with autism spectrum disorder (ASD) are at increased risk of psychosocial difficulties due to altered family dynamics and parental stress. However, the mechanisms linking ASD severity, parental psychopathology, and sibling outcomes remain unclear. This study aimed to identify determinants of psychosocial problems among siblings of children with ASD using a family-systems framework and structural equation modeling (SEM).

Methods. A case–control study was conducted with 67 siblings of children with ASD (ASD-Sibs) and 67 siblings of typically developing children (TD-Sibs), aged 6–18 years. ASD severity was rated using the Childhood Autism Rating Scale (CARS). Sibling depression, anxiety, and emotion regulation were assessed using the Child Depression Inventory (CDI), Screen for Child Anxiety Related Emotional Disorders (SCARED), and Cognitive Emotion Regulation Questionnaire (CERQ). Parents completed the Child Behavior Checklist (CBCL), Beck Depression and Anxiety Inventories (BDI, BAI), and Family Assessment Device (FAD). SEM was used to examine predictors of sibling psychosocial outcomes.

Results. ASD-Sibs reported significantly higher depressive and anxiety symptoms than TD-Sibs. SEM revealed that maternal depression and general family functioning were significant predictors of sibling depression, anxiety, and behavioral problems. ASD severity indirectly influenced sibling outcomes through maternal depression and anxiety. Positive reappraisal emerged as a protective factor against anxiety.

Conclusions. Maternal psychological well-being and family functioning are key determinants of psychosocial adjustment among ASD-Sibs. Autism severity affects siblings indirectly via maternal psychopathology, underscoring the importance of holistic, family-centered interventions to promote resilience in families of children with ASD.

Key words: autism spectrum disorder, siblings, psychosocial adjustment, maternal depression, maternal anxiety, family functioning, structural equation modeling.

The family unit serves as a critical developmental context for children, offering both a primary socialization environment and a secure base.[1] However, within a family systems framework, individual challenges can significantly impact overall family functioning.[2] The presence of a child with autism spectrum disorder (ASD), for instance, profoundly alters family dynamics, affecting not only the child but also all family members due to its pervasive developmental impacts.[3]

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Parents of children with ASD often assume roles beyond typical parenting and become de facto special educators.[4] They navigate complex behavioral challenges[5], strive to meet the needs of other family members, and frequently contend with social isolation and stigma[6,7]. Personal time for self-care and social engagement is often significantly limited.[8]

Siblings of children with ASD (ASD-Sibs) also experience unique challenges related to their sibling's condition, including behavioral issues, communication difficulties, and the demand for continuous support.[9] Reduced parental attention, a common experience for ASD-Sibs, may lead to increased attention-seeking behaviors and internalizing problems. The implicit expectation to provide support can also generate feelings of burden and stress.[10] Difficulties in sibling relationships, potentially marked by complex social interactions and conflicts, may also extend to peer relationships, exacerbating stress levels.[10,11]

Existing literature consistently indicates that ASD-Sibs exhibit a heightened vulnerability to diminished psychological well-being and lower psychosocial functioning compared to siblings of typically developing children (TD-Sibs).[12] Recent research, although focused on identifying risk factors, often reports inconsistent findings due to the heterogeneous nature of ASD and the unique characteristics of families, highlighting the complexity of this area. Among the key variables warranting investigation, family stress stands out. Autism families (families of children with ASD) experience unique daily stressors, which are associated with increased rates of parental anxiety and depression.[13] Parental stress[14] and general family distress[15] are positively correlated with siblings' psychosocial problems. Some research suggests that increased family stress may directly impact siblings' distress more than relational difficulties with their autistic sibling.[14] Conversely, other studies have found no significant association between sibling adjustment and maternal stress or family support.[16]

Another complex area is the relationship between ASD severity and sibling outcomes. While challenging behaviors in children with ASD are consistently linked to sibling outcomes[17], the direct impact of autism severity is less clear, likely due to the spectrum's wide phenotypic variability. Some studies report a positive association between symptom severity and sibling adjustment difficulties[18], while others find no significant relationship[19]. This inconsistency underscores the need to identify mediating variables that clarify how ASD severity influences sibling psychosocial problems.

Emotion regulation skills are also crucial for stress management, conflict resolution, and maintaining emotional balance. Despite their importance, few studies have explored the contribution of emotion regulation skills to psychosocial problems in ASD-Sibs. One intervention program noted improved relationships between autistic siblings and those with enhanced emotion regulation skills.[20] Given that ASD-Sibs frequently encounter chronic and emotionally demanding family environments, examining their cognitive emotion regulation strategies offers a meaningful way to understand both vulnerability and resilience pathways.

Gender significantly shapes sibling relationships[21], and its broad influence on psychosocial development within the context of ASD is also well-established. Sisters often report a stronger sense of responsibility towards their siblings with ASD[22], whereas brothers may exhibit higher rates of emotional and conduct problems and peer difficulties[16]. Consequently, brothers of children with ASD may face more psychosocial challenges than sisters.[23] However, conflicting evidence suggests that sisters may experience elevated anxiety and depression compared to brothers.[24]

Finally, birth order is another critical factor. Older siblings often show better psychological functioning than younger ones.[25] This is hypothesized to occur because older siblings experience a period of typical family life

before the full impact of ASD is felt, while younger siblings encounter these challenges from an earlier developmental stage.[26] Thus, the influence of birth order on sibling understanding, expectations, and engagement warrants further investigation.

This study aimed to identify determinants contributing to psychosocial problems in ASD-Sibs, specifically investigating internalizing and externalizing problems from both sibling and parental perspectives. Predictor variables were categorized into three domains: child-related (autism severity, intelligence level), family-related (maternal and paternal depression/anxiety, household income, family functionality), and sibling-related (birth order, gender, cognitive emotion regulation skills).

Materials and Methods

Study design and participants

The study protocol was approved by the Ankara University Faculty of Medicine Ethics Committee (protocol number: 11-717-18). Written informed consent was obtained from all participants, and procedures adhered to the Declaration of Helsinki. Data were collected between November 2019 and April 2020.

This case-control study included 67 age- and sex-matched ASD-Sibs and TD-Sibs, along with their mothers and fathers. Eligible siblings were 6–18 years old and volunteered to participate. TD-Sibs had no prior psychiatric diagnoses. Exclusion criteria for both groups were ASD or intellectual disability, neurological/chronic illness, and institutional care.

Children with ASD were initially evaluated and ASD diagnoses were confirmed by experienced child psychiatrists and clinical psychologists based on DSM-V criteria. Study participation was announced to physicians at the Child and Adolescent Psychiatry and General Pediatrics clinics of our tertiary care center. Eligible families were referred to our clinic. Siblings and parents attended clinical interviews for the collection of information and sociodemographic data. Following preliminary evaluation, autism severity was rated with the Childhood Autism Rating Scale (CARS), after which siblings and parents completed questionnaires.

In the ASD-Sibs group, 3 siblings were excluded due to intellectual disability, 5 due to ASD, and 3 due to neurological/chronic illness; additionally, 9 families declined participation or did not complete the study forms, resulting in a final ASD-Sibs sample of 67. In the TD-Sibs group, 23 families declined participation and 7 children were excluded due to neurological/chronic illness in themselves or a sibling, resulting in a final TD-Sibs sample of 67.

To ensure developmental comparability, siblings were categorized as children (< 12 years: ASD-Sibs n = 26, TD-Sibs n = 27) and adolescents (≥ 12 years: ASD-Sibs n = 41, TD-Sibs n = 40) for subgroup analyses.

Measures

Sociodemographic information

A semi-structured interview form collected data on sibling, family, and autistic child sociodemographic attributes, including age, gender, parental education and employment, and household income (Table I).

Child autism severity

The Childhood Autism Rating Scale (CARS) was used to rate autism severity.[27] CARS includes 15 items rated from 1–4 (with intermediate ratings), yielding a total score typically ranging from 15 to 60, where higher scores indicate greater autism severity. Turkish validity and reliability have been established, with high internal consistency (α = 0.95) and test-retest reliability (r = 0.98).[28]

Siblings' self-report measures

Child Depression Inventory (CDI) is a self-report scale for depressive symptoms (6–18 years).[29] The CDI consists of 27 items scored on a 0–2 scale (total score range: 0–54), with higher

Table I. Sociodemographic characteristics of groups.

Variables	Study Group Mean ± SD / n (%)		Control Group Mean ± SD / n (%)		*p*
Sibling characteristics	*<12 y*	*≥12 y*	*<12 y*	*≥12 y*	
Age [a]	8.9 ± 1.5		9 ± 1.4		0.717[1]
		14.9 ± 2.2		14.2 ± 2	0.166[2]
Gender [b]					
Female	19.4 (13)	29.9 (20)	20.9 (14)	28.4 (19)	0.893[1]
Male	19.4 (13)	31.3 (21)	19.4 (13)	31.3 (21)	0.908[2]
Parent characteristics					
Mother age [a]	38.4 ± 4.6		38.1 ± 5.5		0.686
Father age [a]	42.6 ± 4.9		41.8 ± 5		0.352
Mother's education (year) [a]	9.3 ± 0.48		9.9 ± 0.4		0.062
Father's education (year) [a]	11.5 ± 0.45		10.6 ± 0.4		0.416
Family characteristics					
Family type [b], (nuclear)	94 (63)		89.6 (60)		0.507
Monthly family income [b]					
Low (≤330$)	11.9 (8)		7.5 (5)		
Medium (330-1000$)	55.2 (37)		62.7 (42)		0.576
High (>1000$)	32.8 (22)		29.9 (20)		

[a] Student's t-test, [b] Chi-square test
[1] *p* value for siblings under 12 years of age (child group), [2] *p* value for siblings aged 12 and older (adolescent group)
SD: standard deviation.

scores indicating greater depressive symptom severity. The Turkish adaptation demonstrated good internal consistency ($\alpha = 0.82$).[30]

Screen for Child Anxiety Related Emotional Disorders (SCARED) is a 41-item self-report measure for childhood anxiety disorders.[31] SCARED includes 41 items rated 0–2 (total score range: 0–82) and yields subscale scores for Panic/Somatic, Generalized Anxiety, Separation Anxiety, Social Anxiety, and School Avoidance; higher scores indicate greater anxiety. Its Turkish adaptation showed strong internal consistency ($\alpha = 0.91$).[32]

Cognitive Emotion Regulation Questionnaire (CERQ) is a 36-item self-report assessing nine cognitive emotion regulation strategies following adverse events.[33] Subscales (four items each) are maladaptive (Self-blame, Rumination, Catastrophizing, Blaming others) or adaptive (Acceptance, Putting into perspective, Positive refocus, Refocus on planning, Positive reappraisal). Each CERQ subscale comprises 4 items scored 1–5 (subscale score range: 4–20); higher scores indicate more frequent use of that strategy. Turkish validation yielded similar results, with subscale α ranging from 0.72 (Self-blame) to 0.83 (Catastrophizing).[34]

Parent-report measures

Child Behavior Checklist (CBCL 6-18): The 2001 version was used to assess behavioral/emotional problems.[35] The CBCL contains 113 problem items rated 0–2 and yields syndrome scales and broadband Internalizing and Externalizing scales; results are typically reported as age- and sex-standardized T-scores (mean = 50, SD = 10), with higher scores indicating more problems. The Turkish version demonstrated good internal consistency for Internalizing ($\alpha = 0.87$, $r = 0.93$), Externalizing ($\alpha = 0.90$, $r = 0.93$), and Total Problems ($\alpha = 0.94$, $r = 0.93$).[36]

Beck Depression Inventory (BDI) is a self-report measure of adult depression severity.[37] The BDI consists of 21 items scored 0–3 (total score range: 0–63), with higher scores indicating more severe depressive symptoms. The Turkish adaptation showed good internal consistency (α = 0.84).[38]

Beck Anxiety Inventory (BAI) is a 21-item self-report for clinical anxiety.[39] The BAI includes 21 items scored 0–3 (total score range: 0–63), with higher scores indicating greater anxiety severity. Its Turkish adaptation demonstrated excellent internal consistency (α = 0.95).[40]

Family Assessment Device (FAD) is a self-administered measure of family functioning based on the McMaster Model.[41] The FAD comprises 60 items rated on a 4-point Likert scale and consists of seven subscales (Problem Solving, Communication, Roles, Affective Responsiveness, Affective Involvement, Behavior Control, General Functioning); higher scores reflect poorer family functioning. Turkish validation indicated subscale α values ranging from 0.62 to 0.90.[42]

Data analysis

Statistical analyses were conducted using SPSS 23.0 (Statistical Package for the Social Sciences), AMOS 23.0 statistical software, and R for bootstrap estimation. Continuous variables are presented as mean ± standard deviation (SD) when normally distributed and as median (Q1–Q3) when non-normally distributed; categorical variables are presented as number (%). Normality was assessed using the Shapiro–Wilk test and visual inspection of histograms and Q–Q plots. Pearson chi-square tests compared categorical variables. For continuous variables, Student's t-test or Mann-Whitney U test was applied after confirming data normality. Pearson or Spearman correlation tests were used to assess relationships, and structural equation modeling (SEM) was used to identify determinants of sibling psychosocial problem scores.

In line with a family-systems framework, variables that were theoretically expected to influence sibling adjustment (autism severity, maternal and paternal depression and anxiety, general family functioning, and siblings' cognitive emotion regulation) were initially entered into the SEM. Non-significant paths and parameters that weakened overall model fit were then trimmed stepwise, particularly in view of the relatively small sample size, yielding a final model that retained only theoretically meaningful and statistically supported predictors. In this process, paternal BDI and BAI were initially included but were removed from the final specification because their structural paths were non-significant and their inclusion did not improve overall model fit. Model fit was evaluated using χ^2, χ^2/df, the Comparative Fit Index (CFI), the Normed Fit Index (NFI), and the Root Mean Square Error of Approximation (RMSEA). Model fit was considered acceptable when CFI and NFI were ≥ 0.90 and RMSEA ≤ 0.08, and indicative of good fit when CFI ≥ 0.95, RMSEA ≤ 0.05, and χ^2/df ≤ 2. SEM findings were interpreted with caution, and a sensitivity analysis re-estimated the final model under a constrained specification in which no correlated residuals were allowed.

Effect sizes were interpreted according to Cohen's guidelines: r = 0.20 for small, r = 0.50 for medium, and r = 0.80 for large effects.[43] All analyses employed a two-tailed p-value of 0.05 for statistical significance.

Results

Demographics

Sociodemographic variables are presented in Table I. No significant differences were observed between ASD-Sibs and TD-Sibs regarding sibling (age, gender, number of siblings), parental (age, education level), and family (family type, household income) characteristics.

Normative comparisons in siblings

In the child group, ASD-Sibs exhibited significantly higher scores on the CDI ($p < 0.001$) and SCARED ($p = 0.001$) compared to TD-Sibs. However, no statistically significant differences were found between these groups on the CBCL Internalizing ($p = 0.123$) and Externalizing Problems ($p = 0.419$) subscales (Table II).

Among adolescent siblings, ASD-Sibs reported significantly higher CDI scores than controls ($p = 0.004$), but no significant difference was observed in anxiety scores ($p > 0.05$) (Table II). Additionally, adolescent ASD-Sibs scored higher on both CBCL Internalizing ($p = 0.01$) and Externalizing Problems ($p = 0.006$) subscales compared to controls (Table II). CERQ subscale scores did not differ significantly between the groups (Table II). Fig. 1 shows the mean CBCL syndrome-scale *T*-scores in adolescent siblings (≥12 years). Compared with TD-Sibs, adolescent ASD-Sibs showed higher *T*-scores across several CBCL domains, with differences particularly evident in the broadband Internalizing and Externalizing scales, consistent with the group comparisons reported in Table II.

Clinical range percentages in siblings

Based on CDI cut-off scores, 13% of ASD-Sibs presented with mild depression, 3% with moderate, and 6% with severe depression. In contrast, 1% of TD-Sibs showed mild depression. For CBCL Internalizing Problems, 16% of ASD-Sibs were in the clinical range and 11% in the borderline range, while 5% of TD-Sibs were in the clinical range and 4% in the borderline range. Regarding CBCL Externalizing Problems, 9% of ASD-Sibs were in the clinical range and 3% in the borderline range, with only 1% of TD-Sibs falling into the borderline range.

Table II. Normative comparisons between sibling groups by age group (<12 years vs ≥12 years).

	<12 years				≥12 years			
	ASD-Sibs Mean±SD	TD-Sibs Mean±SD	*t*	*p*	ASD-Sibs Mean±SD	TD-Sibs Mean±SD	*t*	*p*
CDI	10.96 ± 8	3.85 ± 2.6	4.27	0.000***	8.6 ± 4.9	5.9 ± 2.9	2.97	0.004**
SCARED	27 ± 16.5	14.4 ± 8.2	3.53	0.001**	20 ±10.2	16.6 ± 8.8	1.60	0.112
Internalizing problems (CBCL)	53.2 ± 9.8	49.2 ± 8.2	1.57	0.123	54.4 ± 11.5	48.3 ± 8.8	2.63	0.01*
Externalizing problems (CBCL)	48 ± 10.9	45.8 ± 8.5	0.81	0.419	47.7 ± 11	41.7 ± 6.8	2.90	0.006**
CERQ Subscales								
Self-blame	—	—	—	—	9.8 ± 2.9	9.3 ± 2.7	0.80	0.427
Acceptance	—	—	—	—	11.1 ± 3.8	10.2 ± 3.8	1.00	0.322
Rumination	—	—	—	—	11.6 ± 3.6	10.2 ± 3.2	1.81	0.073
Positive refocus	—	—	—	—	11.7 ± 4.6	12.6 ± 4.4	-0.94	0.349
Refocus on planning	—	—	—	—	14.9 ± 3.9	15.4 ± 3.5	-0.60	0.547
Positive reappraisal	—	—	—	—	14.6 ± 3.9	14.6 ± 3.6	0.04	0.967
Putting into perspective	—	—	—	—	13.2 ± 3.7	12.6 ± 3.8	0.76	0.447
Catastrophizing	—	—	—	—	7.9 ± 3.4	8.2 ± 3.6	-0.32	0.750
Other-blame	—	—	—	—	9.8 ± 3.4	8.6 ± 2.8	1.63	0.106

CERQ was administered to adolescents (≥12 years) only.
Student's t-test, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
ASD: autism spectrum disorder; ASD-Sibs: siblings of children with ASD; TD-Sibs: siblings of typically developing children; CBCL: Child Behavior Checklist; CDI: Child Depression Inventory; CERQ: Cognitive Emotion Regulation Questionnaire; SCARED: Screen for Child Anxiety Related Emotional Disorders.

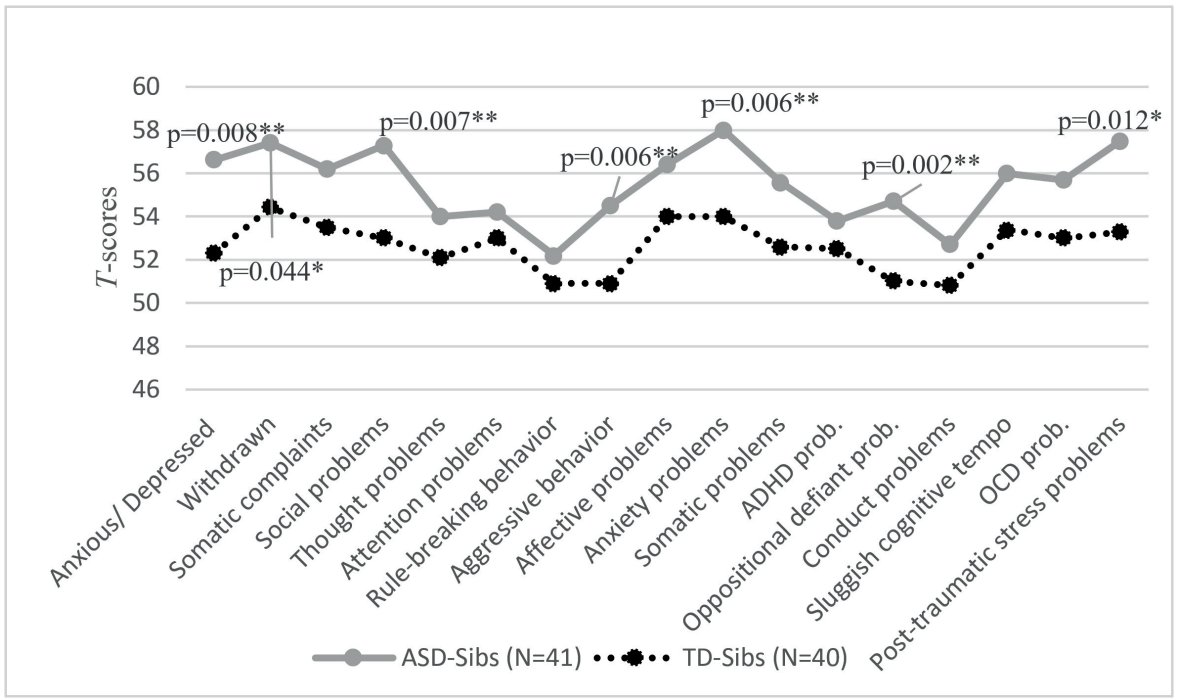

Fig. 1. Mean T-scores of Child Behavior Checklist (CBCL) subscales in adolescent ASD-Sibs and TD-Sibs. This figure presents CBCL T-scores for the adolescent subgroup (≥12 years) to provide a visual summary of syndrome-scale profiles in this age group. *T*-scores are standardized scores with a mean of 50 and standard deviation of 10. T-scores between 60-63 indicate borderline clinical range, and *T*-scores ≥ 64 indicate clinical range. Significant differences between ASD-Sibs and TD-Sibs for each subscale are indicated by asterisks as determined by independent-samples *t*-tests.

*$p < 0.05$, **$p < 0.01$. ASD-Sibs (n = 41), TD-Sibs (n = 40).

ADHD: attention deficit hyperactivity disorder; ASD-Sibs: siblings of children with ASD; OCD: obsessive compulsive disorder; TD-Sibs: siblings of typically developing children.

