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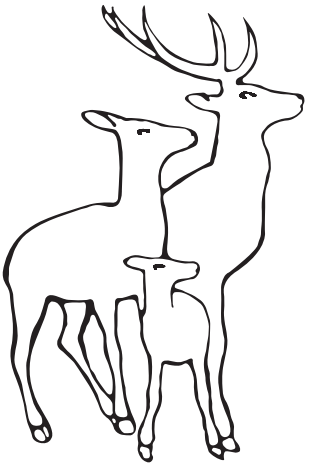

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Review

Chronic nonbacterial osteomyelitis: current perspectives in pediatric practice

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ABSTRACT

Chronic nonbacterial osteomyelitis (CNO) is a rare, autoinflammatory bone disorder that predominantly affects children and adolescents. The disease covers a broad clinical spectrum ranging from isolated bone lesions to its severe multifocal form, chronic recurrent multifocal osteomyelitis (CRMO). Although its exact pathogenesis remains elusive, recent advances highlight a pivotal role of innate immune dysregulation, particularly involving imbalanced cytokine signaling. These abnormalities drive sterile bone inflammation and osteoclast activation, leading to bone pain and lytic or sclerotic lesions. CNO remains a diagnosis of exclusion owing to the lack of specific biomarkers or standardized diagnostic criteria; however, the recently developed European Alliance of Associations for Rheumatology/American College of Rheumatology (EULAR/ACR) classification framework represents an important step toward uniformity in research and clinical trials. Whole-body magnetic resonance imaging has emerged as the imaging modality of choice for diagnosis and monitoring, while biopsy is reserved for atypical or unifocal cases. Management is empirical and guided by disease severity, with nonsteroidal anti-inflammatory drugs as first-line therapy, followed by corticosteroids, disease-modifying antirheumatic drugs, bisphosphonates, and biologic agents such as tumor necrosis factor (TNF) inhibitors in refractory cases. New insights into the interleukin (IL)-1, IL-6, and IL-17/23 pathways have opened avenues for targeted therapies, including Janus kinase (JAK) inhibitors, in difficult-to-treat patients. Despite earlier perceptions of a benign course, long-term follow-up indicates a risk of relapses and structural complications, underscoring the need for early recognition and multidisciplinary management. Ongoing international collaborations are expected to refine diagnostic precision and optimize treatment strategies to improve outcomes in pediatric CNO.

Key words: autoinflammatory bone disease, child, chronic nonbacterial osteomyelitis, recurrent osteomyelitis, pediatric rheumatology.

Chronic non-bacterial osteomyelitis (CNO) or chronic recurrent multifocal osteomyelitis (CRMO) is a noninfectious auto-inflammatory bone disease mainly affecting children.[1,2] It was first described by Gieldon et al. in 1972, as subacute and chronic 'symmetrical' osteomyelitis.[3,4] While CNO predominantly occurs in children and adolescents, cases have been reported in all age groups. The disease expresses a wide clinical spectrum that extends from isolated asymptomatic bone lesions to its most severe