Normative comparisons in parents and general family functioning

Mothers and fathers of children with ASD reported significantly higher depressive and anxiety symptoms compared to parents in the control group (Table III). Significant group differences in family functioning were found in Problem Solving (1.81 ± 0.57 vs. 1.48 ± 0.46; $p < 0.001$), Communication (1.74 ± 0.48 vs. 1.51 ± 0.4; $p = 0.004$), Affective Responsiveness (1.66 ± 0.47 vs. 1.51 ± 0.43; $p = 0.049$), and General Functioning (1.65 ± 0.47 vs. 1.35 ± 0.3; $p < 0.001$) domains. Other FAD subscale scores were comparable between groups ($p > 0.05$). All FAD subscale results are presented in Table III.

Clinical range percentages in parents

Maternal BDI scores indicated that among mothers of children with ASD, 27% experienced mild, 19% moderate, and 3% severe depression; whereas in control mothers, these rates were 7% mild and 1% moderate. Maternal anxiety levels in the ASD group revealed 26% mild, 20% moderate, and 12% severe symptoms in the clinical range. For control mothers, 9% were in the mild, 8% moderate, and 1% severe clinical range.

Among fathers in the ASD group, 21% reported mild depression and 10% moderate depression. In the control group, 5% of fathers had mild and

Table III. Parent psychological distress (BDI, BAI) and family functioning (FAD) in ASD and control families.

	ASD-Pr	TD-Pr	*t* or *z*	*p*
Mothers				
BDI	11.3 ± 8.9	4.6 ± 4	5.65 a	0.000***
BAI	10 (3.5–19.5)	3 (0–7)	-4.61 b	0.000***
Fathers				
BDI	6 (3–11)	3 (0–7)	-2.83 b	0.005**
BAI	5 (2–12.5)	2 (0–7)	-2.93 b	0.003**
FAD subscale	ASD-Pr	TD-Pr	*t*	*p*
Problem Solving	1.82 ± 0.58	1.5 ± 0.47	3.54	0.000***
Communication	1.75 ± 0.49	1.52 ± 0.41	2.86	0.005**
Roles	1.83 ± 0.37	1.76 ± 0.40	1.06	0.293
Affective Responsiveness	1.66 ± 0.47	1.51 ± 0.43	1.99	0.049*
Affective Involve	1.88 ± 0.37	1.82 ± 0.40	0.92	0.361
Behavior Control	1.76 ± 0.35	1.78 ± 0.37	-0.38	0.704
General Function	1.65 ± 0.47	1.36 ± 0.32	4.13	0.000***

For BDI and BAI, values are presented as Mean ± SD for variables analyzed with Student's t-test and as median (Q1–Q3) for variables analyzed with the Mann–Whitney U test. FAD subscale values are presented as Mean ± SD and compared using Student's t-test.
[a] Student's t-test, [b] Mann-Whitney U Test, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
ASD: autism spectrum disorder; ASD-Pr: parents of children with ASD; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; FAD: Family Assessment Device; SD: standard deviation; TD-Pr: parents of typically developing children.

3% moderate depressive symptoms. Paternal anxiety scores in the ASD group showed 21% in the mild, 11% moderate, and 7% severe clinical range, compared to 16% mild, 4% moderate, and 1% severe clinical range in control fathers.

Correlations

Correlations among the main study measures in the ASD-Sibs group are presented in Supplementary Table S1. Sibling outcomes (CDI, SCARED, CBCL Internalizing and Externalizing) were not significantly correlated with parental age, parental education, household income, autism severity (CARS), or the autistic child's intelligence level (all $p > 0.05$). In contrast, maternal depressive and anxiety symptoms and poorer general family functioning were positively correlated with siblings' psychosocial outcomes, whereas CERQ positive reappraisal showed an inverse association with sibling anxiety (Supplementary Table S1).

Gender and birth order comparisons

Regarding gender (33 girls, 34 boys), no statistically significant difference was observed in psychosocial problems between girls and boys in either age group ($p > 0.05$), except for anxiety scores ($p = 0.001$).

In birth order comparisons, younger siblings (n = 15) displayed numerically higher scores than older siblings (n = 47) on CDI (10.0 ± 8.6 vs. 8.9 ± 6.1; $p = 0.790$), SCARED (23.4 ± 13.2 vs. 21.8 ± 11.8, $p = 0.64$), Internalizing Problems (57.6 ± 7.7 vs. 53.2 ± 11.1, $p = 0.161$), and Externalizing Problems (51.6 ± 7.63 vs. 46.5 ± 10.8, $p = 0.093$). However, these differences were not statistically significant ($p > 0.05$).

Predictors of psychosocial problems in siblings of children with ASD

SEM was employed to investigate predictors of siblings' psychosocial problems and to examine indirect effects. Potentially confounding

demographic variables (age, gender, and family income) were controlled, and a confirmatory factor analysis supported the measurement model's adequacy for SEM. The measurement model demonstrated good fit to the data ($\chi^2(17) = 10.244$, $p = 0.893$; $\chi^2/df = 0.603$; CFI = 1.000; NFI = 0.957; RMSEA = 0.000). Given the modest sample size (n = 67), these indices should be interpreted cautiously and considered alongside theoretical plausibility and a simple, theory-driven model specification.

Bootstrap-based parameter estimates (standard errors, 95% confidence intervals, *z* statistics, and *p*-values) for both direct and indirect effects are presented in Table IV (direct paths) and Supplementary Table S2 (indirect effects).

Indirect effects were evaluated using bootstrap confidence intervals, and results are reported to facilitate transparent interpretation of precision alongside point estimates.

Sensitivity analysis (model without correlated residuals): To address concerns regarding potential overfitting, we additionally estimated a more constrained specification in which no correlated error terms were allowed. As expected, this constraint resulted in poorer global fit ($\chi^2(22) = 68.885$, $p < 0.001$; $\chi^2/df = 3.13$; CFI = 0.104; NFI = 0.246; RMSEA = 0.180), likely reflecting shared variance among conceptually related outcomes and measurement-method overlap. We therefore report the constrained model fit transparently and interpret the final SEM findings primarily on the basis of theoretical coherence.

The SEM results (Fig. 2) indicate that maternal depression (0.25) and family general functioning (0.17) were positive predictors of sibling depression. For sibling anxiety, maternal depression (0.29) and maternal anxiety (0.16) were positive predictors, while positive reappraisal (-0.25) was a negative

Table IV. Direct effects in final SEM (bootstrap estimates).

Path (predictor → outcome)	Std β	SE (Std)	95% CI (Std)	p (Std)	B	SE	95% CI	*p*
CARS → BDI	0.296	0.092	0.116, 0.477	0.001	0.408	0.142	0.112, 0.677	0.004
CARS → BAI	0.334	0.103	0.133, 0.536	0.001	0.577	0.187	0.19, 0.914	0.002
FAD–Gen. → BDI	0.380	0.111	0.162, 0.599	<0.001	7.081	2.390	2.494, 11.878	0.003
FAD–Gen. → BAI	0.291	0.123	0.049, 0.533	0.018	6.796	3.197	0.845, 13.869	0.034
FAD–Gen. → CDI	0.173	0.116	-0.053, 0.4	0.133	2.440	1.644	-0.715, 5.702	0.138
FAD–Gen. → SCARED	-0.122	0.141	-0.399, 0.155	0.388	-2.375	2.730	-8.516, 2.528	0.384
FAD–Gen. → Int. Prob.	0.425	0.097	0.23, 0.62	<0.001	7.245	1.670	4.119, 10.832	<0.001
FAD–Gen. → Ext. Prob.	0.511	0.091	0.322, 0.7	<0.001	6.508	1.177	4.023, 8.858	<0.001
BDI → CDI	0.251	0.111	0.032, 0.47	0.024	0.181	0.082	0.027, 0.37	0.022
BDI → SCARED	0.291	0.114	0.067, 0.515	0.011	0.377	0.160	0.045, 0.657	0.026
BDI → Int. Prob.	0.168	0.085	0.003, 0.333	0.046	0.169	0.085	0.005, 0.332	0.043
BDI → Ext. Prob.	0.170	0.073	0.027, 0.313	0.020	0.122	0.055	0.018, 0.232	0.024
BAI → SCARED	0.159	0.073	0.016, 0.301	0.029	0.135	0.064	0.012, 0.262	0.030
CERQ - Positive reap. → SCARED	-0.248	0.086	-0.418, -0.078	0.004	-0.780	0.276	-1.333, -0.239	0.004

Columns include standardized (Std β) and unstandardized (B) coefficients with bootstrap SE and 95% CI.
BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; CARS: Childhood Autism Rating Scale; CBCL: Child Behavior Checklist; CDI: Child Depression Inventory; CERQ - Positive reap.: Cognitive Emotion Regulation Questionnaire—Positive reappraisal subscale; Ext. Prob.: CBCL Externalizing Problems; FAD–Gen.: Family Assessment Device—General Functioning; Int. Prob.: CBCL Internalizing Problems; SCARED: Screen for Child Anxiety Related Emotional Disorders.

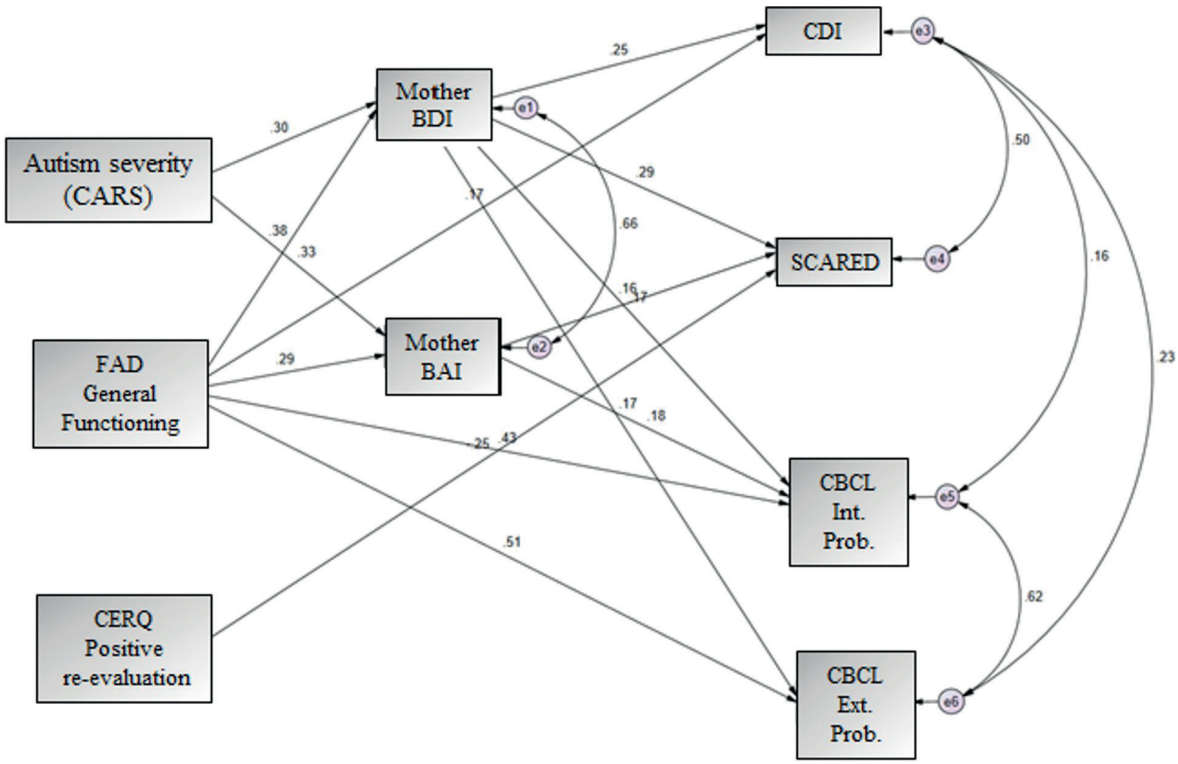

Fig. 2. The structural equation model for predictors of ASD-Sibs' psychosocial problems. All values are standardized beta coefficients. The model showed good fit (χ^2/df = 0.603; CFI = 1.000; NFI = 0.957; RMSEA = 0.000); however, fit should be considered alongside a simple, theory-driven model specification and the modest sample size.BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; CARS: Childhood Autism Rating Scale; CBCL: Child Behavior Checklist; CDI: Child Depression Inventory; CERQ: Cognitive Emotion Regulation Questionnaire; Ext. Prob.: Externalizing Problems; FAD: Family Assessment Device; Int. Prob.: Internalizing Problems; SCARED: Screen for Child Anxiety Related Emotional Disorders.

predictor. In terms of internalizing problems, maternal depression (0.17), maternal anxiety (0.18), and family general functioning (0.43) emerged as positive predictors. Finally, maternal depression (0.17) and family general functioning (0.51) were positive predictors for externalizing problems.

The model also revealed that autism severity positively predicted maternal depression (0.30) and maternal anxiety (0.33) but did not directly predict outcomes in ASD-Sibs. However, autism severity exerted an indirect effect on ASD-Sibs' problems, mediated through maternal depression and anxiety. The indirect effects of autism severity on sibling outcomes were: depression = 0.076, anxiety = 0.285, internalizing problems = 0.185, and externalizing problems = 0.085.

Discussion

This study investigated various potential predictors of psychosocial problems in ASD-Sibs, including parental psychological well-being, family functioning, ASD symptom severity, and sibling characteristics.

A key finding from our SEM analysis was that maternal depression significantly predicted siblings' psychosocial outcomes, with maternal anxiety symptoms specifically associated with higher sibling anxiety and internalizing problems. These results align with previous research demonstrating a strong link between parental psychological distress and sibling adjustment.[14,44] This is further supported by meta-analytic evidence highlighting a robust association between maternal depressive

symptoms and children's internalizing, and externalizing problems, as well as general psychopathology.[45,46] However, a contrasting study by Hesse et al. found that while parental stress correlated with sibling challenges, this relationship did not fully explain adjustment issues when other parent-related factors were considered.[47] This discrepancy might stem from their focus on parental stress rather than clinical depression. While stress may indicate the severity of situational challenges, depressive symptoms reflect a more profound emotional impact on mothers.

Furthermore, our model revealed that the impact of autism symptom severity on sibling outcomes was fully mediated by maternal depressive and anxiety symptoms. This suggests that ASD severity does not directly influence sibling psychosocial problems but rather acts through its effect on maternal psychological well-being. This mediation is consistent with the results of Meyer et al., who found that maternal depression was the primary mediator of siblings' problems.[48] This outcome provides clarity to the mixed findings often reported in the literature regarding the direct relationship between ASD severity and sibling adjustment.

Another significant finding was the notable effect of general family functioning on sibling problems. Our model confirms that robust family functioning is a vital determinant of sibling outcomes, aligning with prior research indicating that family factors, such as cohesion and a positive family climate, are associated with better sibling psychological well-being.[49] Collectively, our results strongly support the existing literature emphasizing family functionality and parental psychological well-being as primary predictors of siblings' psychosocial challenges.[14,15]

Regarding initial group comparisons, self-report measures indicated that ASD-Sibs, particularly in the child group, reported higher levels of depression and anxiety compared to TD-Sibs. This was an unexpected finding, as adolescents typically show greater susceptibility to internalizing problems. This could suggest that younger ASD-Sibs may struggle more with processing and adjusting to family changes, leading to heightened distress[24], potentially due to less developed cognitive coping mechanisms or a more immediate and less filtered perception of family stressors compared to adolescents. However, it is important to note that only a minority of ASD-Sibs met clinical diagnostic criteria, implying that while they experience elevated problems, it is more accurate to identify those at heightened risk and their specific vulnerabilities rather than to universally conclude that all ASD-Sibs experience clinical-level psychosocial issues.

Our study also explored the influence of birth order and gender on the psychological well-being of ASD-Sibs. Consistent with a recent meta-analysis by Park et al.[50] and previous literature[25,26], our findings specifically indicated that younger ASD-Sibs were more vulnerable to internalizing problems than older ones. This heightened vulnerability in younger siblings may stem from their developmental context, often being born into a family already navigating significant burdens, whereas older siblings might have experienced a period of typical family life before the full impact of ASD was felt, potentially fostering greater psychological resilience.[26]

Furthermore, our findings are in line with previous reports suggesting that birth order and developmental timing may shape vulnerability among ASD-Sibs. Consistent with a recent meta-analysis by Park et al. and earlier studies, younger siblings appeared more prone to internalizing difficulties than older ones, possibly because they were born into a family system that was already under the strain of caring for a child with ASD.[25,26,50] In this context, older siblings may have benefited from a period of relatively typical family functioning before the onset or recognition of ASD-related challenges, which could support greater psychological resilience. However, our sample size did not allow for adequately powered tests of more fine-grained interactions between birth

order, age-spacing, and gender, and future studies with larger cohorts are needed to clarify these patterns.

Conversely, younger female ASD-Sibs with wider age-spacing were more likely to develop anxiety symptoms. This is consistent with the literature indicating that typically developing sisters of individuals with ASD often report higher negative emotionality than their male counterparts[51], and our results further suggest that specific birth order and age-spacing dynamics for younger females may exacerbate this predisposition to anxiety. These findings collectively highlight that while general demographic factors like age and gender influence adjustment, a finer-grained analysis of birth order and age-spacing reveals distinct pathways of vulnerability to specific internalizing problems within the ASD-Sib population.

While overall emotion regulation strategies did not differ between groups, our SEM analysis revealed a crucial finding: positive reappraisal emerged as a significant negative predictor of sibling anxiety. This suggests that siblings who frequently employ positive reappraisal – reframing negative events in a more positive light or focusing on potential positive outcomes – experience lower levels of anxiety. This finding aligns with the broader literature on emotion regulation, which emphasizes adaptive cognitive strategies in mitigating psychological distress.[52] For ASD-Sibs, facing unique and ongoing family stressors, the ability to find positive meaning or growth in challenging situations may serve as a vital protective factor against anxiety. This highlights the importance of fostering such adaptive cognitive strategies in interventions aimed at supporting the mental health of ASD-Sibs.

Finally, our findings imply that autism families may face difficulties in problem-solving, communication, and overall general family functioning compared to families with typically developing children. Effective communication and problem-solving skills are crucial for family resilience and for modeling adaptive coping strategies in children.[14]

Strengths, limitations, and directions for future research

This study contributes significantly to understanding predictors of psychosocial problems in ASD-Sibs within a Turkish context. Key strengths include the use of both self- and parent-reports (from both mothers and fathers), a carefully matched control group, and a relatively homogeneous sample of children with ASD. Additionally, the separate analysis of child and adolescent sibling groups, despite the broad age range, enhances precision and allows for developmental considerations.

Despite these strengths, several methodological limitations warrant consideration. First, the SEM was conducted only in the ASD-Sibs group (n = 67), which is a modest sample size for multivariable modeling. Although SEM can be applied to smaller samples in simple, theory-driven models, parameter estimates and global fit indices may be unstable and potentially optimistic, increasing the risk of overfitting—particularly when model refinement is guided by modification indices. In a sensitivity analysis, the model fit worsened when correlated residuals were not allowed, suggesting that global fit may be sensitive to model constraints and shared variance among conceptually related outcomes. Therefore, the SEM findings should be interpreted with caution and require replication in larger and independent samples, ideally with external validation, before strong generalizable inferences are made. Second, the study was not powered to test more fine-grained interactions between birth order, age-spacing, and gender, and larger samples will be needed to clarify these more specific patterns of vulnerability. Third, we did not investigate certain unexamined confounders in ASD-Sibs, such as subthreshold autism-like traits, or school-related adjustment issues (e.g., bullying, academic performance). In addition, maternal psychological well-being, identified as a key mediator in our model, may be influenced

by unmeasured factors like coping skills and social support. Future research would benefit from incorporating these variables to gain a more comprehensive understanding. Finally, the study's primary focus on psychopathology might restrict broader conclusions regarding overall well-being and adaptive functioning.

Future research should therefore adopt a more holistic approach, considering a wider range of individual and social characteristics that foster resilience or vulnerability within the family system, moving beyond a sole focus on psychopathology. Larger and more diverse samples will also be important to test the robustness and generalizability of the SEM pathways identified in this study.

Conclusions

In summary, our study provides robust evidence that maternal psychological well-being and family functionality are primary determinants of psychosocial problems in ASD-Sibs. A crucial insight from our structural equation model is that ASD severity does not directly impact sibling problems but rather exerts its influence indirectly, with maternal depressive and anxiety symptoms acting as key mediators. Furthermore, we identified a significant finding regarding cognitive emotion regulation: the frequent use of positive reappraisal strategies was associated with lower anxiety levels in siblings, suggesting a potential protective factor.

These results underscore the necessity of a family systems perspective when evaluating the mental health needs of children with ASD and their siblings. Early identification and intervention for family dysfunction, particularly addressing maternal psychological distress, can significantly prevent mental health problems across family members. Developing tailored social support interventions for autism families, especially mothers, holds substantial public health and preventive medicine importance, strengthening family resilience and promoting overall well-being.

Supplementary materials

Supplementary materials for this article are available online at https://doi.org/10.24953/turkjpediatr.2026.7288

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Ethical approval

The study was approved by Ankara University Faculty of Medicine Ethics Committee (date: June 25, 2018, number: 11-717-18). Written informed consent was obtained from all participants, and procedures adhered to the Declaration of Helsinki.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: GİE, BGK; Data collection: GİE; Analysis and interpretation of results: GİE, BGK; Draft manuscript preparation: GİE, BGK. 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

Evolution toward ovarian-sparing surgery in pediatric ovarian tumors: a 20-year single-center experience

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ABSTRACT

Background. Ovarian tumors are rare in children, accounting for 1-2% of all pediatric malignancies. Recent trends emphasize fertility preservation, but data on the evolution of practice and outcomes remain limited. This study examines changes in surgical management and outcomes of pediatric ovarian tumors over two decades.

Methods. All children who underwent surgery for ovarian pathologies at a tertiary pediatric surgery center between 2002 and 2021 were reviewed. Patients with histopathologically confirmed ovarian tumors were included. Clinical characteristics, surgical approaches, histopathology, and outcomes were analyzed. Patients were divided into two 10-year periods to evaluate trends over time, and age-based subgroup analysis compared prepubertal (≤12 years) and pubertal (>12 years) patients.

Results. Of 324 children undergoing ovarian surgery, 87 had histologically confirmed tumors. The most common histological type was mature cystic teratoma (54.0%). Eighteen tumors (20.7%) were malignant. Ovarian-sparing surgery (OSS) increased from 20.0% (6/30) to 61.4% (35/57) ($p<0.001$), and the laparoscopic approach increased from 6.7% to 35.1% ($p=0.008$). Patients undergoing OSS had significantly smaller tumors (median 7.0 cm vs 12.0 cm, $p<0.001$) and lower malignancy rates (2.4% vs 37.0%, $p<0.001$). Prepubertal patients had higher malignancy rates than pubertal patients (29.5% vs 11.6%, $p=0.039$). During a mean 4-year follow-up, recurrence rates were similar between OSS and oophorectomy groups (4.9% vs 2.2%, $p=0.90$).

Conclusions. Surgical management of pediatric ovarian tumors has evolved significantly toward fertility-preserving approaches. OSS is safe and effective in appropriately selected patients. The higher malignancy rate in prepubertal patients highlights the importance of age-specific evaluation. Careful preoperative assessment and case selection remain essential for optimal outcomes.

Key words: ovarian tumor, pediatric, ovarian-sparing surgery, fertility preservation, oophorectomy, mature cystic teratoma.

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Ovarian tumors are uncommon in the pediatric population, representing 1-2% of all childhood malignancies and approximately 1% of pediatric tumors overall.[1-3] Despite their rarity, pediatric ovarian tumors pose distinct challenges in diagnosis and management. The clinical presentation varies widely; most patients present with abdominal pain, often due to complications such as torsion, rupture, or rapid tumor growth.[1,4,5] Hormone-secreting tumors may cause precocious puberty or virilization in rare cases.[2,6] The tumor profile in children differs markedly from adults; germ cell tumors account for the majority (~60-70%) of pediatric ovarian neoplasms, whereas epithelial tumors predominate in adults.[3,7] Mature teratomas are the single most common pediatric ovarian tumor, accounting for 30-50% of all pediatric ovarian masses.[2,5] Although most ovarian tumors in children are benign, about 10-20% prove to be malignant, especially in younger patients or when tumors exceed 10 cm in size.[1,7,8]

Historically, the surgical management of pediatric ovarian tumors predominantly involved oophorectomy or salpingo-oophorectomy.[8,9] This approach resulted in permanent loss of ovarian function on the affected side with potential implications for fertility and hormonal function. In the last two decades, surgical practice has shifted markedly toward fertility-sparing approaches.[9-11] Multiple studies demonstrate that in carefully selected cases, ovarian-sparing surgery (OSS) can be performed safely without compromising oncologic outcomes.[12,13] Modern high-resolution imaging and tumor markers now allow more accurate preoperative assessment of malignancy risk, and a growing body of evidence confirms that OSS in children is both safe and effective, with low recurrence rates.[12-22] Reported recurrence rates are low, and most recurrences are themselves benign and manageable with repeat conservative surgery.[18,20,21] Minimally invasive techniques have also become more common, as pediatric surgeons recognize that laparoscopy can achieve oncologic goals while significantly reducing postoperative pain and recovery time.[19,20] In particular, questions remain about how best to select patients for OSS, the utility of intraoperative frozen-section analysis, and the long-term fertility outcomes after OSS.[23,24]

Despite these advances, longitudinal data on the temporal evolution of surgical practice patterns and long-term outcomes of OSS in pediatric populations remain limited. Additionally, differences in tumor characteristics and surgical approach between prepubertal and pubertal patients have not been well characterized. This study aimed to describe the epidemiological distribution of pediatric ovarian tumors at a tertiary pediatric surgery center, analyze the temporal evolution in surgical management over 20 years, compare tumor characteristics and outcomes between prepubertal and pubertal patients, and evaluate the safety and oncologic outcomes of OSS.

Materials and Methods

This retrospective cohort study was conducted at a tertiary referral center. After ethics approval, medical records of all patients aged 0-18 years who underwent surgical intervention for ovarian pathologies between January 2002 and December 2021 were reviewed. Only patients with histopathologically confirmed neoplastic disease were included. Isolated ovarian torsion without underlying tumor and non-neoplastic ovarian lesions (functional cysts, simple cysts, hemorrhagic cysts) were excluded. A total of 87 patients met the inclusion criteria and formed the study cohort. Demographic characteristics, clinical presentation, preoperative imaging findings, laboratory data, surgical details, histopathological diagnosis, postoperative course, follow-up data, and outcomes were collected for each patient.

The 20-year study period was divided into two equal decades (2002-2011 and 2012-2021) to analyze temporal trends in surgical management. This division allowed comparison of practice changes, particularly the increasing

adoption of laparoscopic surgery and ovarian-sparing approaches, consistent with evolving trends reported in the literature.

For age-based subgroup analysis, patients were divided into prepubertal (≤12 years) and pubertal (>12 years) groups based on the average age of menarche in the Turkish population.

Ovarian-sparing surgery (OSS) was defined as any surgical procedure that preserved ovarian tissue; oophorectomy was defined as complete removal of the affected ovary, and salpingo-oophorectomy (S-O) as removal of both the ovary and fallopian tube on the affected side. Tumors were classified as benign or malignant based on the final histopathological diagnosis. Histological types were categorized into germ cell tumors, epithelial tumors, sex cord-stromal tumors, lymphoma, and metastatic tumors according to standard classification systems.

Surgical decision-making was based on an individualized assessment integrating preoperative evaluation and intraoperative findings. Factors considered included patient age, tumor size and characteristics on imaging, serum tumor marker levels (alpha-fetoprotein [AFP], beta-human chorionic gonadotropin [β-hCG], lactate dehydrogenase [LDH]), intraoperative appearance of the tumor, frozen section examination when available, and fertility preservation considerations. In general, OSS was preferred for benign-appearing tumors with normal tumor markers. Oophorectomy or salpingo-oophorectomy was performed for tumors with malignant features, large tumors precluding safe ovarian preservation, and cases with complete ovarian replacement by tumor.

In cases with ovarian torsion, detorsion was performed initially to assess ovarian viability. During the earlier study period, surgical decision-making was primarily based on ovarian circulation after detorsion, with oophorectomy performed for non-viable ovaries or when malignancy was confirmed or suspected. As our practice evolved in line with current evidence, ovarian circulation status was no longer considered a determining factor. In our current protocol, OSS is performed in all torsion cases regardless of circulation status after detorsion, unless the ovary is frankly necrotic or malignancy is confirmed or suspected.

Surgery was performed via either open laparotomy or laparoscopic approach. The surgical approach was determined based on tumor size, patient age, and body habitus, surgeon preference and experience, and institutional resources. Frozen section examination was utilized selectively at the surgeon's discretion, particularly when malignancy was suspected. In cases of confirmed or suspected malignancy, staging procedures were performed, including inspection of all peritoneal surfaces, peritoneal washings, omentectomy, peritoneal biopsies, and contralateral ovarian inspection or biopsy as indicated. Malignant germ cell tumors were staged according to the Children's Oncology Group (COG) staging system.[25]

Statistical analyses were performed using Jamovi software (version 2.5). Descriptive statistics were calculated for all variables. Continuous variables were expressed as means ± standard deviations (SD) for normally distributed data, or as median (Q1–Q3) for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. The normality of continuous variables was assessed using the Shapiro-Wilk test. For normally distributed data, independent samples t-tests were used; for non-normally distributed data, Mann-Whitney U tests were employed. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test. A p-value of <0.05 was considered statistically significant.

Results

Patient demographics and clinical characteristics are summarized in Table I. During the 20-year study period (2002-2021), a total of 324 patients underwent surgery for ovarian pathologies at our institution. Of these, 237 patients were

Table I. Patient demographics and clinical characteristics (N=87).

Characteristic	Value
Age, years, median (Q1–Q3)	11.9 (9.2–15.1)
Presenting symptom, n (%)	
Abdominal pain	41 (47.1)
Abdominal distension	11 (12.6)
Menstrual irregularity	6 (6.9)
Precocious puberty	5 (5.7)
Incidental finding	5 (5.7)
Other	14 (16.1)
Tumor laterality, n (%)	
Right	46 (52.9)
Left	37 (42.5)
Bilateral	4 (4.6)
Tumor size, cm, median (Q1–Q3)	10.0 (6.0–15.0)
Ovarian torsion, n (%)	18 (20.7)
Mean follow-up, years (mean ± SD)	4.0 ± 3.6

excluded due to non-neoplastic conditions. The final analysis included 87 patients (26.9%) with histopathologically confirmed ovarian tumors. The median age at presentation was 11.9 years (Q1–Q3: 9.2–15.1 years). The most common presenting symptom was abdominal pain, occurring in 41 patients (47.1%), followed by abdominal distension (12.6%), menstrual irregularity (6.9%), and precocious puberty (5.7%). Five patients (5.7%) had incidentally discovered tumors. Eighteen patients (20.7%) presented with ovarian torsion and underwent emergency surgery at the time of admission, while the remaining 69 patients (79.3%) underwent elective surgery for ovarian masses.

Tumor laterality showed a right-sided predominance, with 46 tumors (52.9%) occurring on the right ovary, 37 (42.5%) on the left, and 4 patients (4.6%) presenting with synchronous bilateral involvement. The median tumor size at surgery was 10.0 cm (Q1–Q3: 6.0–15.0 cm).

The temporal evolution of surgical approaches is summarized in Table II. Overall, ovarian-sparing surgery (OSS) was performed in 41 patients (47.1%), while oophorectomy or salpingo-oophorectomy was performed in 46 patients (52.9%). The surgical approach was predominantly open surgery in 65 cases (74.7%), with laparoscopic surgery performed in 22 cases (25.3%). When analyzing temporal trends, a dramatic shift in surgical practice was observed. The rate of ovarian-sparing surgery increased significantly from 20% (6/30) in the first period to 61.4% (35/57) in the second period ($p<0.001$). Concurrently, the use of the laparoscopic approach increased from 6.7% to 35.1% between the two periods ($p=0.008$). Laparoscopy was used significantly more often in OSS than in oophorectomy (39.0% vs 13.0%, $p=0.011$). Patients in the more recent period were older (median age 12.8 vs 11.1 years, $p=0.025$), had smaller tumors (median size 8.0 cm vs 13.5 cm, $p<0.001$) and a lower rate of malignancy (14.0% vs 33.3%, $p=0.019$).

Table II. Evolution of surgical approaches by time period.

Variable	2002–2011 (n=30)	2012–2021 (n=57)	p-value
Surgery type, n (%)			<0.001
OSS	6 (20.0)	35 (61.4)	
Oophorectomy/S-O	24 (80.0)	22 (38.6)	
Surgical approach, n (%)			0.008
Open	28 (93.3)	37 (64.9)	
Laparoscopic	2 (6.7)	20 (35.1)	
Tumor size, cm, median (Q1–Q3)	13.5 (10.0–20.0)	8.0 (5.0–11.3)	<0.001
Malignancy, n (%)	10 (33.3)	8 (14.0)	0.019
Age, years, median (Q1–Q3)	11.1 (7.8–13.9)	12.8 (10.3–16.0)	0.025

OSS = ovarian-sparing surgery; S-O = salpingo-oophorectomy.

Table III. Comparison between ovarian-sparing surgery and oophorectomy.

Variable	OSS (n=41)	O/SO (n=46)	p-value
Age, years (mean ± SD)	11.9 ± 3.8	11.7 ± 3.9	0.79
Tumor size, cm, median (Q1–Q3)	7.0 (5.0–10.0)	12.0 (9.0–20.0)	<0.001
Malignancy, n (%)	1 (2.4)	17 (37.0)	<0.001
Torsion, n (%)	6 (14.6)	12 (26.1)	0.188
Histological type, n (%)			<0.001
Germ cell tumors	21 (51.2)	41 (89.1)	
Epithelial tumors	16 (39.0)	1 (2.2)	
Sex cord-stromal	4 (9.8)	1 (2.2)	
Other	0 (0)	3 (6.5)	
Recurrence, n (%)	2 (4.9)	1 (2.2)	0.90

OSS = ovarian-sparing surgery; O/SO = oophorectomy/salpingo-oophorectomy.

Comparison of surgical groups is presented in Table III. Patients who underwent ovarian-sparing surgery had significantly smaller tumors compared to those who underwent oophorectomy (median size 7.0 cm, Q1–Q3: 5.0–10.0 vs median 12.0 cm, Q1–Q3: 9.0–20.0, p<0.001; mean size 8.1 ± 5.0 cm vs 14.5 ± 7.7 cm). Only 1 of 41 patients (2.4%) who underwent OSS had a malignant tumor, compared to 17 of 46 patients (37.0%) in the oophorectomy group (p<0.001).

Torsion was present in 18 of 87 patients (20.7%). Among torsion cases, the malignancy rate was notably low at 5.6% (1/18), compared to 24.6% (17/69) in patients without torsion (p=0.075) (Table III). There was no significant difference in tumor size between patients with and without torsion (median 10.0 cm vs 9.5 cm, p=0.773). Among those with torsion, 6 of 18 (33.3%) underwent ovarian-sparing surgery, compared with 35 of 69 (50.7%) in patients without torsion (p=0.188).

Histopathological findings are detailed in Table IV. Histopathological examination revealed that 69 tumors (79.3%) were benign and 18 tumors (20.7%) were malignant. Germ cell tumors comprised the majority of cases (62 tumors, 71.3%), followed by epithelial tumors (17 tumors, 19.5%), sex cord-stromal tumors (5 tumors, 5.7%), lymphoma (2 cases, 2.3%), and metastatic rhabdomyosarcoma (1 case, 1.2%).

Table IV. Histopathological distribution of ovarian tumors (N=87).

Histological Type	n (%)
Benign tumors	69 (79.3)
Malignant tumors	18 (20.7)
Germ cell tumors	62 (71.3)
Mature cystic teratoma	47 (54.0)
Immature teratoma	5 (5.7)
Dysgerminoma/gonadoblastoma	6 (6.9)
Yolk sac tumor	3 (3.4)
Mixed germ cell tumor	1 (1.1)
Epithelial tumors	17 (19.5)
Serous cystadenoma/cystadenofibroma	12 (13.8)
Mucinous cystadenoma	5 (5.7)
Sex cord-stromal tumors	5 (5.7)
Lymphoma	2 (2.3)
Rhabdomyosarcoma (metastatic)	1 (1.2)

Mature cystic teratoma was the most common diagnosis, accounting for 47 cases (54.0%). All epithelial tumors were benign, consisting of serous cystadenoma or cystadenofibroma (12 cases, 13.8%) and mucinous cystadenoma (5 cases, 5.7%). The sex cord-stromal tumors included sclerosing stromal tumor (4 cases) and one unspecified sex cord-stromal tumor.

The 18 malignant tumors consisted of 15 malignant germ cell tumors (83.3% of malignant cases), 2 lymphomas (11.1%), and 1 rhabdomyosarcoma (5.6%). No malignant

epithelial or sex cord-stromal tumors were identified. Among the 15 malignant germ cell tumors, staging according to COG criteria revealed 8 (53.3%) Stage I, 6 (40.0%) Stage III with malignant cytology or peritoneal/omental implants, and 1 (6.7%) Stage IV with liver and diaphragmatic metastasis (Table IV). Patients with malignant tumors had significantly larger masses compared to those with benign tumors (median size 17.5 cm vs 8.5 cm, p=0.005).

The distribution of tumor histology differed significantly between surgical groups (p<0.001). In the ovarian-sparing surgery group, germ cell tumors (21 cases, 51.2%) predominated, followed by epithelial tumors (16 cases, 39.0%) and sex cord-stromal tumors (4 cases, 9.8%). The oophorectomy/salpingo-oophorectomy group also consisted primarily of germ cell tumors (41 cases, 89.1%), with only 1 epithelial tumor (2.2%), 1 sex cord-stromal tumor (2.2%), and 3 cases of lymphoma or rhabdomyosarcoma (6.5%).

Age-based subgroup comparisons are presented in Table V. Age-based subgroup analysis revealed significant differences between prepubertal (≤12 years, n=44) and pubertal (>12 years, n=43) patients. Prepubertal patients had a significantly higher malignancy rate (29.5% vs 11.6%, p=0.039). The distribution of tumor types differed between groups: germ cell tumors predominated in prepubertal patients (84.1%) while epithelial tumors were more common in pubertal patients (30.2% vs 9.1%). Notably, all sex cord-stromal tumors (n=5) occurred in pubertal patients. Tumor size did not differ significantly between age groups (p=0.495). The rate of ovarian-sparing surgery was higher in pubertal patients, though not statistically significant (55.8% vs 38.6%, p=0.109). Torsion was more common in prepubertal patients (27.3% vs 14.0%), but this difference was not statistically significant (p=0.125).

Frozen section examination was documented in 9 cases (10.3%). Additional staging procedures were performed in cases of confirmed or suspected malignancy, including omentectomy, peritoneal biopsies, and contralateral ovarian biopsies when clinically indicated.

The mean hospital stay was 4.4 ± 3.8 days. Postoperative complications were documented in 6 patients and included wound infections, prolonged ileus, and other minor complications, all of which resolved with conservative management. No major surgical complications or perioperative mortality occurred in this series.

The mean follow-up duration was 4.0 ± 3.6 years. During the follow-up period, 3 patients (3.4%) developed local recurrence: one serous cystadenoma and one mucinous cystadenoma, both following ovarian-sparing surgery, and one yolk sac tumor following salpingo-oophorectomy. Both benign recurrences were

Table V. Comparison between prepubertal and pubertal patients.

Variable	Prepubertal ≤12 y (n=44)	Pubertal >12 y (n=43)	p-value
Malignancy, n (%)	13 (29.5)	5 (11.6)	0.039
OSS, n (%)	17 (38.6)	24 (55.8)	0.109
Torsion, n (%)	12 (27.3)	6 (14.0)	0.125
Tumor size, cm, median (Q1–Q3)	8.0 (5.8–15.0)	10.0 (7.0–17.3)	0.495
Tumor type, n (%)			
Germ cell	37 (84.1)	25 (58.1)	
Epithelial	4 (9.1)	13 (30.2)	
Sex cord-stromal	0 (0)	5 (11.6)	
Other	3 (6.8)	0 (0)	

OSS = ovarian-sparing surgery.

successfully managed with repeat ovarian-sparing surgery. The patient with recurrent yolk sac tumor underwent re-resection and chemotherapy. One additional patient (1.2%) with an immature teratoma developed metastatic disease following salpingo-oophorectomy. All four patients with recurrence or metastasis had tumor rupture during the initial surgery ($p<0.001$). The overall recurrence rate was similar between the ovarian-sparing surgery group (2 of 41, 4.9%) and the oophorectomy group (1 of 46, 2.2%) ($p=0.90$).

One patient died during the follow-up period due to progressive lymphoma. No patient developed contralateral ovarian tumors requiring surgical intervention during the follow-up period, although 2 patients had metachronous bilateral disease at initial presentation.

Discussion

From a comprehensive review of 324 patients who underwent surgery for ovarian pathologies over the 20-year period, this study focused on the 87 patients (26.9%) with histopathologically confirmed ovarian tumors. This proportion is consistent with reported rates in the literature, where true neoplasms account for 20-30% of pediatric ovarian masses requiring surgical intervention.[1-3]

The demographic and clinical characteristics of our cohort align with previously published pediatric series.[1-8,12,13,17,18] The median age of 11.9 years is consistent with the peak incidence of ovarian tumors in late childhood and adolescence. The predominance of abdominal pain as the presenting symptom reflects the high frequency of complications such as torsion, rupture, or rapid tumor growth in this age group.[1,4,5]

Our age-based subgroup analysis revealed important differences between prepubertal and pubertal patients. The significantly higher malignancy rate in prepubertal patients (29.5% vs 11.6%, $p=0.039$) is consistent with the literature suggesting that malignant germ cell tumors are more common in younger children.[7,8] This finding has important implications for surgical planning, as prepubertal patients may warrant more thorough preoperative evaluation for malignancy. The predominance of germ cell tumors in prepubertal patients (84.1%) versus the higher proportion of epithelial tumors in pubertal patients (30.2%) reflects the different tumor biology across age groups. Notably, all sex cord-stromal tumors occurred in pubertal patients, which may be related to hormonal influences on these tumor types. These age-related differences support the recommendation for age-specific risk assessment algorithms in pediatric ovarian tumors.

The presence of ovarian torsion in 20.7% of cases deserves special mention, as torsion is one of the most common complications of pediatric ovarian masses and often necessitates emergency surgery.[9,15] The American Pediatric Surgical Association systematic review of 96 studies found overwhelming evidence supporting ovarian detorsion rather than oophorectomy, with no reported thromboembolic events after detorsion and minimal risk of occult malignancy.[26] Our analysis revealed that torsion was associated with a remarkably low malignancy rate of only 5.6%, consistent with the 0.4–5% malignancy rate reported in torsed ovaries.[26] However, despite this low malignancy rate, ovarian-sparing surgery was performed in only 33.3% of torsion cases compared to 50.7% in non-torsion cases, reflecting earlier institutional practice where surgical decision-making was primarily driven by ovarian viability and circulation status after detorsion. Current evidence demonstrates that gross ovarian appearance does not correlate with long-term viability, as follicular development has been documented even in necrotic-appearing ovaries.[9,15,26] Accordingly, our protocol has evolved: ovarian-sparing surgery is now performed in all torsion cases regardless of circulation status, unless the ovary is frankly necrotic or malignancy is confirmed or suspected.

Consistent with pediatric tumor patterns, over half of our cases were mature teratomas, whereas epithelial tumors predominate in adults.[3,7] Our overall malignancy rate (~20%) lies within the expected 10-20% range for pediatric ovarian tumors.[1,7,8] The decrease in malignancy rate from 33.3% in the earlier decade to 14.0% in the later decade likely reflects enhanced preoperative diagnostics, including better imaging and malignancy risk algorithms, which allow identification and removal of benign tumors earlier before they become so large that they appear malignant.[10,14] We observed significantly smaller tumors in the later period (median 8.0 cm vs 13.5 cm, $p<0.001$), consistent with earlier detection through improved imaging.

The most notable finding in our study is the dramatic three-fold increase in ovarian-sparing surgery over time, from 20.0% in the first decade to 61.4% in the second decade. This evolution parallels global trends reported in the literature.[16-24] Abbas et al. and Oue et al. found that OSS can be performed safely not only for benign tumors but even for select borderline or low-grade malignant cases, without compromising outcomes.[12,13] In Poland, Szymon et al. observed OSS usage climb from 31% to 75% over 20 years, reflecting a similar change in practice.[21] A recent systematic review and meta-analysis by Pio et al., encompassing 1,734 cases, demonstrated that ovarian-sparing surgery achieves excellent oncologic outcomes with no recurrence disadvantage compared to oophorectomy.[18] Similarly, Łuczak et al. reported over two decades of success with ovarian preservation, emphasizing the importance of thorough preoperative evaluation.[23,24]

Importantly, the favorable outcomes observed in our OSS group must be interpreted in the context of careful patient selection. Patients selected for ovarian-sparing surgery had significantly smaller tumors (median 7 cm vs 12 cm) and markedly lower malignancy rates (2.4% vs 37.0%) compared to those undergoing oophorectomy. This selection bias is inherent to the surgical decision-making process: surgeons appropriately reserve OSS for tumors that appear benign based on preoperative and intraoperative assessment. Therefore, while our data confirm that OSS is safe in appropriately selected patients, they cannot demonstrate equivalence between OSS and oophorectomy for all tumor types. The excellent outcomes in the OSS group reflect successful identification of suitable candidates rather than proof that OSS would be equally safe for tumors currently treated with oophorectomy.

Tumor size emerged as an important discriminator between the OSS and oophorectomy groups (median 7 cm vs 12 cm, $p<0.001$). In general, larger tumors are more often malignant and can completely obliterate the normal ovary, making preservation unfeasible.[8,12,14,23] However, size alone is not an automatic contraindication for OSS; we successfully performed OSS on some very large masses (up to 25 cm) when other factors indicated benign disease. This experience, similar to Łuczak et al.'s report, underscores that the surgeon's intraoperative evaluation of tumor characteristics is more important than any strict size cutoff for deciding on ovarian preservation.[23] This approach is also supported by McCauley et al., who demonstrated that OSS is feasible even for giant cystic masses ≥15 cm, with 62.5% of preoperative candidates successfully undergoing ovarian preservation and 100% showing morphologically normal ovarian tissue on postoperative imaging.[27] Each case should be assessed individually, integrating imaging, tumor marker results, intraoperative findings, and frozen section pathology when available.[16,18,21,23]

Frozen section analysis has limited utility in pediatric ovarian tumors, largely because most are germ cell in origin and exhibit marked histologic diversity.[25] In our study, frozen section was used in only 9 patients (10.3%). A recent Children's Oncology Group study demonstrated only 61.7% diagnostic accuracy in pediatric germ cell tumors.[25] The poor performance reflects the heterogeneous and

often mixed composition of these tumors, predisposing them to sampling error.

Our outcomes affirm that OSS did not increase recurrence risk. Recurrence occurred in 4.9% of OSS patients versus 2.2% of those who had an oophorectomy, a non-significant difference (p=0.90). This aligns with published recurrence rates of 2-5% after fertility-sparing ovarian surgery.[18,20,21,23] The two benign recurrences in the OSS group (serous cystadenoma and mucinous cystadenoma) were effectively treated with repeat conservative surgery, preserving ovarian function. The single malignant recurrence (yolk sac tumor) occurred in a patient who had undergone salpingo-oophorectomy, demonstrating that recurrence risk is not unique to OSS. Notably, all patients with recurrence or metastasis had experienced intraoperative tumor rupture during initial surgery, highlighting tumor rupture as a critical modifiable risk factor.[8,23,24] McCauley et al. further confirmed the safety of OSS, reporting that all patients who underwent ovarian-sparing surgery for giant masses showed morphologically normal ovarian tissue on postoperative imaging with only one recurrence.[27]

The use of laparoscopy increased markedly in our cohort, rising from 6.7% to 35.1% (p=0.008), paralleling the global shift toward minimally invasive surgery in pediatric practice. Piotrowska-Gall et al. and Guillén et al. have demonstrated that laparoscopic ovarian-sparing surgery is both safe and feasible.[19,20] In our series, laparoscopy was used significantly more often in ovarian-sparing operations than in oophorectomy (39.0% vs 13.0%, p=0.011), likely reflecting its suitability for smaller, benign-appearing tumors.

The importance of fertility preservation cannot be overstated in this young population. Even the loss of one ovary can potentially diminish future ovarian reserve and hormonal function, a concern that becomes critical if a problem later arises in the remaining ovary.[11,13,21] The sharp rise in our use of OSS reflects growing awareness of these fertility issues among both surgeons and families. However, fertility preservation should never compromise oncologic safety, and our data demonstrate that these goals are compatible when patients are carefully selected. Zhao et al. recently demonstrated excellent fertility-sparing outcomes even in borderline ovarian tumors in children and adolescents, further supporting the safety of this approach.[22]

Several limitations of our study merit consideration. The retrospective design carries inherent limitations, including potential selection bias. As a single-center study, our findings may not be fully generalizable. The mean follow-up of 4 years may be insufficient to capture late complications or assess long-term fertility outcomes. Importantly, we did not systematically assess long-term ovarian function; anti-Müllerian hormone levels and pubertal hormone profiles were not routinely measured during follow-up, precluding direct evaluation of fertility preservation outcomes. Our sample size, particularly for malignant tumors, limits the power to detect differences in rare outcomes. Despite these limitations, our data provide valuable epidemiological information on pediatric ovarian tumor distribution, and the 20-year timeframe documents a significant paradigm shift toward fertility preservation.

In conclusion, our 20-year experience demonstrates a significant evolution in the surgical management of pediatric ovarian tumors, with ovarian-sparing surgery rates increasing from 20% to 61.4%. This shift toward fertility preservation has been achieved without compromising oncologic safety as evidenced by comparable recurrence rates between surgical approaches. The higher malignancy rate in prepubertal patients highlights the importance of age-specific evaluation. Torsion was associated with low malignancy risk, supporting a conservative approach. Our findings support individualized surgical decision-making that prioritizes fertility preservation in appropriately selected patients based on careful preoperative evaluation and intraoperative

assessment, while acknowledging that the favorable outcomes in OSS reflect careful patient selection. Future research should focus on developing validated risk stratification tools, standardized management protocols for torsion cases, and prospective assessment of long-term fertility outcomes.

Ethical approval

The study was approved by Dr Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital Ethics Committee (date: September 22, 2020, number: 2020-KAEK-141/432-E-22/09-427). Due to the retrospective nature of this study and the use of anonymized data from medical records, the requirement for informed consent was waived by the ethics committee.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: ÖB, AK; data collection: ÖB, ÖBo; analysis and interpretation of results: ÖB, BY; draft manuscript preparation: ÖB; critical revision: İK, BY, GŞ, AK. All authors reviewed the results and approved the final version of the manuscript.

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Case Report

Should we prioritize proton beam therapy before making a decision on orthotopic liver transplantation for unresectable hepatoblastoma?

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ABSTRACT

Background. In unresectable hepatoblastoma (HB), particularly "pre-treatment extent of tumor" (PRETEXT) IV tumors or those with positive annotation factors, standard management consists of intensive chemotherapy followed by surgical resection or orthotopic liver transplantation (OLT). Radiotherapy has traditionally been avoided because of the liver's radiosensitivity and the risk of radiation-induced liver disease. Proton beam therapy (PBT), owing to its dosimetric advantage and ability to spare uninvolved liver parenchyma, may represent a potential local control strategy in selected pediatric patients for whom curative surgery or OLT is not feasible.

Case Presentation. We describe five pediatric patients with advanced hepatoblastoma treated with proton beam therapy at our institution between February 2022 and January 2024. The cohort included three girls and two boys, with a median age of 3.0 years (interquartile range [IQR], 1.6–4.0) and a median alpha-fetoprotein level of 435,453 ng/mL (IQR: 7,668–1,276,681) at diagnosis. All patients were initially considered inoperable because of extensive hepatic involvement, inadequate future liver remnant, or multifocal disease, and OLT was not feasible owing to donor limitations or medical comorbidities. All received neoadjuvant chemotherapy using SIOPEL-based regimens, achieving partial tumor response. Tumors ranged from 5 to 12 cm and involved central hepatic segments, the portal region, or both lobes. PBT was delivered at a total dose of 50 GyE in 10–25 fractions as definitive or consolidative therapy, followed by surgical resection in three patients. Two patients additionally received targeted therapy and immunotherapy. At last follow-up, four patients were alive with no evidence of disease, while one patient died from tumor progression.

Conclusions. These cases suggest that proton beam therapy may serve as a feasible liver-sparing local treatment option for selected pediatric patients with unresectable or residual hepatoblastoma when surgery or OLT is not possible. While limited by availability and cost, PBT may facilitate multimodal therapy and preserve future treatment options.

Key words: hepatoblastoma, proton beam therapy, pediatric liver tumor, unresectable cancer, radiotherapy, PRETEXT.

Hepatoblastoma (HB) is the most common pediatric liver malignancy, with surgery and chemotherapy as the main treatment pillars. Complete resection, via partial hepatectomy or orthotopic liver transplantation (OLT), remains the only curative approach. Tumors are

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considered unresectable when there is extensive vascular involvement, multifocal bilobar disease, or an inadequate residual liver volume post-resection. OLT is indicated for unresectable disease without extrahepatic spread.

Radiotherapy has traditionally been avoided in HB due to liver radiosensitivity, but modern techniques, particularly proton beam therapy (PBT), allow for conformal dose delivery with reduced low-dose exposure to the normal liver, lungs, heart, and kidneys. This makes PBT attractive for selected pediatric liver tumors. In adults, PBT has shown encouraging results in hepatocellular carcinoma,[1,2] supporting its potential pediatric application. Selection criteria for pediatric PBT may include a tumor size < 12 cm, location near critical structures, the absence of widespread metastases, and preserved liver function.[3]

Case Presentations

Ethical approval

This study was reviewed and approved by the Institutional Review Board of Chang Gung Medical Foundation (IRB No. 202500060B0, date September 1, 2025). The requirement for informed consent was waived by the IRB due to the retrospective nature of the study and the use of anonymized clinical data. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

Patient-1

A 6-year-old girl with recurrent HB involving segments 7 and 8 and an associated portal vein thrombus was deemed inoperable due to an inadequate future liver remnant. She received four cycles of salvage chemotherapy with carboplatin plus etoposide, followed by PBT (50 GyE in 10 fractions), which resulted in significant tumor shrinkage. She has remained with no evidence of disease (NED) at 55 months of follow-up.

Patient-2

A 3-year-old girl with pre-treatment extent of tumor (PRETEXT) IV HB, complicated by lung metastases and celiac lymph node involvement, achieved a partial response following neoadjuvant chemotherapy. She subsequently underwent hepatectomy and pulmonary metastasectomy, followed by PBT to the residual hepatic lesion (50 GyE in 25 fractions). She has remained with NED at 108 months of follow-up.

Patient-3

A 6-month-old boy presented with a centrally located PRETEXT IV HB. He underwent eight cycles of neoadjuvant chemotherapy, followed by right hepatectomy and adjuvant chemotherapy. PBT was subsequently administered for a residual lesion. The patient has remained with NED at 55 months of follow-up.

Patient-4

An 18-month-old boy with PRETEXT IV HB and pulmonary metastases, with a history of extremely low birth weight, underwent a multi-step hepatectomy and pulmonary metastasectomy. Salvage targeted therapy with bevacizumab and sorafenib, followed by PBT and nivolumab, was administered. The patient died of disease at 28 months of age.

Patient-5

A 4-year-old girl with PRETEXT III HB involving the portal region received six cycles of neoadjuvant chemotherapy, followed by targeted therapy with bevacizumab and sorafenib, PBT, and nivolumab immunotherapy. Tumor resection was performed 16 months after diagnosis. She has remained with NED at 21 months of follow-up.

Table I outlines the PRETEXT stage, chemotherapy regimen, tumor location, surgical details, and PBT indication for these five patients. Fig. 1. presents a treatment algorithm

Table I. Patient characteristics and treatment outcomes.

Case	Age / Sex	PRETEXT stage	Tumor location	Metastasis / Other involvement	Chemotherapy regimen	Surgical details	PBT indication	PBT dose / Fractions	Outcome / Follow-up
1	6 y / F	Recurrent HB	Segments 7–8	Portal vein thrombus	4 cycles carboplatin + etoposide (salvage)	None (inoperable)	Primary inoperable tumor with vascular involvement	60 GyE / 10 Fr	NED at 55 mo
2	3 y / F	IV	Right lobe	Lung metastases, celiac LN involvement	Neoadjuvant chemotherapy	Hepatectomy + pulmonary metastasectomy	Residual hepatic lesion post-surgery	50 GyE / 25 Fr	NED at 108 mo
3	6 mo / M	IV	Central	None	8 cycles neoadjuvant (cisplatin-based) + adjuvant chemotherapy	Right hepatectomy	Residual hepatic lesion post-hepatectomy	50 GyE / 10 Fr	NED at 55 mo
4	18 mo / M	IV	Multifocal	Pulmonary metastases; history of extremely low birth weight	Multi-step surgery + salvage targeted therapy (bevacizumab, sorafenib)	Multi-step hepatectomy + pulmonary metastasectomy	Residual/refractory disease	50 GyE / 10 Fr	DOD at 28 mo
5	4 y / F	III	Portal region	None	6 cycles neoadjuvant chemotherapy + targeted therapy (bevacizumab, sorafenib)	Tumor resection (16 mo post-diagnosis)	Preoperative downstaging	50 GyE / 10 Fr	NED at 21 mo

DOD, died of disease; Fr, fractions; HB, hepatoblastoma; NED, no evidence of disease; PRETEXT, pre-treatment extent of tumor.

for HB that is based on PRETEXT staging. It illustrates the pathways from initial diagnosis through surgical resection, chemotherapy, targeted therapy and immunotherapy, PBT, and OLT.

Discussion

Surgery remains the definitive therapy for HB, with OLT as the standard for unresectable disease without extrahepatic spread.[4] However, in cases where OLT is not feasible, PBT can provide local control with reduced normal tissue toxicity.[5] In our series, PBT was delivered with curative or consolidative intent, enabling surgical resection in some patients and durable disease control in others.

PBT advantages include dosimetric precision, a reduction in high-grade toxicities, and preservation of liver function, which is critical for pediatric patients with high long-term survival expectations.[6-9] Drawbacks include the high cost, limited global availability, and the logistical complexity of daily anesthesia.[10]

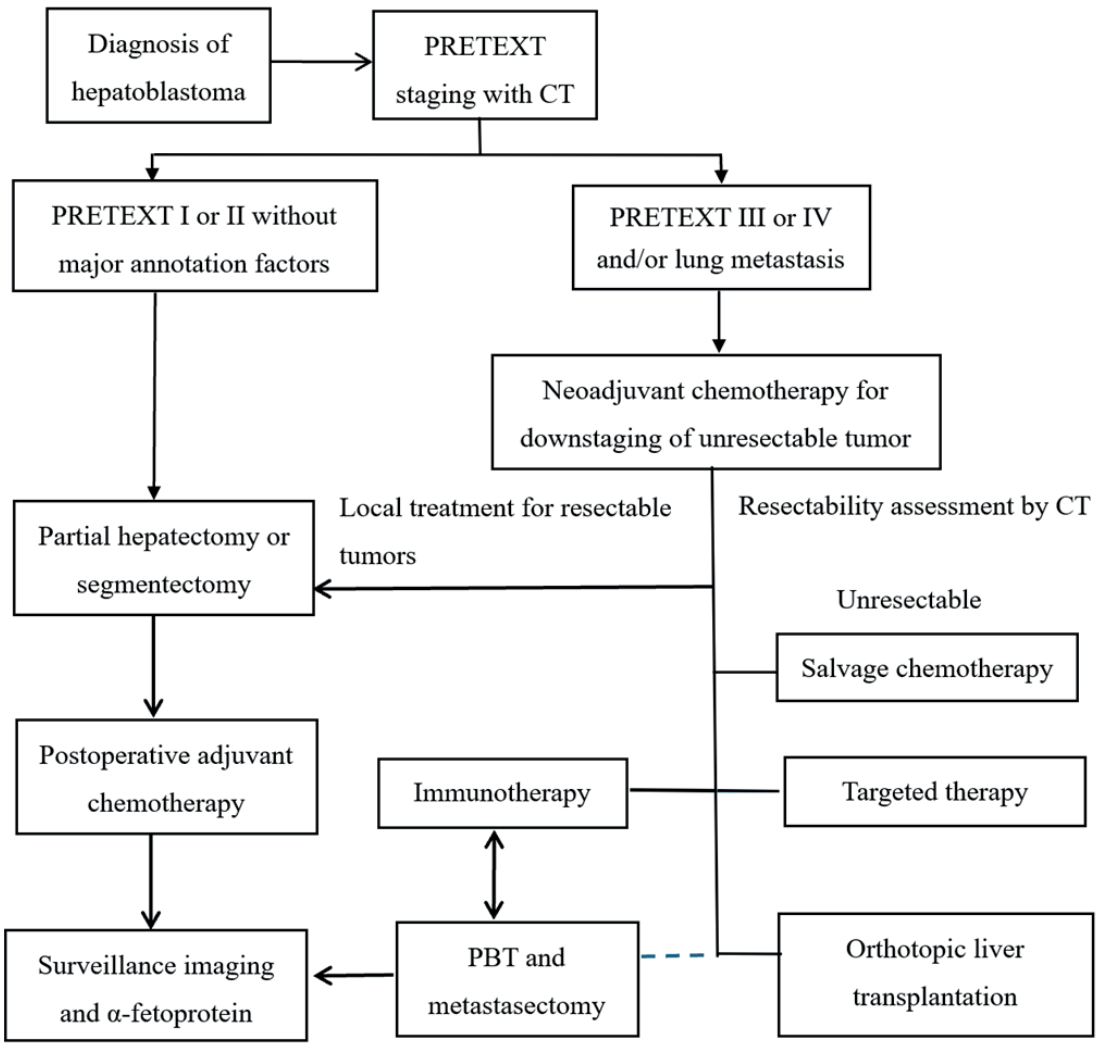

Fig. 1. The authors propose a treatment algorithm for hepatoblastoma cases, tailored to the clinical scenario and treatment response, considering primary liver involvement and lung metastases. In this context, local treatment refers to either hepatectomy or lung radiotherapy combined with pulmonary metastasectomy.

CT, chemotherapy; PBT, proton beam therapy; PRETEXT, PRE-Treatment Extent of tumor.

Our findings, supported by existing literature, indicate that PBT is best suited for patients with localized unresectable tumors (such as central or hilar lesions with an inadequate future liver remnant), those who have failed or are unsuitable for orthotopic liver transplantation, candidates for potential resection following downstaging, or individuals requiring re-irradiation or salvage therapy.[11]

Future studies should prioritize multicenter registries and prospective trials to evaluate the role of PBT in HB,[12] its integration with systemic and immunotherapies, and long-term outcomes including growth, development, and the risk of secondary malignancies.

Conclusion

PBT offers a safe, precise, and potentially effective local treatment option for selected pediatric HB cases in which surgical resection or OLT is not feasible. Optimal utilization requires multidisciplinary patient selection, careful integration with systemic therapies, and consideration of resource availability. Further prospective research is warranted to clarify its long-term efficacy and outcomes.

Ethical approval

The study was approved by Institutional Review Board of Chang Gung Medical Foundation (date: September 1, 2025, number: 202500060B0).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: YWN, THJ; data collection: YWH, YLW; analysis and interpretation of results: CKT, TYC; draft manuscript preparation: SHC, THJ. All authors reviewed the results and approved the final version of the manuscript.

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The authors declare that there is no conflict of interest.

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Case Report

Leber hereditary optic neuropathy (LHON) in a 6-year-old boy with a transient spinal cord lesion

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ABSTRACT

Background. Leber hereditary optic neuropathy (LHON) is a maternally inherited mitochondrial disorder that predominantly manifests as bilateral, painless vision loss in young males. While traditionally associated with the optic nerves, a subset of patients exhibits additional neurological symptoms, referred to as LHON-plus syndrome. Involvement of the spinal cord is uncommon, particularly among the pediatric population, and may result in diagnostic challenges, potentially leading to confusion regarding acquired demyelinating diseases.

Case Presentation. We report a 6-year-old boy with near-complete vision loss in the right eye and blurred vision in the left eye. Demyelinating diseases were suspected in the case of acute bilateral optic neuropathy. Cranial and orbital magnetic resonance imaging (MRI) showed no demyelinating lesions, whereas spinal MRI revealed a T2-hyperintense lesion at the C3–C6 levels. Due to unresponsiveness to conventional treatment for demyelinating diseases, genetic testing confirmed the homoplasmic m.11778G>A variant in NADH dehydrogenase subunit 4 (*MT-ND4*), establishing an LHON diagnosis. Spinal cord involvement supported the LHON-plus syndrome classification. Idebenone therapy was initiated, and follow-up was scheduled. During the 1.5-year follow-up, right eye visual loss persisted, while the left eye showed gradual vision decline. A second spinal MRI performed at 6 months showed complete resolution of the previous lesion without new lesions.

Conclusion. Since optic neuropathy and spinal cord involvement typically indicate demyelinating diseases, these should be prioritized in initial evaluation due to their frequency and need for early immunomodulatory treatment. However, spinal cord involvement can occur in mitochondrial diseases, as demonstrated in this case. The presence of a transient and asymptomatic spinal cord lesion in this patient expands the recognized spectrum of central nervous system involvement in LHON. Therefore, LHON-plus syndrome should be considered when spinal cord involvement accompanies optic neuropathy after excluding other demyelinating diseases.

Key words: Leber hereditary optic neuropathy, LHON-plus syndrome, optic neuropathy, mitochondrial disease, *MT-ND4* m.11778G>A mutation.

Acute or subacute vision loss in children may result from various causes, including demyelinating optic neuritis, increased intracranial pressure, toxic or metabolic optic neuropathy, mitochondrial disorders and hereditary optic neuropathy. However, because children may have difficulty accurately describing visual symptoms, some cases that appear to present with acute vision loss may represent a slowly progressive or chronic decline in vision that has only recently become evident.[1]

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Leber hereditary optic neuropathy (LHON) is a genetic disorder that is transmitted through maternal inheritance. A mutation in the mitochondrial DNA (mtDNA) causes this disorder, leading to the degeneration of retinal ganglion cells and the subsequent optic nerve. LHON manifests as a gradual, painless loss of central vision in both eyes, primarily affecting young adult males.[2] Although LHON predominantly affects young males, homoplasmic males are at particularly high risk of developing visual loss, whereas disease penetrance is substantially lower in females, even among homoplasmic carriers.[2] While LHON is generally confined to the optic nerves, a subset of patients present with additional neurological and non-neurological manifestations, a condition known as the LHON-plus syndrome. Extraocular manifestations have been documented, including cardiac arrhythmias, skeletal changes, myopathy, dementia, movement disorders, peripheral neuropathy, brainstem and basal ganglia involvement and multiple sclerosis (MS)-like syndromes. Such extraocular manifestations complicate the clinical presentation and pose diagnostic challenges.[3,4]

Herein, we report the detection of spinal cord involvement in a 6-year-old boy who presented with optic neuropathy and was subsequently diagnosed with LHON following comprehensive investigations. We underscore that LHON should be considered as a differential diagnosis for optic neuropathy, even in the presence of spinal cord lesions.

Case Presentation

A 6-year-old boy presented with a one-week history of difficulty focusing on objects and a deviated gaze, as noted by his mother. She also reported that he had been watching television from a closer distance over the previous month, and recent photographs showed an inability to focus on the camera. Initial ophthalmological examination revealed a visual acuity of 0.1 in the right eye, consistent with severe visual impairment, and subjective blurred vision in the left eye, despite normal visual acuity. Bilateral papilledema was observed during fundoscopic examination. Based on these findings, the patient was referred to the pediatric neurology department for further evaluation.

On comprehensive ophthalmological examination, the right optic disc exhibited blurred margins, whereas the left optic disc showed swelling consistent with papilledema. The right eye demonstrated diminished light reflexes, and optical coherence tomography (OCT) revealed retinal nerve fiber layer (RNFL) thickening in the left eye and thinning in the right eye, reflecting different stages of optic neuropathy. Despite these ocular findings, the patient exhibited no additional neurological deficits on physical examination, and motor and sensory functions remained intact.

At initial presentation, there was no known family history of visual loss or hereditary optic neuropathy. The family history was specifically questioned and was unremarkable at that time. The patient was also evaluated early by an experienced neuro-ophthalmologist, who did not consider hereditary optic neuropathy as the primary diagnosis based on the clinical findings.

Given the severity of visual impairment and absence of other neurological signs, the patient underwent advanced imaging studies. Spinal and brain magnetic resonance imaging (MRI) was taken to differentiate demyelinating optic neuropathies (myelin oligodendrocyte glycoprotein antibody disease - MOGAD, neuromyelitis optica – NMO, and MS) in the differential diagnosis of optic neuropathy. Spinal MRI revealed diffuse intramedullary increased signal intensity in the cervical spinal cord at the C3–C6 levels on T2-weighted images; however, no associated cord edema was observed (Fig. 1). Furthermore, brain imaging demonstrated no evidence of demyelination in T2 and fluid-attenuated inversion recovery (FLAIR) sequences (Fig. 2).

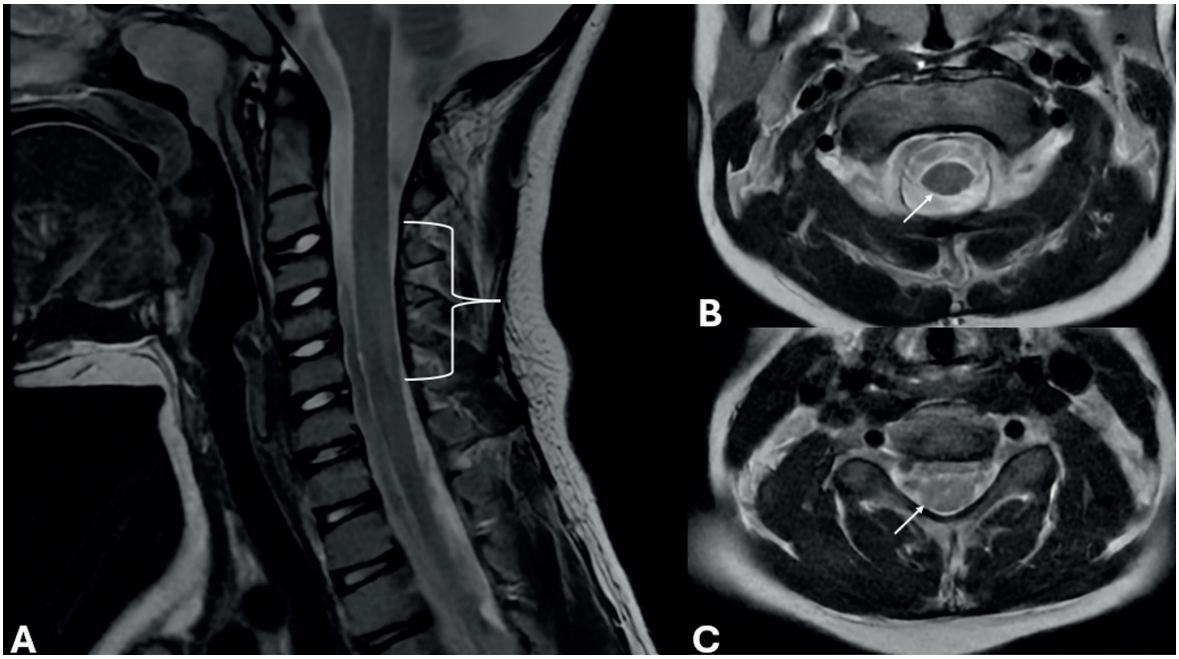

Fig. 1. (A) Sagittal T2-weighted cervical spinal magnetic resonance imaging demonstrates an increased intramedullary signal intensity extending from the C3 to C6 segments. The bracket indicates the longitudinal extent of the involved spinal cord segments. (B) Axial T2-weighted image obtained immediately above the affected segment shows normal spinal cord signal intensity (arrow). (C) Axial T2-weighted image obtained at the level of the involved segment demonstrates diffuse spinal cord involvement with intramedullary T2 hyperintensity (arrow).

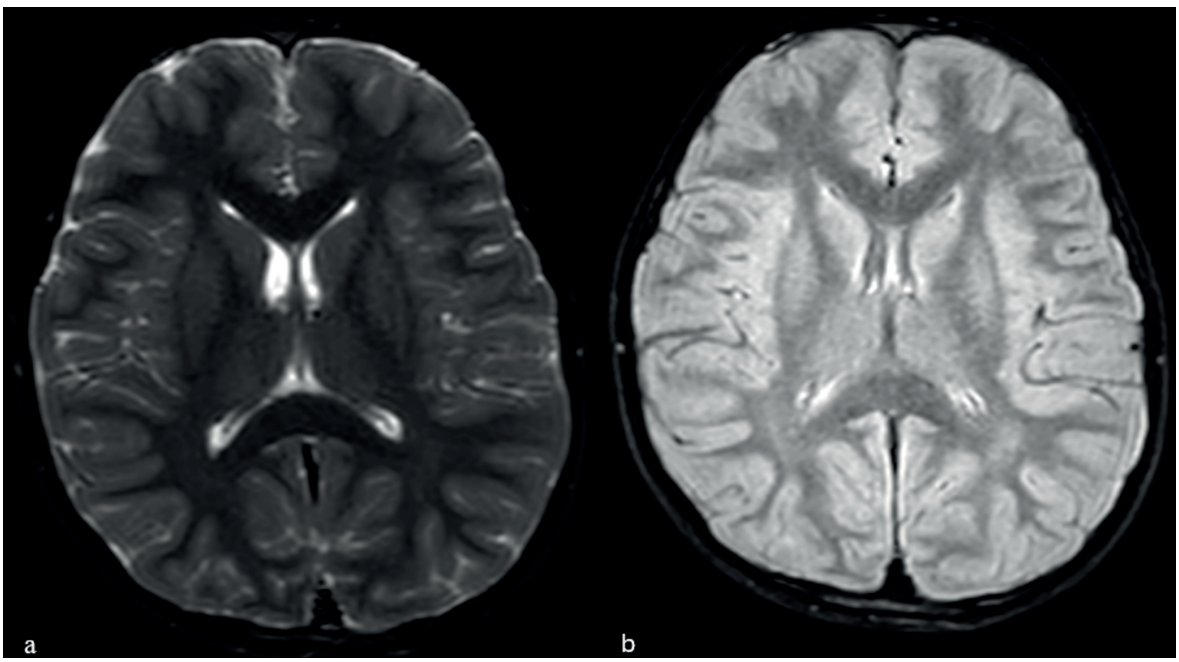

Fig. 2. Brain magnetic resonance imaging, showing no evidence of demyelinating disease. Axial T2-weighted image (a) and FLAIR image (b) demonstrate normal findings without demyelinating lesions.

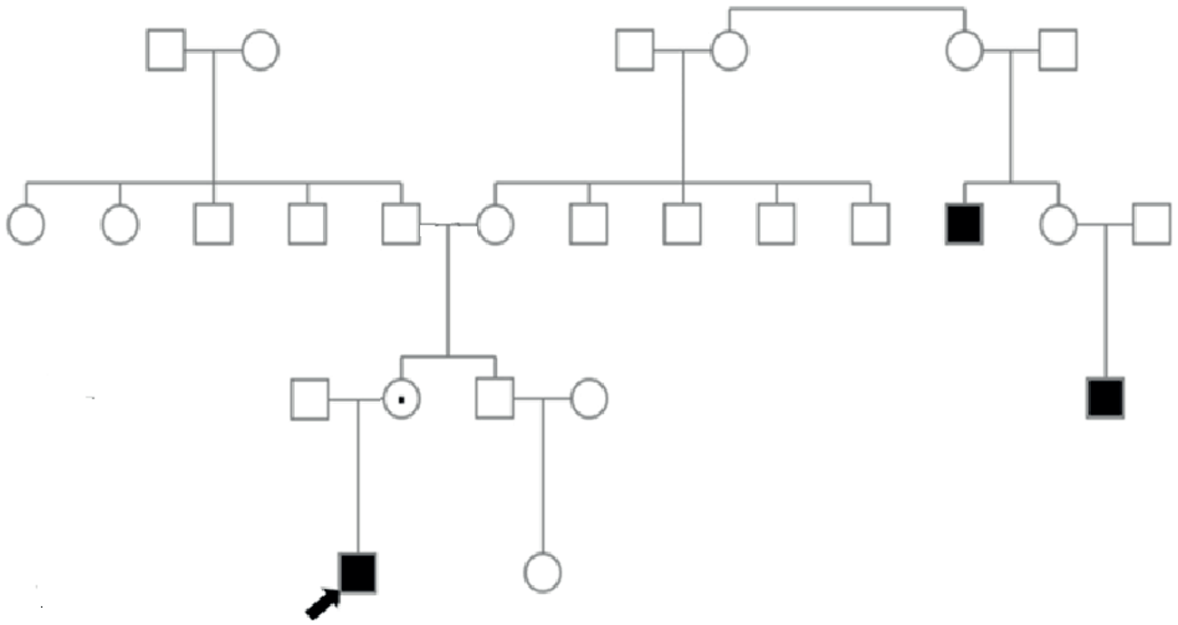

Fig. 3. Pedigree of the family. The index case is indicated by an arrow. Filled symbols represent individuals reported to carry the same mitochondrial DNA variant and to have visual impairment only, without known extraocular manifestations. The mother is shown as an asymptomatic carrier, indicated by a dot within the symbol. No consanguinity is present. Detailed clinical and genetic information was unavailable for several asymptomatic family members, as they declined further evaluation and genetic testing.

The MRI findings, combined with ophthalmologic examination, prompted further investigation into potential demyelinating optic neuropathies. These were ultimately ruled out through cerebrospinal fluid (CSF) analysis and antibody testing. Both serum myelin oligodendrocyte glycoprotein (MOG) and aquaporin-4 (AQP4) antibodies were negative and CSF oligoclonal bands were absent, and the IgG index was within the normal range.

Pending the availability of results, the patient was initiated on therapy for autoimmune and demyelinating diseases and the therapeutic response was subsequently monitored. Initial management consisted of high-dose intravenous methylprednisolone administration at 30 mg/kg/day for five days. Due to the lack of clinical improvement, the steroid course was extended to a total of seven days; however, no significant response was observed. Consequently, the patient underwent seven courses of daily plasma exchange therapy, again without substantial clinical improvement.

During the prolonged hospital stay, increased intra-family communication led distant relatives to become aware of the patient's condition. As a result, a family member with a known diagnosis of LHON directly contacted the patient's family. This information emerged after spinal cord involvement had been identified and plasma exchange therapy had already been initiated. The newly obtained family history subsequently prompted reconsideration of the diagnosis and targeted genetic evaluation.

Given the family history of a distant maternal relative who was previously diagnosed with LHON, genetic testing was conducted to confirm the diagnosis. Genetic analysis revealed the same homoplasmic m.11778G>A variant in the NADH dehydrogenase subunit 4 (*MT-ND4*) gene, which is strongly associated with LHON. Genetic analysis of the patient's mother revealed the same homoplasmic variant. Mitochondrial DNA testing was conducted on peripheral blood samples collected from the patient and his mother. The mother, who

was asymptomatic, was closely monitored as an asymptomatic carrier. Fig. 3 illustrates the pedigree. Detailed genetic counseling regarding LHON was provided to the mother and other family members at risk.

The diagnosis of LHON was genetically confirmed, and spinal involvement was classified as LHON-plus syndrome. Idebenone therapy was initiated at a daily dose of 900 mg, and the patient was followed up for changes in visual acuity and overall clinical course.

During follow-up, no improvement was observed in the right eye, whereas the left eye showed a gradual decline in visual acuity over time. However, due to the variable visual performance across different visual field regions, the ophthalmologist did not report a single consistent visual acuity value for the left eye. A follow-up spinal MRI performed six months later demonstrated complete resolution of the previous lesion.

Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images.

Discussion

Acute optic neuropathy in children represents a diagnostic challenge due to its broad etiological spectrum of causes. A thorough history, ophthalmological examination, and neuroimaging are essential for narrowing the differential diagnosis. In the initial evaluation, it is important for clinicians, especially pediatricians, to first consider demyelinating disorders, given their higher prevalence and the critical importance of early immunomodulatory therapy. MRI of the brain and orbits is typically indicated within the first few days of presentation to identify demyelinating or compressive causes of the symptoms. Spinal MRI is usually not a routine part of the initial evaluation in children without signs of spinal cord dysfunction; however, it may be warranted when optic neuropathy is accompanied by atypical imaging findings or when demyelinating diseases are considered. Lumbar puncture and CSF analysis are valuable for excluding inflammatory or infectious etiologies and may reveal demyelinating markers.

Although LHON most commonly manifests in young adulthood, pediatric-onset cases are rare; therefore, the onset of symptoms at 6 years of age represents an unusual and noteworthy aspect of this case.

LHON is traditionally characterized as an isolated optic neuropathy. However, a subset of patients exhibit additional neurological and non-neurological features collectively referred to as "LHON-plus".[5] The documented neurological manifestations of LHON-plus include movement disorders, peripheral neuropathy, dysfunction of the brainstem or basal ganglia, and demyelinating syndromes that resemble MS.[6] In a case series involving patients with LHON (n = 46), 59% (n = 27) demonstrated neurological or extraocular symptoms.[2] To our knowledge, spinal cord involvement in children with LHON has only been reported in isolated cases. For instance, Bursle et al.[5] described an 8-year-old boy with dual mitochondrial DNA mutations at positions 14484 (*MT-ND6*) and 4160 (*MT-ND1*) who developed longitudinally extensive transverse myelitis (LETM). Another recent report described a 2-year-old girl who was initially diagnosed with antibody-negative NMO spectrum disorder (NMOSD) before genetic testing revealed a LHON mutation (m.14484T>C), subsequently diagnosed as LHON-plus.[6] This LHON-plus case was initially treated as a demyelinating disease for two years until the mitochondrial mutation was identified. In our patient, early genetic diagnosis helped avoid prolonged immunosuppression and allowed appropriate management (initiation of idebenone) and genetic counseling for the family. Despite the rarity of both LHON and NMO, there have been documented instances of individuals possessing both the pathogenic mtDNA sequence variants associated with LHON and anti-AQP4 seropositive NMOSD.[7-9] McClelland et al.[10] described a 65-year-old woman with LHON who had

been masquerading as NMOSD, and they emphasized that LHON should be considered in any case of bilateral or atypical optic neuritis, even in presumed seronegative NMO.

Mitochondrial disorders are increasingly being recognized as multisystem diseases that can affect the spinal cord, resulting in a diverse range of neurological manifestations. The identification of spinal cord involvement is essential for appropriate management.[11] In a 2021 study by Alves et al.[12], spinal MRI scans of 33 children with genetically confirmed primary mitochondrial disorders were retrospectively analyzed. Notably, 19 (58 %) patients had spinal cord lesions. These lesions were classified into two radiological patterns: Group A (n=12) displayed white ± gray matter involvement, resembling acquired demyelinating disorders, such as neuromyelitis optica spectrum disorders, multiple sclerosis, or MOG-antibody-associated disease; Group B (n=7) showed isolated gray matter involvement, mimicking ischemic or infectious etiologies. These findings highlight the diversity of spinal cord presentations in MIDs and their potential for misdiagnoses.

The limited visual recovery observed in our patient despite idebenone therapy may be explained by the underlying genetic variant and the rapid disease course. The m.11778G>A variant is known to be associated with the poorest visual prognosis among the common LHON mutations. In addition, rapid progression of visual symptoms, as observed within one week in this case, has been reported as an unfavorable prognostic factor for visual recovery.[13]

In cases where optic neuropathy is accompanied by spinal cord lesions, demyelinating diseases should be primarily considered, as spinal involvement is not typical of LHON. The presence of a transient spinal cord lesion without clinical symptoms appears to be a rare and potentially novel finding in LHON, broadening the recognized spectrum of central nervous system involvement.

Pediatricians, pediatric neurologists, and eye care professionals should include LHON in their differential diagnoses when evaluating patients with unexplained optic neuropathy even when additional neurological symptoms or imaging findings are present. From a general pediatrics perspective, this case highlights the critical importance of a detailed family history, which ultimately played a key role in establishing the diagnosis and redirecting the diagnostic approach. Even if this had been the first affected individual in the family without a known family history, the treatment-resistant and atypical clinical course would have prompted consideration of genetic testing for hereditary optic neuropathies, but at a later stage. A detailed and repeatedly revisited family history played a crucial role in enabling a more timely diagnosis in this case.

Ethical approval

Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: AG, BK; data collection: GC, AD; analysis and interpretation of results: AG, GC, AD, ASG, LTO, BK; draft manuscript preparation: AG, BK. All authors reviewed the results and approved the final version of the manuscript.

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The authors declare that there is no conflict of interest.

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Case Report

Three cases of tufting enteropathy and review of literature

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ABSTRACT

Background. Congenital tufting enteropathy (CTE) is a rare autosomal recessive enteropathy characterized by intractable watery diarrhea independent of feeding, electrolyte imbalances and severe malnutrition. The aim of this case series is to highlight the characteristic yet easily overlooked histological features of tufting enteropathy, especially in cases where initial biopsies may be reported as nonspecific, and to emphasize the importance of clinicopathological correlation and genetic confirmation.

Case Presentation. Here we report 3 patients with tufting enteropathy who have the characteristic histological findings and demonstrate the use of EpCAM (epithelial cell adhesion molecule) immunohistochemistry. One case was diagnosed by histopathological examination, while the other 2 were diagnosed by genetic analysis.

Conclusions. These cases illustrate that the histopathological features of CTE, though subtle, are usually present from the outset and can be recognized when specifically sought. Correlation with genetic testing is essential for confirmation, but increased awareness of the characteristic epithelial tufts may reduce diagnostic delay and improve patient management.

Key words: congenital diarrhea, EpCAM, intestinal epithelial dysplasia, pediatric, tufting enteropathy.

Congenital tufting enteropathy (CTE) was first described in 1994[1] and its incidence is estimated at 1/50,000-100,000 live births in Western Europe.[2] For this rare disease, approximately 200 cases have been reported (details are summarized in Table I).[3-10] Biallelic inactivation of epithelial cell adhesion molecule gene (*EPCAM*), which is located on chromosome 2p21, was identified as the cause of CTE in 2008.[11] More recently, variants in *SPINT2* (serine peptidase inhibitor kunitz-type 2) have also been implicated in the syndromic form of this disease, which causes an indirect loss of epithelial cell adhesion molecule (EpCAM) protein due to proteolysis by activation of matriptase.[12] Of all the cases reported in English literature, approximately 74% have *EPCAM* variants, while 26% show variants in *SPINT2*.[13]

Variants in or loss of *EPCAM* lead to many defects, the most important being the disruption of the cell-cell junction which leads to defective barrier function. Disruption of the intestinal epithelial homeostasis, defective enterocyte function and impaired cell-matrix interactions have also been found in CTE patients.[3] Clinically, these patients usually present in the first few months of life with intractable diarrhea and nutrient malabsorption, resulting in impaired growth.[11] In addition to primary intestinal symptoms, patients, especially those who have the syndromic form associated with *SPINT2* variants[13,14] can have extra-intestinal symptoms,

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Table I. Summary of clinical features, genes and histologic findings reported in literature

Study	Number of cases	Year	Symptoms	Genetic variants	Histological findings	Outcome
Reifen et al[1]	3	1994	Diarrhea, vomiting	N/A*	N/A	1 died
Patey et al[4]	6	1997	Diarrhea	N/A	Villous atrophy, focal epithelial tufts, decreased number of IELs	Unknown
Goulet et al[10]	10	1998	Diarrhea	N/A	Villous atrophy, epithelial tufting	Unknown
Bird et al[5]	3	2007	Diarrhea, choanal atresia; eye, hematologic and hair abnormalities	N/A	Villous atrophy, crypt hyperplasia, chronic inflammation, tufting of surface enterocytes	Unknown
Sivagnanam et al[11]	5	2008	Diarrhea	EPCAM in 4/5 cases	Crowding of epithelial cells and tufting	Unknown
Sivagnanam et al[6]	1	2010	Diarrhea, cholestatic liver disease	SPINT2	N/A	Alive
Salomon et al[14]	57	2014	Diarrhea, superficial punctuated keratitis, choanal atresia, other atresia, dermatological anomalies, and bone malformations	EPCAM in 41 cases, SPINT2 in 12 cases	Villous atrophy, crowding epithelium/ tufts, abnormal crypts	8 died
Ranganathan et al[7]	17	2014	Diarrhea	N/A	Focal epithelial tufts and vacuolation	Alive
Pathak et al[12]	17	2019	Diarrhea	EPCAM	N/A	Alive
Holt-Danborg et al[8]	3	2019	Diarrhea, Choanal atresia, enterocutaneous fistula, atrial septal defect, cleft lip and palate, and toe abnormalities	SPINT2	Partial villous atrophy, normal brush border, focal epithelial tufts	Alive
Ayyildiz Civan et al[9]	6	2021	Diarrhea	EPCAM	Total villous atrophy, mild inflammation	3 died
Ozler et al[19]	2	2020	Diarrhea, tenosynovitis	EPCAM	Partial villous atrophy, crypt hyperplasia, focal tufting in surface epithelium, normal number of IELs	Alive (after long term follow up)

IEL: intraepithelial lymphocyte, N/A: not available.

such as superficial punctuated keratitis, corneal erosions[15], cataracts[16], skeletal dysplasia, cholestatic liver disease, chronic arthritis, bone and dermatological abnormalities.[3] Typical histopathological findings of CTE are partial or total villous atrophy, crypt hyperplasia without inflammation and focal epithelial tufts. The tufts consist of tightly packed enterocytes at villous tips and basement membrane abnormalities which results in teardrop-like configurations.[3] However, cases reported in the literature are clinically heterogenous, with varying severity and not all cases display the typical histopathological findings, which poses a diagnostic challenge.[17] BerEP4 immunohistochemistry (monoclonal antibody to EpCAM) can be helpful in the diagnosis of cases that do not have the typical morphological findings. In addition to intestinal epithelial cells, loss of BerEP4 can also be seen in hepatocytes

and bile duct epithelium in liver biopsies of patients with tufting enteropathy.[18]

Although large series of tufting enteropathy have been published, most emphasize the genetic basis or clinical spectrum.[14-16] Our series draws attention to the diagnostic challenge that these cases pose and highlights the fact that the characteristic histological findings of tufting enteropathy can usually be detected if carefully sought, which may shorten diagnostic delay.

Case Presentations

Case 1

A 2-month-old girl was admitted to the pediatric intensive care unit with prerenal acute kidney failure due to profuse watery diarrhea that had been resistant to treatment. The family pedigree showed that the parents were consanguineous (second-degree cousins). There were two family members reported to have had similar symptoms during childhood, including the father's younger brother who died in early infancy. Unfortunately, no reliable information on their age, sex, clinical features, or outcome was available. The patient had symptoms of watery diarrhea that occurred 8 to 9 times a day. Before admission to our center, she was hospitalized for two weeks at another hospital and had received antibiotic treatment. Breastfeeding was discontinued due to a preliminary diagnosis of cow's milk protein allergy. The patient was fed with an enteral nutrition formula however oral intake was completely discontinued after a few days due to worsening of symptoms.

On admission, the patient was found to be severely dehydrated. The birth weight of the patient was 2900 grams (-0.8 standard deviation score [SDS]). Her body weight at admission was 2600 grams (-7.2 SDS) consistent with severe growth faltering. Laboratory examination revealed metabolic acidosis with a blood pH of 7.16 , bicarbonate of 9 mEq/L and creatinine of 1.52 mg/dL (normal range, 0.2-0.4 mg/dL). Stool examination revealed no reducing substances, parasites, or amoebae. After starting intravenous fluids and stabilization, endoscopic biopsies from various parts of the stomach, small intestine, and colon were taken to shed light on the etiology of the chronic diarrhea. The preliminary diagnoses included cytomegalovirus (CMV) colitis, enteric anendocrinosis, lymphangiectasia and cow's milk protein allergy.

At initial examination, the endoscopic biopsies showed no specific findings. The diagnoses of lymphangiectasia and cow's milk protein allergy were ruled out immediately because there were no dilated lymphatic channels or an increase in eosinophils in the lamina propria. CMV and chromogranin immunohistochemistry studies were performed for the remaining diagnoses. CMV was negative in all tissues. Chromogranin revealed fewer neuroendocrine cells (1-2 NECs per crypt) than the normal number of 4-5 NECs per crypt. However, this was not enough to support the diagnosis of enteric anendocrinosis as most cases lack NECs completely or have 1 NEC per 10 crypts. After these findings, whole exome sequencing (WES) was performed to evaluate variants in *NEUROG3.* However, the WES study revealed a pathogenic homozygous *EPCAM* variant (NM_002354.3: c.227C>G [p.Ser76Ter]) instead. The biopsies were re-evaluated in this view with additional hematoxylin and eosin (H&E) staining and immunohistochemical staining for EpCAM. In the H&E sections of the duodenum, terminal ileum and colon, focal, subtle epithelial disorganization and tear-drop formation were found (Fig. 1A-B). Immunohistochemistry revealed complete loss of EpCAM expression in the intestinal and colonic tissues, which is specific for CTE (Fig. 1C).

The patient was fed with total parenteral nutrition after the diagnosis and per oral feeding could not be achieved. At 1 year of age, despite parenteral nutrition support, the patient developed progressive feeding intolerance with vomiting and abdominal distension, followed by respiratory distress and circulatory collapse. Cardiopulmonary resuscitation

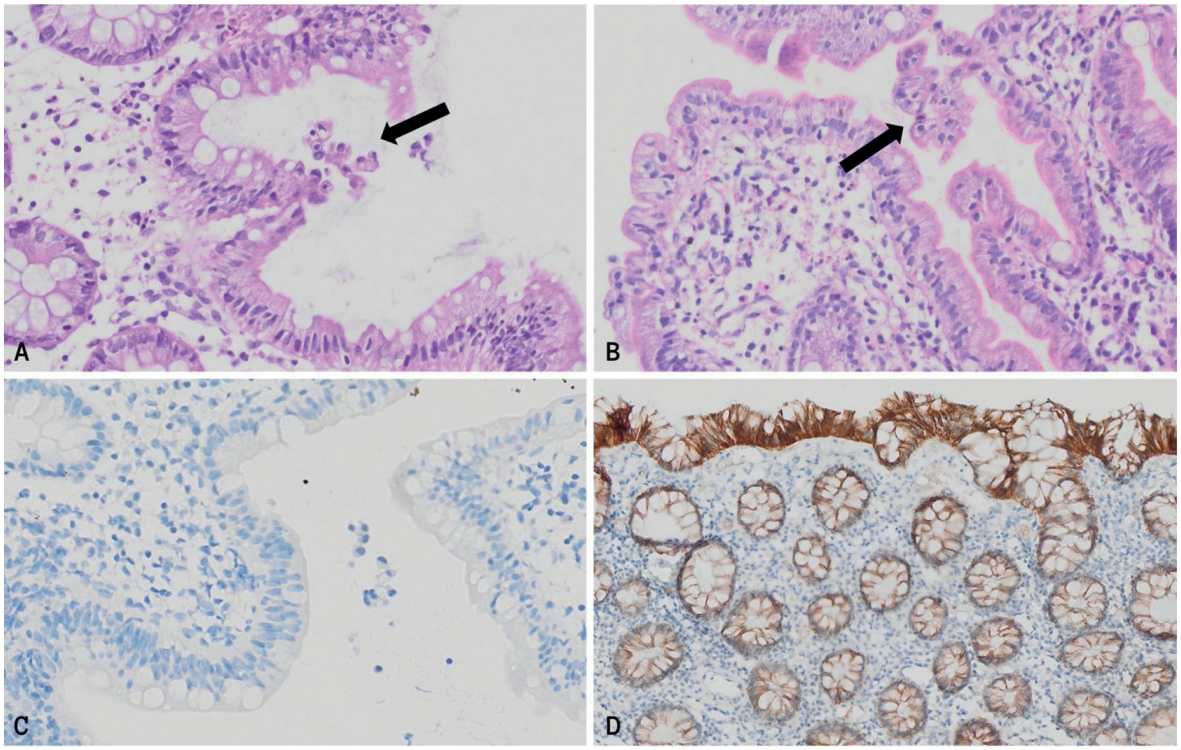

Fig. 1. Histopathological findings of Case 1. **A.** Endoscopic biopsy of the colon showing characteristic tear-drop formation (arrow) of shedding surface epithelium (H&E, original magnification 200x). **B.** Tear-drop formation and epithelial tufts (arrow) are seen in the duodenum (H&E, original magnification 200x). **C.** BerEP4 immunohistochemistry shows complete loss of staining (original magnification 200x). **D.** Normal colonic control tissue shows diffuse positivity with BerEP4 on the surface epithelium and colonic crypts (original magnification 100x).

was unsuccessful, and the patient could not be resuscitated. The outcome was attributed to complications of severe malnutrition and intestinal failure.

Case 2

A 17-month-old boy was admitted to the intensive care unit with severe malnutrition and dehydration due to watery diarrhea that had been increasing since birth. The parents were first cousins and were healthy. They had another child who passed away soon after birth due to similar symptoms. The patient was born at 35 weeks of gestation, weighing 2700 grams. When he was admitted to our center at 17 months of age, he weighed 3,600 g (-9.7 SDS) and his height was 61 cm (-7.7 SDS). The patient was previously hospitalized in multiple centers and no etiology could be identified for the intractable diarrhea. Endoscopic and colonoscopic biopsies were performed and they revealed crypt hyperplasia, villous atrophy, and an increase in intraepithelial lymphocytes. Soon after admission the clinical condition of the patient deteriorated, and he passed away. The family consented to an autopsy and molecular genetic studies. The autopsy revealed villous atrophy in the small intestine, hydrops in the gallbladder, severe malnutrition and cachexia and reactive enlargement of mesenteric lymph nodes. The duodenum sections were examined by electron microscopy. There were a few microvilli however no microvillus inclusions were identified. No definitive cause could be identified for chronic diarrhea. To rule out genetic causes, whole exome sequencing was performed. A homozygous missense variant in *EPCAM* (NM_002354.3: c.757G>A [p.Asp253Asn]) compatible with the

disease phenotype in the affected individual was found. This case has been previously published in 2022 by Güvenoğlu et al.[17] The additional details regarding genetic studies can be found in their article. We reviewed the autopsy sections of this patient and performed EpCAM immunohistochemistry on the duodenal tissue. The histologic examination of the duodenum showed villous atrophy and classic teardrop formation on the surface (Fig. 2A). In addition, there was a slight increase in intraepithelial lymphocytes. The BerEP4 immunohistochemistry was negative as expected (Fig. 2B).

Case 3

The third case is a 10-month-old male infant who had vomiting and diarrhea that commenced 2 days following birth. The parents were first-degree relatives who were healthy. The patient was initially examined for metabolic diseases due to the presence of reducing substances in urine. However, tandem mass spectrometry was normal. Sweat test for cystic fibrosis was also negative. The endoscopic biopsy from the duodenum was diagnostic as it revealed clustering of epithelial cells forming characteristic teardrop cells (Fig. 3A). The brush border was examined with periodic acid-Schiff (PAS) staining and was preserved. There was also partial villous atrophy, a minimal increase in lymphocytes in the lamina propria and crypt hyperplasia. The EpCAM immunohistochemistry was negative (Fig. 3B). Genetic testing could not be performed for this patient and no follow-up information was available.

Informed consent could not be obtained from the families because one case dated back more than 10 years and the other two families could not be reached. Therefore, permission from the ethics committee was obtained (number: 2024/17-03).

Discussion

Our three cases illustrate the diagnostic challenges of CTE. Although the disease is genetically defined, the histological findings

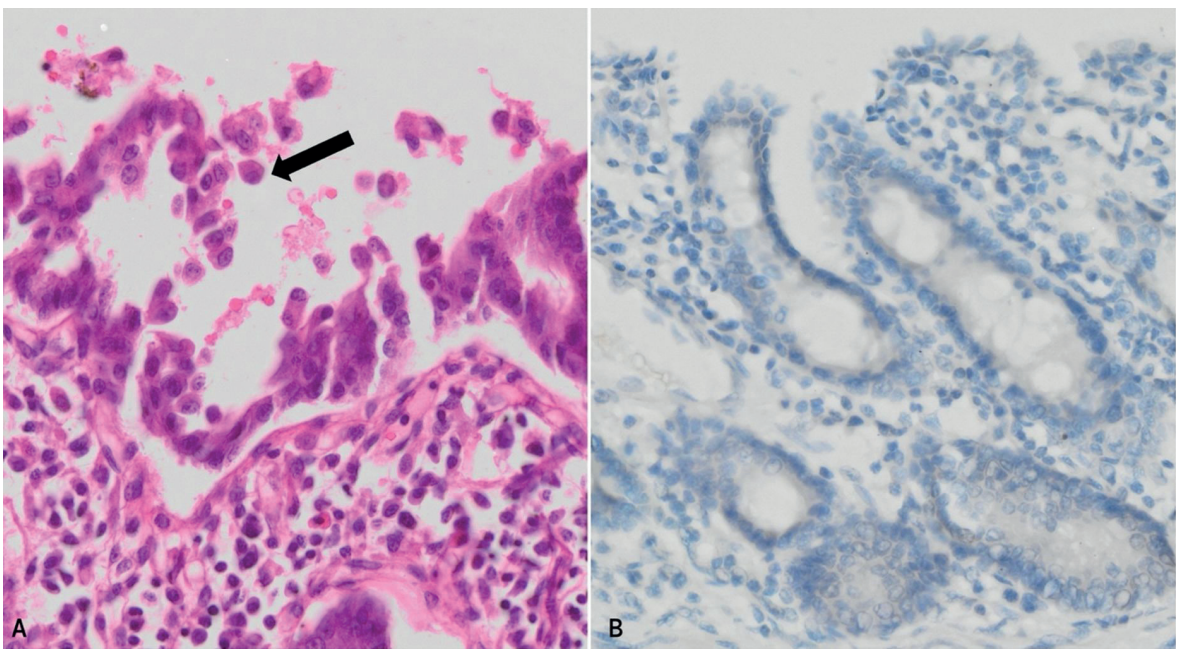

Fig. 2. Histopathological findings of Case 2. **A.** Diffuse tear-drop formation forming tufts (arrow) on the surface epithelium of duodenal sections obtained during autopsy (H&E, original magnification 200x). **B**. Complete lack of staining in BerEP4 immunohistochemistry (original magnification 200x).

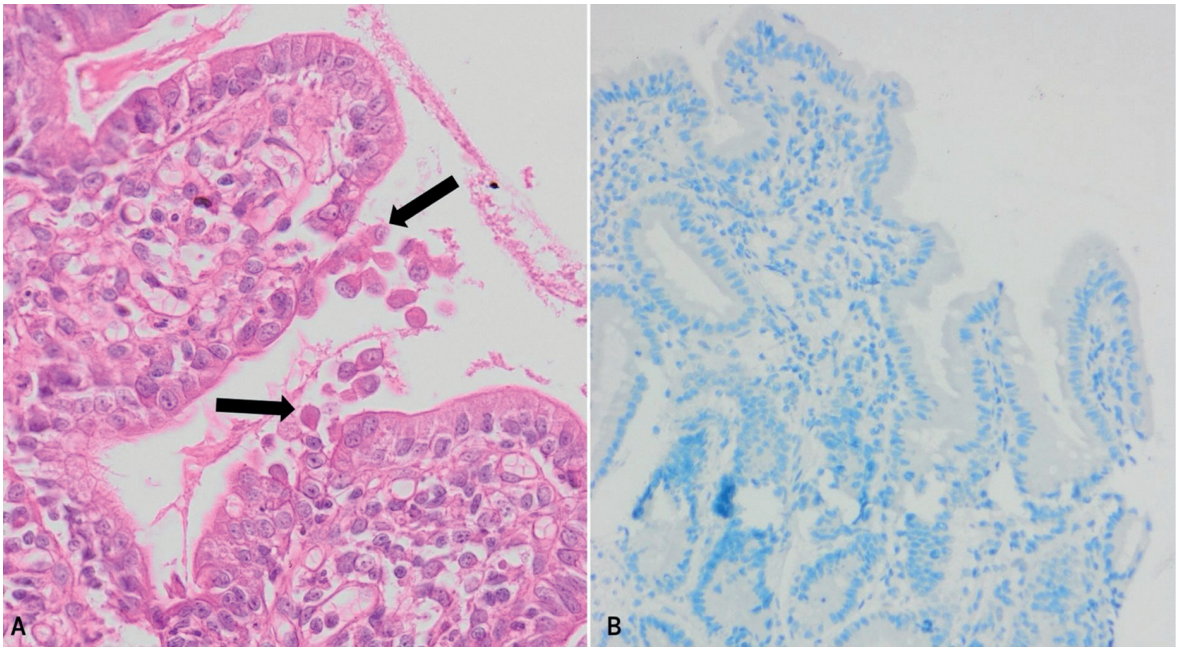

Fig. 3. Histopathological findings of Case 3. **A.** Endoscopic biopsy of duodenal tissue shows shedded tear-drop epithelial cells (arrows) (H&E, original magnification 200x). **B.** BerEP4 immunohistochemistry was negative (original magnification 100x).

can also aid in the diagnosis. In this section, we highlight the variability of the clinical course and emphasize the complementary value of histopathology and genetics in diagnosis.

While most patients depend on total parenteral nutrition (PN), there are reported cases where weaning from PN was achieved.[11,19] One of these case reports describing two siblings with tufting enteropathy showed complete loss of EpCAM in immunohistochemistry and a homozygous variant in the *EPCAM* gene. Certain patients may have a better prognosis due to unknown factors.[19] The only accepted treatment to date is small bowel transplantation, which has many complications such as liver failure, infections and rejection.[3]

Although the diagnosis of tufting enteropathy usually depends on genetic analysis, the histopathological examination can also be diagnostic if the pathologist is aware of CTE in the differential diagnosis. However, the histological findings of CTE can be overlooked and interpreted as nonspecific, which was the major challenge in 2 of our cases. Only after genetic confirmation did retrospective review reveal the subtle epithelial tufts and teardrop formations. This highlights the risk of underdiagnosis if CTE is not specifically considered. When provided with a history of intractable diarrhea in an infant, the gastrointestinal biopsies should be carefully examined for epithelial tufts and villous atrophy, and BerEP4 immunohistochemistry can be performed on cases showing villous atrophy without inflammation or when the histological findings are equivocal. Genetic testing remains essential for definitive diagnosis, prognosis, and family counseling, but increased histopathological awareness can reduce diagnostic delay and guide appropriate workup.[14]

In conclusion, our experience shows that while subtle, the histological features of CTE are characteristic when interpreted in the correct clinical context. Greater awareness of these findings, combined with timely EpCAM immunohistochemistry and genetic analysis, can improve recognition of this rare but important cause of intractable infantile diarrhea.

Ethical approval

The study was approved by Hacettepe University Ethics Committee (date: October 08, 2024, number: 2024/17-03).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: DO, literature review: AN, draft manuscript preparation: AN, EG, HHG, HD, DO. 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

Effect of mesenchymal stem cell treatment on retinopathy of prematurity in patients with bronchopulmonary dysplasia: experience of a tertiary center

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ABSTRACT

Background. Retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD) share overlapping mechanisms involving oxidative stress, inflammation, and aberrant angiogenesis. Mesenchymal stem cell (MSC) therapy has shown promise in the treatment of BPD through paracrine modulation and anti-inflammatory effects, but its influence on retinal vascular development remains uncertain.

Case Presentation. This retrospective case series included five extremely low birth weight (ELBW) infants (<1000 g) who received allogeneic umbilical cord–derived MSC therapy for severe BPD between October 2021 and May 2023. Each infant received intravenous (2×10^6 cells/kg) and intratracheal (1×10^7 cells/kg) MSC administration in a single session. ROP screening and treatment were conducted in accordance with national guidelines. Clinical data and ocular outcomes were analyzed descriptively.

Conclusions. The mean gestational age was $26^2/_7$ weeks (range, 25–$28^3/_7$) and the mean birth weight was 810 g (580–1060 g). MSC therapy was given between postnatal days 36–126 (mean, 74 days). No systemic or ocular complications occurred during hospitalization or follow-up. One infant had no ROP, one developed Type 2 ROP with spontaneous regression, and three developed Type 1 ROP requiring intravitreal bevacizumab. All treated cases achieved complete regression after a single intravitreal bevacizumab injection, without recurrence, repeat injection, or need for laser therapy. MSC therapy appeared clinically safe in ELBW infants with BPD, with no adverse ocular effects. However, ROP developed in most infants despite MSC treatment, suggesting that MSCs do not prevent disease onset. The potential modulatory role of MSCs on retinal angiogenesis warrants further investigation through larger, controlled trials.

Key words: bronchopulmonary dysplasia, mesenchymal stem cells, retinopathy of prematurity.

Retinopathy of prematurity (ROP) is a major cause of childhood blindness worldwide and remains a significant challenge among surviving preterm infants despite major advances in neonatal care. The global pooled prevalence of ROP has been reported as 31.9%, with severe ROP accounting for 7.5% (6.5–8.7%) over the past four decades.[1] Standard treatment options include laser photocoagulation and intravitreal anti–vascular endothelial growth factor (VEGF) injections.[2,3] Bronchopulmonary dysplasia (BPD) and ROP share common pathogenic pathways, including inflammation, oxidative stress, and dysregulated neovascularization.[4-8] Both disorders involve aberrant vascular development in the retina and lungs. Although preventive agents such as glucocorticoids, vitamin A, and caffeine

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have demonstrated benefits in BPD, their long-term efficacy is limited, and adverse effects are considerable.[9,10] In recent years, mesenchymal stem cell (MSC) therapy has emerged as a promising intervention for neonatal diseases, including hypoxic–ischemic encephalopathy and BPD.[11-13] Evidence from preclinical and clinical studies suggests that the therapeutic benefits of MSCs are primarily mediated through paracrine signaling and exosome release, rather than direct engraftment.[14-16] MSC-derived secretomes contain bioactive molecules such as VEGF, insulin-like growth factor 1 (IGF-1), transforming growth factor beta (TGF-β), fibroblast growth factor (FGF), and interleukin-10, which together modulate angiogenesis, apoptosis, and inflammation.[14] Given these multifaceted effects, MSC therapy for BPD could theoretically influence retinal vascularization and ROP development either beneficially or adversely. However, no clinical data currently evaluate the ocular outcomes of MSC therapy in extremely low birth weight (ELBW) preterm infants.

Our study reports on the ROP course in five preterm infants who received MSC therapy for BPD and discusses whether MSC administration may affect ROP progression.

Case Presentation

Patient selection

Our study was approved by the Ondokuz Mayis University local ethics committee (approval number B.30.2.ODM.0.20.08/407-549) and conducted in accordance with the Declaration of Helsinki. Clinical data were retrospectively reviewed. Informed consent for participation was obtained from the child's legal parent or guardian. Between October 2021 and May 2023, 52 of the 1,500 infants treated in the neonatal intensive care unit (3.47%) were diagnosed with BPD. BPD diagnosis was established according to the Jensen criteria.[17] Five preterm infants (9.6%) were treated with MSCs for BPD. Demographic and clinical characteristics—including gestational age, birth weight, ventilation mode, fraction of inspired oxygen (FiO_2), and postnatal support type were recorded.

Clinical protocols

Standard BPD management in our unit included mechanical ventilation, systemic low-dose dexamethasone, and caffeine therapy (maintenance dose 5 mg/kg/day), which was initiated on the 28th postnatal day while the infants were still receiving ventilatory support. A second corticosteroid course was administered if extubation failed after the first course. ROP screening was performed by an experienced ophthalmologist according to the guidelines of the Turkish Neonatal Society and the Turkish Ophthalmology Association.[18] The first examination was performed by indirect ophthalmoscopy between 4 and 6 weeks after birth. The ophthalmologic findings determined examination intervals. All infants were re-examined before MSC transfer, and ROP treatment, if needed, was performed by a retina specialist using intravitreal bevacizumab (IVB) (0.25 mg/0.01 mL).

MSC therapy protocol

Allogeneic umbilical cord tissue–derived MSCs were prepared in an accredited laboratory and delivered under sterile conditions. Each infant received MSCs intravenously (2×10^6 cells/kg) and intratracheally (1×10^7 cells/kg) during the same session. Infants were closely monitored for hemodynamic instability, desaturation, or other adverse events. Weekly laboratory evaluations continued until discharge and during follow-up visits to detect potential complications. After discharge, all infants were followed monthly at the neonatal outpatient clinic for at least six months. The retina specialist maintained ophthalmologic follow-ups.

The mean birth weight was 810 g (range, 580–1060 g), and the mean gestational age was $26^2/_7$ weeks (range, $25–28^3/_7$ weeks). MSC therapy was administered between postnatal

days 36 and 126 (mean, 74 days). Clinical characteristics are summarized in Table I. No systemic complications were observed during hospitalization or during the six-month post-discharge follow-up.

One infant received MSC therapy at 38 weeks postmenstrual age (PMA); retinal vascularization was in Zone 2 without any ROP signs. No ROP developed, and complete vascularization was achieved at 68 weeks PMA.

Another infant received MSC therapy at 43 weeks PMA, with preexisting Zone 2 Type 2 ROP. ROP regressed spontaneously after MSC therapy, and complete vascularization occurred at 85 weeks PMA.

Table I. Clinical characteristics of infants receiving mesenchymal stem cell therapy.

Parameter	Infant I	Infant II	Infant III	Infant IV	Infant V
Antenatal condition	Preeclampsia	Preeclampsia	PPROM	Oligohydramnios	IVF triplet pregnancy
Gestational age (weeks)	$26^{0}/_{7}$	$25^{0}/_{7}$	$26^{4}/_{7}$	$25^{1}/_{7}$	$28^{3}/_{7}$
Sex	Female	Male	Female	Female	Male
Birth weight (g)	750	740	920	580	1060
Delivery mode	Cesarean	Cesarean	Vaginal	Cesarean	Cesarean
Postnatal clinical data	RDS, LOS	RDS, LOS, Surgical PDA ligation	RDS, LOS, PDA, Grade II IVH	RDS, Surgical PDA ligation, Osteopenia of prematurity	RDS, LOS, Pneumothorax
Systemic corticosteroid therapy for BPD	2 courses	2 courses	2 courses	2 courses	2 courses
Postnatal day at MSC administration	69	126	36	90	49
Postmenstrual age at MSC administration (weeks)	$31^{2}/_{7}$	$43^{0}/_{7}$	$32^{0}/_{7}$	$38^{0}/_{7}$	$35^{4}/_{7}$
Respiratory status at MSC transfer	Mechanical ventilation (PSV) (FiO_2 45%)	Mechanical ventilation (PSV) (FiO_2 45%)	Mechanical ventilation (PSV) (FiO_2 45%)	High-frequency oscillation (HFO) (FiO_2 50%)	Mechanical ventilation (PSV) (FiO_2 45%)
Days from MSC transfer to extubation	25	3	13	47	25
Length of hospital stay (days)	145	190	81	185	118
Postmenstrual age at discharge (weeks)	$46^{3}/_{7}$	$52^{0}/_{7}$	$38^{0}/_{7}$	$51^{4}/_{7}$	$54^{0}/_{7}$
Discharge weight (g)	3160	3800	2400	2990	2010
Respiratory support at home	CPAP for 21 days	CPAP	Low-flow oxygen	Low-flow oxygen	Low-flow oxygen
Time to discontinue supplemental oxygen (chronological age)	3.5 months	2 months	40 weeks	4 months	5 months

BPD: Bronchopulmonary Dysplasia, CPAP – Continuous Positive Airway Pressure, FiO_2 : fraction of inspired oxygen; HFO: High-Frequency Oscillation, IVH: Intraventricular Hemorrhage, IVF: In Vitro Fertilization, LOS: Late-Onset Sepsis, MSC: Mesenchymal Stem Cell, PDA: Patent Ductus Arteriosus;; PSV: Pressure support ventilation, RDS: Respiratory Distress Syndrome.

Three infants developed Type 1 ROP after MSC therapy. In these cases, retinal vascularization was in Zone 1 prior to MSC administration. A single IVB injection induced rapid regression of ROP without complications, repeat injections, or laser photocoagulation. During long-term follow-up, complete vascularization in Zone 3 was achieved in all cases. In summary, one infant showed no ROP, one had spontaneously regressed Type 2 ROP, and three developed Type 1 ROP that regressed after a single anti-VEGF treatment. The detailed course of ROP examinations is shown in Table II.

Discussion

In our case series, we investigated the progression of ROP in 10 eyes of five infants following MSC treatment BPD. The coexistence of BPD and ROP is well documented in many studies, and this association is largely attributed to their overlapping risk profiles, as ELBW infants born at very early gestational ages are at the highest risk for both conditions.[19-22] Infants with BPD experience more hypoxemic/hyperoxemic episodes, longer oxygen exposure, and prolonged positive pressure ventilation (PPV) and continuous positive airway pressure (CPAP) use, all of which contribute to the development and severity of ROP. Prolonged PPV has been reported as an independent risk factor for ROP, and prolonged CPAP has been shown to predict severe or treatment-requiring disease.[21,22]

In our study, the average birth weight was 810 g and the gestational age was $26^{2}/_{7}$ weeks. Remarkably, two infants (40%) did not require ROP treatment, which may be interpreted as a favorable outcome given the high baseline risk of this population. Although MSC treatment

Table II. Course of retinopathy of prematurity (ROP) in infants receiving mesenchymal stem cell therapy.

Parameter	Infant I	Infant II	Infant III	Infant IV	Infant V
First ROP examination (PMA, weeks)	$29^{3}/_{7}$	$29^{0}/_{7}$	$30^{4}/_{7}$	$29^{1}/_{7}$	$32^{2}/_{7}$
Initial findings (both eyes)	Incomplete vascularization to Zone I	Incomplete vascularization to Zone I	Incomplete vascularization to Zone I	Incomplete vascularization to Zone I	Incomplete vascularization to Zone I
Maximum ROP stage (PMA, weeks)	$36^{3}/_{7}$	$41^{0}/_{7}$	$35^{5}/_{7}$	–	$37^{3}/_{7}$
Maximum stage (both eyes)	Aggressive posterior ROP (Type 1)	Stage 2, posterior Zone II (Type 2)	Stage 2, posterior Zone II (Type 1)	No ROP	Aggressive posterior ROP (Type 1)
Plus disease	Bilateral plus	Bilateral pre-plus	Bilateral plus	–	Bilateral plus
Bevacizumab treatment (PMA, weeks)	$36^{3}/_{7}$	–	$35^{5}/_{7}$	–	$37^{3}/_{7}$
Outcome after Bevacizumab	Regression	–	Regression	–	Regression
Final ROP examination (PMA, weeks)	82	85	99	68	79
Final retinal status	Complete vascularization	Complete vascularization	Complete vascularization	Complete vascularization	Complete vascularization
PMA at MSC administration (weeks)	$31^{2}/_{7}$	$43^{0}/_{7}$	$31^{4}/_{7}$	$35^{4}/_{7}$	$38^{0}/_{7}$

MSC – Mesenchymal Stem Cell, PMA – Postmenstrual Age, ROP – Retinopathy of Prematurity.

did not prevent ROP onset in all infants, it did not appear to exacerbate progression. As discussed in previous studies, the underlying pathophysiology of both BPD and ROP involves dysregulation of angiogenic factors such as VEGF, IGF-1, and TGF-β.[23,24] The close relationship between angiogenic pathways in the developing lung and retina supports the hypothesis that interventions that affect pulmonary angiogenesis could simultaneously influence retinal vascular development. Initially, it was believed that MSCs repaired tissue by engrafting into damaged sites.[14,15] However, later studies demonstrated that their therapeutic benefit primarily derives from paracrine mechanisms, including immunomodulatory, anti-inflammatory, antibacterial, antioxidative, angiogenic, and regenerative effects.[16] MSCs have been successfully investigated in adult retinal degenerative diseases such as age-related macular degeneration, diabetic retinopathy, and glaucoma. Experimental studies further support their cytoprotective potential: Ezquer et al. showed that intravitreal MSCs created a cytoprotective microenvironment in diabetic mouse retina.[16] Noueihed et al. demonstrated that MSCs reduced vaso-obliteration by 75%, inhibited neovascularization, and migrated toward avascular zones in a mouse model of oxygen-induced retinopathy.[15] Similarly, Kim et al. reported that human placental amniotic membrane–derived MSCs secreted high levels of TGF-β1, suppressing endothelial proliferation and pathological neovascularization; importantly, injected MSCs were shown to migrate into the retina.[14]

Consistent with these findings, in the present study, four infants developed ROP, and three progressed to aggressive posterior ROP requiring treatment. One infant had Type 2 ROP that regressed spontaneously after MSC transfer, and one infant did not develop ROP at all. ROP regressed after a single IVB injection in all treated infants, and vascularization was completed without recurrence during follow-up. The rapid regression after anti-VEGF may indicate that the bioactive molecules released by MSCs did not induce aberrant neovascularization and may even have contributed to stabilization of the retinal vasculature. Importantly, MSC administration did not elicit an inflammatory ocular response in any case.

When these results are compared with national and international data, our findings appear promising. In a meta-analysis by Ramaswamy et al., the incidence of ROP and ROP requiring treatment was 49% and 18%, respectively.[25] In a multicenter study from Türkiye, these rates were higher: 68% and 26%.[19] In two separate studies from our NICU, in 2013 and 2022, the incidence of ROP in infants ≤1000 g was 70.7% and 81%, respectively, and the incidence of ROP requiring treatment was 30.2% and 23.9%, respectively.[20,26] In our series, only two of five infants (40%) did not require ROP treatment despite ELBW and BPD. However, this rate does not appear to be lower than that reported in previous studies. Therefore, the potential contribution of MSC treatment to systemic stability and retinal outcomes should be carefully evaluated.

One critical consideration is the timing of MSC administration. Phase II trials recommend administering MSCs within 5–14 days to prevent early pulmonary injury.[13] However, legal requirements in Türkiye mandate that infants remain dependent on mechanical ventilation despite two courses of postnatal steroids before MSC eligibility. Additionally, parental hesitation and administrative approval processes delayed treatment. As a result, MSC infusion occurred at a median of 74 days (range 36–126). Infants who later required ROP treatment received MSCs earlier, likely reflecting worse initial lung maturity. It is possible that earlier MSC administration could have contributed to earlier lung stabilization and potentially mitigated ROP progression. Nonetheless, early intervention raises theoretical concerns, particularly because MSC-derived exosomes contain VEGF and IGF-1, which might exacerbate pathological retinal neovascularization similar

to the increased ROP risk observed with early recombinant erythropoietin therapy.[27] Therefore, determining the optimal timing of MSC administration remains a critical objective for future research.

Despite limitations-including small sample size, retrospective design, heterogeneous timing of MSC administration, and relatively short follow-up—our study provides one of the earliest clinical descriptions of retinal outcomes following systemic MSC therapy in ELBW infants. The absence of ocular or systemic adverse events suggests that MSC administration is clinically safe, but its protective or therapeutic effect on ROP remains uncertain.

Previous studies indicate that MSC therapy can lessen the severity of BPD in very low birth weight infants, yet its effect on ROP remains unclear. These findings raise the possibility that MSCs might influence ROP risk or contribute to a more favorable disease trajectory. However, larger studies are required to understand better whether the timing of MSC administration—early or delayed—has any meaningful impact on ROP development or severity.

Ethical approval

The study was approved by Clinical Research Ethics Commitee of the Ondokuz Mayıs University (date: 07.08.2024, number: B.30.2.ODM.0.20.08/407-549).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: CS, ECC; Data collection: ECC; analysis and interpretation of results: CS, ECC, OEY; draft manuscript preparation: CS, OEY. All authors reviewed the results and approved the final version of the manuscript.

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Case Report

When a handle bar accident leads to hernia: report of three cases

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ABSTRACT

Introduction. Blunt impact-induced traumatic abdominal wall hernia (TAWH) is classically associated with handlebar injury caused by direct trauma to the anterior abdominal wall, hence the term "handlebar hernia." It is uncommon in children and associated with significant morbidity if diagnosis is delayed.

The aim of this study is to present our experience in treating bicycle handlebar-associated TAWH, highlight the likelihood of associated intra-abdominal injuries, and emphasize the importance of early imaging and surgical intervention when necessary.

Case Presentation. Three cases of abdominal wall hernia were included. All patients were boys, with a mean age of 8.6 years (range: 7–11 years). All patients presented with swelling in the iliac fossa (right n= 2 and left n= 1). Emergency computed tomography (CT) was performed in all cases: two revealed a muscular defect, while the third showed pneumoperitoneum. The musculoaponeurotic defect was surgically repaired in each case. In the third patient, a small intestinal perforation was also identified and sutured. All patients recovered uneventfully.

Conclusion. TAWH is a rare clinical entity that may signal more significant associated injuries, such as hollow viscus perforation, which often requires urgent surgery. A high index of suspicion is necessary in children presenting with bruising, abrasions, ecchymosis, hematoma, or peritoneal signs following blunt abdominal trauma, and there should be a low threshold for additional imaging.

Key words: abdominal injuries, child, hernia, trauma.

Traumatic abdominal wall hernia (TAWH) typically results from blunt trauma to the abdominal wall, leading to disruption of the muscular and fascial layers while the skin remains intact. This injury allows intra-abdominal contents, such as the small bowel, to protrude through the defect.[1] The incidence of TAWH is estimated at up to 9% of abdominal wall defects caused by trauma.[2] The first case of TAWH described in the literature occurred in 1906, in an adult injured by a wheelbarrow handle.[3] Pediatric TAWH was first reported in 1956, in a 14-year-old boy struck in the abdomen by motorcycle handlebars.[4] These injuries are difficult to diagnose clinically and lack standardized treatment strategies. Repair usually involves surgical exploration and layered closure of the defect, depending on its size, location, and the condition of surrounding tissues.[5] Reporting rare and distinctive presentations, such as traumatic hernia without skin penetration, enriches the literature and helps guide optimal management. In this article, we present three pediatric cases of handlebar-associated abdominal wall hernia.

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Case Presentations

Case 1

A 7-year-old boy with no relevant medical history presented to the pediatric surgery emergency department after falling from his bicycle. On examination, a 3-cm swelling with bruising was observed in the right iliac fossa (RIF), extending to the right inguinal region (Fig. 1). Manual palpation revealed tenderness in the lower abdomen. The patient's pulse was 94 bpm, and his blood pressure was 110/60 mmHg.

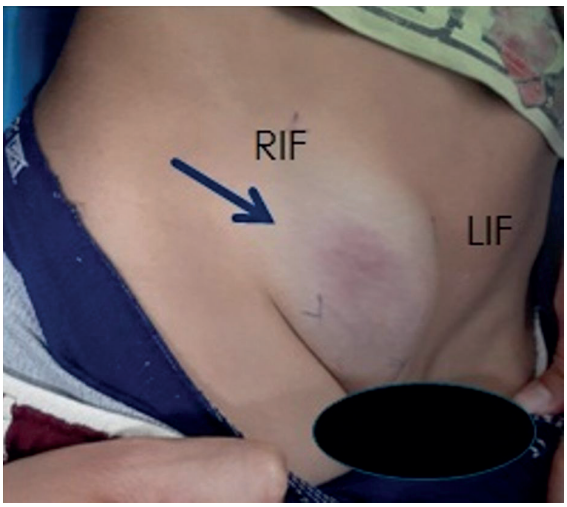

Fig. 1. Visible swelling with bruising involving the right iliac fossa.
RIF: right iliac fossa, LIF: left iliac fossa

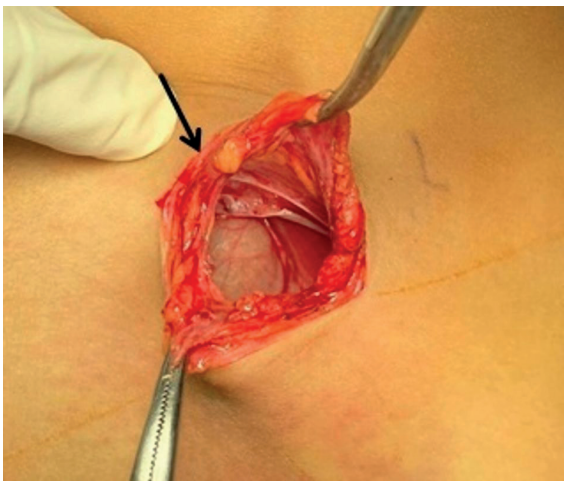

Fig. 2. Intraoperative view showing a 2-cm musculoaponeurotic defect.

An emergency abdominal computed tomography (CT) scan revealed a 30-mm muscular defect in the external oblique muscle, with no associated intestinal perforation.

Emergency surgery was performed, during which a 2-cm musculoaponeurotic defect was identified (Fig. 2). The abdominal wall was repaired in layers using interrupted sutures. The postoperative course was uneventful. At 3 months postoperatively, the patient had a strong and intact abdominal wall.

Case 2

An 11-year-old boy with no relevant medical history presented with blunt abdominal trauma caused by impact from a bicycle handlebar to the RIF. Examination revealed a painful 5-cm swelling in the RIF with a 2-cm contusion. The rest of the abdomen was soft, compressible, and non-tender. The patient was hemodynamically stable.

An abdominal CT scan showed a 20-mm defect in the right anterolateral abdominal wall with herniation of subcutaneous epiploic fat (Fig. 3). No other injuries were noted.

An urgent laparotomy was performed through local wound exploration. A 2-cm parietal defect was identified without digestive perforation. The abdominal wall was repaired in layers. Postoperative recovery was uneventful.

Case 3

An 8-year-old boy was referred for abdominal pain following a fall from a bicycle. The child had no relevant medical history, including no history of abdominal hernias. He presented with abdominal pain, vomiting, and bowel dysfunction. Physical examination revealed a tender lump in the left iliac fossa. No additional symptoms were reported. Vital signs were within normal limits.

An abdominal CT scan demonstrated intestinal loops protruding through a 30-mm defect in the abdominal wall, along with significant

pneumoperitoneum and subcutaneous emphysema—findings consistent with a perforated hollow viscus.

An emergency laparotomy was performed following a diagnostic laparoscopy. A 3-cm defect in the abdominal wall, a perforation in a viable segment of the small bowel, and a tear in the mesentery of the mid-jejunum were found (Fig. 4). The procedure included a primary wedge resection and closure of the enterotomy, repair of the mesenteric tear, and layered closure of the abdominal wall hernia. The postoperative course was uneventful.

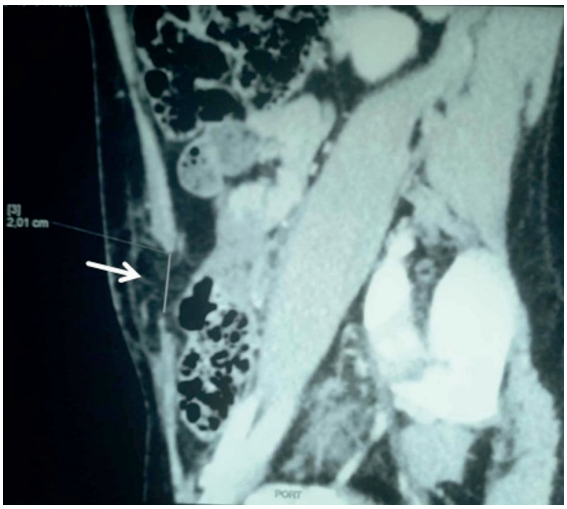

Fig. 3. Computed tomography showing a muscular defect in the abdominal wall with a herniation of subcutaneous epiploic fat (arrow).

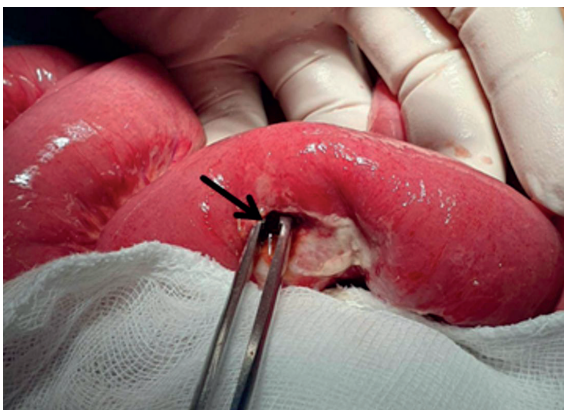

Fig. 4. Intraoperative view showing the perforation (arrow) in the lateral wall of the small bowel.

Written informed consent for the publication of the patients' clinical data and images was obtained from their parents.

Discussion

TAWH is a rare pediatric condition, mostly recorded in case reports, with anatomical abnormalities that vary from minor muscular tears to significant aponeurotic and skeletal damage.[6] These injuries often originate from a rapid, localized application of severe blunt force to the abdomen, such as from a bicycle handlebar. This impact causes tangential shearing forces and abrupt increases in intra-abdominal pressure, which disrupts deeper muscle and fascial tissues while the very elastic overlying skin often remains intact.[7,8]

Due to the great variety in presentation, even expert pediatricians or surgeons may overlook minor injuries, especially when confounding symptoms are present. However, several factors should raise suspicion of TAWH, such as a history of abdominal trauma or a pre-existing hernia. TAWH commonly affects school-aged children and often presents with non-specific symptoms like fever, vomiting, or abdominal pain. Physical examination may reveal bruising, ecchymosis, swelling, or a tender mass—though skin defects are often absent.[9-11]

Bicycle handlebar trauma should always raise suspicion, even if external signs seem trivial. Studies have shown that physical examination has low sensitivity for detecting TAWH, with rates between 29.4% and 42.3%.[12,13] Vu and Klinkner reported that patients with severe handlebar injuries often had only a minor fall at low speeds, with minimal external evidence of trauma.[14]

TAWH is rarely isolated and is frequently accompanied by associated intra-abdominal injuries, occurring in 25%-79% of cases—as seen in our third case.[15,16] The risk of intra-abdominal injuries increases significantly when the handlebar impact occurs in the upper abdomen.

Given the limitations of physical examination in diagnosing TAWH, paraclinical investigations are essential. Although ultrasonography can sometimes detect a TAWH, CT remains the most reliable diagnostic modality.[17]

According to Burt et al.[13], CT imaging has a sensitivity of 98% for identifying traumatic abdominal wall hernias. In addition to visualizing the hernia itself, CT scans can reveal other surgically significant injuries, such as bowel perforations or hemoperitoneum, and can clearly delineate muscular disruptions, which may otherwise be misinterpreted as hematomas or remain undetected altogether.[18] It is believed that pain and muscle spasms can obscure these defects on initial imaging, leading to delayed diagnosis.[19] In our cases, the clinical presentations were typically marked, and diagnosis was confirmed via CT imaging.

The most severe form of abdominal wall injury, characterized by evisceration, occurs in fewer than 1.5% of blunt abdominal trauma patients.[14] In non-operative settings, emergency physicians may attempt gentle reduction of eviscerated bowel loops without applying force. If unsuccessful, the herniated contents should be covered with sterile, non-adhesive, water-impermeable material, and broad-spectrum antibiotics should be initiated immediately.[20]

Immediate surgical exploration and repair are generally recommended to prevent early complications from unrecognized intra-abdominal injuries, and late complications such as incarceration, strangulation, or bowel ischemia.[21]

Some authors recommend early repair via a midline incision for anterior TAWHs, particularly in patients already undergoing laparotomy. In contrast, elective repair may be considered for isolated lumbar or lateral TAWHs. Primary closure of all abdominal wall layers is the standard approach. While prosthetic mesh is often used in adults for larger defects, in children, the vast majority of TAWHs in children can be repaired primarily without mesh.[22,23]

If the overlying skin shows signs of trauma (e.g., abrasions or hematomas), elective surgery is often postponed until soft-tissue recovery to minimize the risk of wound dehiscence and further tissue damage.[24]

Although laparotomy is the most commonly used surgical approach in the literature (approximately 85%), laparoscopy has emerged as a valuable alternative. Minimally invasive techniques can help exclude intra-abdominal injuries and may eliminate the need for a midline laparotomy, particularly in hemodynamically stable patients—as illustrated by our third case.[10]

In carefully selected cases with no associated intra-abdominal injuries, conservative management may be considered. However, this requires close clinical and radiological monitoring, and current evidence does not support routine non-operative management of TAWH.[25,26]

Conclusion

Traumatic abdominal wall hernia caused by bicycle handlebar injuries in children is a rare but important clinical entity. Early recognition and intervention are crucial to prevent morbidity associated with bowel strangulation and incarceration.

Clinicians should maintain a high index of suspicion for TAWH in any child presenting with abdominal trauma from handlebars—especially when accompanied by the "handlebar sign" (localized bruising or swelling). A low threshold for imaging, particularly with CT scanning, is essential.

Surgical repair, whether open or laparoscopic, remains the cornerstone of management. While non-surgical approaches have been reported in isolated, uncomplicated cases, current data do not support them as a standard

recommendation. Prompt diagnosis and tailored surgical intervention offer the best outcomes for pediatric TAWH cases.

Ethical approval

The parents of the patients gave their written informed consent for this report to be published.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: ZH; data collection: RW; analysis and interpretation of results: ZH, RW; draft manuscript preparation: ZH. 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

Effective interleukin-6 inhibition in a pediatric patient with mevalonate kinase deficiency and chronic nonbacterial osteomyelitis–like bone lesions under interleukin-1 blockade

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ABSTRACT

Background. Mevalonate kinase deficiency (MKD) is a rare autosomal recessive autoinflammatory disease. Chronic nonbacterial osteomyelitis (CNO) represents another autoinflammatory disorder characterized by sterile bone inflammation. Although musculoskeletal pain is common in MKD, CNO-like bone lesions have rarely been described. Tocilizumab has been used separately in MKD / hyper-IgD syndrome (HIDS) and in CNO; however, pediatric cases showing both conditions together and responding completely to IL-6 blockade have not been previously reported.

Case Presentation. We present a 16-year-old boy born to consanguineous parents who experienced early-onset recurrent fever episodes with abdominal pain, maculopapular rash, oral ulcers, and conjunctival injection. He was initially misdiagnosed with FMF and IgA vasculitis and treated with colchicine with partial improvement. Persistent systemic inflammation prompted referral to our tertiary center at age 9. A periodic fever gene panel revealed a homozygous *MVK* p.V377I mutation, confirming MKD.

Anakinra therapy was initiated. Although no attacks occurred during the first month, flares characterized by fever, abdominal pain, rash, and elevated acute-phase reactants recurred in the second and third months, reflecting a partial response. Consequently, treatment was switched to canakinumab. Toward the end of the second year of IL-1 blockade, attack frequency increased to once every three months, and at age 12 he developed diffuse musculoskeletal pain. Whole-body magnetic resonance imaging demonstrated multifocal metaphyseal bone marrow edema compatible with CNO-like lesions. Sulfasalazine was added but discontinued after drug-induced pancreatitis. Given persistent systemic inflammation and inadequate response to IL-1 inhibitors, canakinumab was replaced with weekly subcutaneous tocilizumab, resulting in rapid improvement in bone pain and systemic inflammation. Since the third month of tocilizumab therapy, he has remained clinically stable with normalized inflammatory markers and only a single mild flare over the last year.

Conclusion. This case highlights the potential role of IL-6 inhibition in complicated MKD presenting with autoinflammatory bone disease refractory to standard therapies.

Key words: mevalonate kinase deficiency, hyper-IgD syndrome, chronic nonbacterial osteomyelitis, autoinflammatory bone disease, tocilizumab.

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Mevalonate kinase deficiency (MKD) is a rare autosomal recessive autoinflammatory disease that encompasses a clinical spectrum ranging from the milder hyperimmunoglobulin D syndrome (HIDS) to the more severe mevalonic aciduria.[1,2] MKD typically manifests with early-onset recurrent febrile episodes accompanied by cervical lymphadenopathy, abdominal pain, diarrhea, and aphthous ulcers.[1,2] The disorder is caused by biallelic mutations in the *MVK* gene, with the p.V377I variant being the most frequently identified mutation associated with the HIDS phenotype.[2-5]

Chronic nonbacterial osteomyelitis (CNO) represents another autoinflammatory disorder characterized by sterile, relapsing-remitting bone inflammation mediated by dysregulated interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-6 pathways.[6-9] While musculoskeletal manifestations such as arthralgia and transient arthritis are commonly observed during MKD flares, radiologically confirmed CNO-like bone lesions have only rarely been described in the context of monogenic autoinflammatory diseases.[9,10]

IL-1 inhibitors are the primary biologic therapy in MKD; however, refractory cases exist.[2,11-13] Alternative cytokine pathways, including IL-6, play important roles in systemic inflammation and bone remodeling.[8-10] Tocilizumab, a monoclonal antibody targeting the IL-6 receptor, has been utilized independently in the management of both MKD/HIDS and CNO.[12-15]

To date, pediatric cases presenting with a coexistence of both conditions, particularly those demonstrating a complete clinical and radiological response to IL-6 blockade after failing IL-1 inhibition, have not been previously reported. Herein we present this case to underscore the diagnostic and therapeutic challenges involved and to highlight the potential role of the IL-6 pathway in refractory musculoskeletal involvement of MKD.

Case Presentation

A 16-year-old boy, born to consanguineous parents (first-degree cousins), had recurrent fever episodes beginning at 4 months of age. Attacks were associated with abdominal pain, maculopapular rash, oral ulcers, and conjunctival injection. He was initially followed with a clinical suspicion of familial Mediterranean fever (FMF) and IgA vasculitis at another clinic. *MEFV* gene analysis was performed during this period and showed no pathogenic mutations; however, he was treated with colchicine with partial improvement due to the symptomatic overlap.

At age 9, he was referred to our center due to persistent systemic inflammation despite treatment. He had a history of spontaneous epistaxis and isolated thrombocytopenia at age 8. Anti-nuclear antibody (ANA) testing was positive at 2+ intensity with a granular pattern. Given the ANA positivity and history of thrombocytopenia, further evaluation was performed to rule out systemic lupus erythematosus (SLE). Although the extractable nuclear antigen (ENA) panel showed isolated anti-DFS70 positivity, this was considered clinically insignificant. Anti-dsDNA was negative and complement levels were normal. Ultimately, the absence of specific clinical features and a normal urinalysis supported the exclusion of SLE.

A periodic fever gene panel (*MEFV, ADA2, MVK, NLRP3, NLRP12, TNFRSF1A, TNFRSF11A, LPIN2, PSTPIP1, IL1RN, IL10RA, IL10RB, and NOD2*) identified a homozygous *MVK* p.V377I mutation, confirming MKD with a HIDS phenotype.

Anakinra 100 mg/day (3 mg/kg/day) was initiated. After approximately three months of therapy, no attacks occurred during the first month; however, in the second and third months he experienced flares lasting about seven days, characterized by fever, abdominal pain, rash,

and elevated acute-phase reactants. Therefore, his response to anakinra was considered partial, and treatment was switched to canakinumab 150 mg/month (4 mg/kg/month). Toward the end of the second year, the attack frequency increased to once every three months, and at age 12 he developed progressive, diffuse musculoskeletal pain while still receiving canakinumab. He had no morning stiffness or inflammatory back pain; however, there was marked bone tenderness on palpation, particularly in the clavicle, femur, tibia, and humerus. Whole-body magnetic resonance imaging (MRI) revealed multifocal metaphyseal bone marrow edema in these regions, compatible with CNO-like lesions (Fig. 1).

In addition to ongoing canakinumab, initial management included non-steroid anti-inflammatory drugs, followed by the introduction of sulfasalazine. However, approximately five months after starting sulfasalazine, he presented to the emergency department with severe abdominal pain. Laboratory tests showed elevated amylase and lipase levels, and abdominal computed tomography (CT) demonstrated findings consistent with acute pancreatitis. Drug-induced pancreatitis was considered the most likely etiology, and sulfasalazine was discontinued.

Given refractory systemic inflammation, persistent bone pain, and inadequate response to IL-1 inhibitors, canakinumab was discontinued and subcutaneous tocilizumab 162 mg/week (4 mg/kg/week) was initiated. The patient showed rapid improvement in systemic symptoms and bone pain, with normalization of inflammatory markers. Since approximately the third month of tocilizumab therapy, he has had no recurrence of bone pain. Over the past year, he experienced only a single mild flare characterized by fever and abdominal pain, and no evidence of subclinical inflammation has been detected, with acute-phase reactants consistently remaining within normal ranges. He has been maintained on weekly tocilizumab for 24 months and remains in sustained remission.

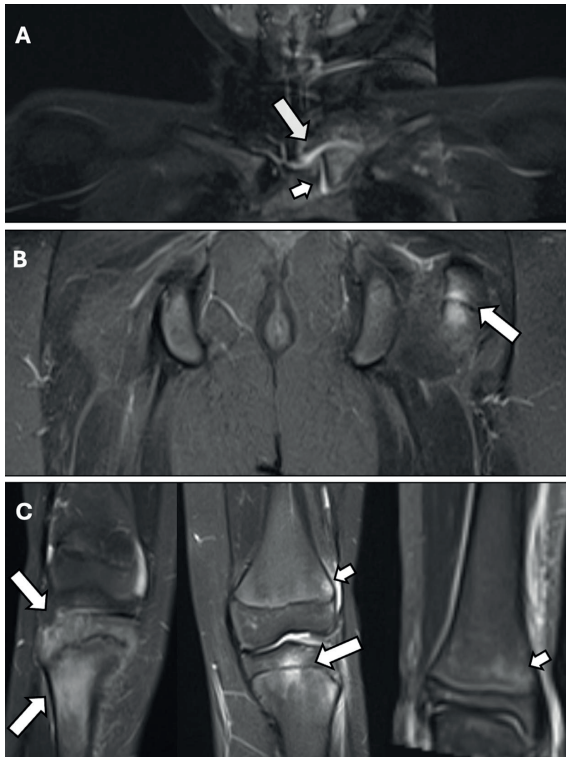

Fig. 1. Coronal STIR magnetic resonance imaging (MRI) findings of the clavicle, femur, and knee. (A) Bone marrow edema/inflammatory signal changes in the medial metaphysis of the left clavicle (long arrow), along with minimal fluid in the sternoclavicular insertion (short arrow). (B) Focal bone marrow edema/inflammation adjacent to the secondary ossification center in the left greater trochanter of the femur (arrow). (C) Bone marrow edema/inflammatory changes in the proximal metaphysis and epiphysis of bilateral tibiae (long arrows). Similar signal alterations are also seen in the lateral distal metaphysis of the left femur and distal metaphysis of left tibia (short arrows).

Written informed consent was obtained from the patient's parents.

Discussion

The coexistence of MKD and CNO-like lesions highlights a significant overlap in autoinflammatory pathways, primarily mediated by the dysregulation of IL-1β, TNF-α, and IL-6.[6,9,10] Rather than being a simple association of two separate entities, this case suggests a shared pathogenic theme of innate immune overactivation. While musculoskeletal manifestations such as arthralgia and transient arthritis are commonly observed during MKD flares, radiologically confirmed sterile osteitis resembling CNO has been only rarely reported in monogenic autoinflammatory diseases.[9,10] This case illustrates an unusual clinical phenotype where both systemic inflammation and focal bone lesions responded completely to IL-6 inhibition.

Recent pediatric cohorts have broadened the phenotypic spectrum of MKD and highlighted its variable musculoskeletal involvement.[1-5] Evaluating other autoinflammatory diseases associated with CNO-like bone involvement further strengthens this diagnostic framework. Given that our patient was initially suspected of having FMF, the relatively frequent association between FMF and CNO should be addressed.[16] While this link is well-documented in FMF, MKD-associated CNO-like lesions remain extremely limited in the literature.[6,10,16] Our patient expands this spectrum by demonstrating characteristic multifocal metaphyseal bone marrow edema on whole-body MRI. In the absence of a bone biopsy, the diagnostic value of MRI in CNO is paramount; the specific multifocal distribution and high-intensity signals on STIR sequences provided high diagnostic confidence, effectively supporting the diagnosis through non-invasive means.[9,10,17]

CNO is the most common autoinflammatory bone disease in childhood and is driven by dysregulated innate immunity.[6,9] Evidence indicates that tocilizumab may be beneficial in refractory cases, supporting the pathogenic role of IL-6 in autoinflammatory bone inflammation.[14,15] In parallel, IL-1 inhibitors are considered standard therapy for MKD; however, incomplete responses have been described, particularly in patients with multisystem involvement.[2,11-13] Our patient demonstrated persistent inflammatory attacks and progressive bone pain despite sequential IL-1 blockade, indicating the need for alternative cytokine-directed therapy.

IL-6 contributes to osteoclast activation and bone marrow edema, providing a biologically plausible target in patients with MKD and concomitant bone involvement.[8-10] Supportive evidence for IL-6 inhibition in MKD comes from small series showing reduced flare frequency under tocilizumab treatment.[12,13] It should be noted that while many cited studies regarding IL-6 blockade describe primary CNO patients without MKD, we extrapolated from the established role of IL-6 in CNO to propose its potential effectiveness in MKD-associated bone lesions.[14,15] The complete clinical and radiological remission achieved with tocilizumab in our patient suggests that IL-6 may play a key pathogenic role in both conditions, especially in phenotypes refractory to IL-1 inhibition.

This case demonstrates that radiologically confirmed CNO-like bone lesions can occur as a rare manifestation of mevalonate kinase deficiency. In pediatric patients presenting with autoinflammatory features and persistent bone pain, the use of whole-body MRI is a crucial, non-invasive diagnostic tool that can identify sterile osteitis without the need for bone biopsy. Furthermore, when standard IL-1 blockade fails to achieve full remission, IL-6 inhibition with tocilizumab should be considered as an effective therapeutic alternative for managing both systemic and musculoskeletal involvement in MKD. Further research into the shared cytokine pathways of these rare disorders may lead to more targeted and personalized treatment strategies.

Ethical approval

Written informed consent was obtained from the legal guardians of the patient. The signed consent forms are retained by the corresponding author.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: BS, ET; data collection: ET, SAU, ST, ME; analysis and interpretation of results: ET, SAU, BS; draft manuscript preparation: ET, SAU, BS. All authors reviewed the results and approved the final version of the manuscript.

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Revisiting maternal perception and objective nutritional status in children with reported poor appetite

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Dear Editor,

I read the article "Dietary adequacies and anthropometric measurements in children with poor appetite according to their mothers" by Bozbulut et al., recently published in the Turkish Journal of Pediatrics, which presents an important evaluation of discrepancies between maternal perception and objective nutritional indicators among children aged 2-9 years.[1]

The findings contribute valuable insight, particularly in outpatient pediatric settings where appetite-related concerns are common. However, the manuscript does not sufficiently address the remaining knowledge gaps or propose practical strategies that could translate these findings into improved outcomes.

First, the study highlights that 55% of mothers perceived their children as underweight, although nearly 90% had a normal body mass index age. Exploring the sociocultural determinants underlying these perceptions would strengthen the interpretation, as cultural norms and expectations frequently shape parental judgments about appetite and body size.[2]

Second, the reported nutrient adequacy, particularly the apparently high protein intake despite perceived poor appetite, raises concerns about the accuracy of maternal reporting. Three-day dietary recalls are inherently vulnerable to recall bias and overestimation. Complementing parental reports with observational measures or school meal records could help minimize reporting discrepancies.

Third, although weak positive correlations were identified between anthropometric z-scores and nutrient adequacy ratios, the clinical significance of these modest associations remains uncertain. Longitudinal studies may help determine whether these associations persist in children with chronic appetite issues.

In conclusion, Bozbulut et al.[1] provide important evidence underscoring the limitations of relying solely on maternal perception when evaluating nutritional status. The findings reinforce the necessity of objective anthropometric assessment and professional guidance to prevent unnecessary parental anxiety and potentially inappropriate feeding practices. In this context, the validated Comprehensive Feeding Practices Questionnaire (CFPQ) may serve as a useful complementary instrument.[3]

I look forward to further research in this area, particularly studies that address the limitations and practical implications of appropriate feeding practices. I believe this article will spark important discussions among clinicians and researchers and to contribute to improving nutritional care for children.

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Author contribution

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Comment on dynamic plasma biomarker trajectories in pediatric sepsis

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Dear Editor,

The study by Tian et al. on the prognostic value of dynamic plasma biomarker trajectories in pediatric sepsis was read with great interest.[1] The prospective design and the use of systematic serial measurements are clear strengths of the study. At the same time, it is believed that several aspects related to the study population, analytical strategy, and biological framework merit further consideration in order to better place the findings within a clinical context.

First, the study population primarily consists of children with early-recognized, mild-to-moderate sepsis. Low Pediatric Sequential Organ Failure Assessment Score (pSOFA) scores at admission, infrequent intensive care unit admissions, limited need for invasive organ support, and the absence of mortality indicate that the cohort represents a relatively narrow severity spectrum.[1] This may limit the applicability of the findings to children with more severe forms of sepsis. In higher-acuity settings, factors such as delayed presentation, immune dysregulation, endothelial injury, and exposure to advanced organ support therapies are known to substantially influence biomarker behavior and its prognostic meaning.[2,3] From this perspective, the high discriminative performance reported for the proposed two-step algorithm should be interpreted cautiously, as it may partly reflect derivation from a low-risk and relatively homogeneous population.

Second, the model focuses exclusively on inflammatory and coagulation biomarkers, resulting in a somewhat limited biological scope. Increasing evidence suggests that pediatric sepsis is a heterogeneous condition involving not only inflammation but also metabolic failure, endothelial dysfunction, and immune exhaustion.[3,4] In more severe clinical phenotypes, traditional inflammatory markers may lose discriminatory capacity. Incorporating biomarkers that reflect additional pathophysiological pathways could therefore improve the clinical relevance and robustness of the proposed approach.

Finally, although the authors emphasize the prognostic significance of serial declines in biomarker levels, the analyses presented are primarily associative. In clinical environments with early recognition and standardized sepsis management, reductions in inflammatory biomarkers may simply parallel clinical improvement rather than serve as independent predictors of outcome. This raises questions regarding the directionality of the observed associations between biomarker trajectories and clinical endpoints.[2,5] Furthermore, the lack of analyses demonstrating incremental prognostic value beyond established clinical variables and

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severity scores makes it difficult to determine whether serial biomarker measurements meaningfully influence bedside decision-making.[5]

In summary, Tian et al.[1] provide valuable descriptive insights into biomarker kinetics in pediatric sepsis. However, interpretation of the proposed algorithm should consider the study's methodological and biological constraints. The restricted severity range of the cohort, the largely associative analytical approach, and the limited breadth of the biomarker panel may temper the generalizability and clinical impact of the findings. Future studies that include broader and more severe patient populations, rigorously assess the added prognostic value of biomarker kinetics beyond clinical evaluation, and integrate complementary biomarker domains may further advance both understanding and clinical application in this complex area.

Author contribution

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CASE REPORTS

LETTERS TO THE EDITOR

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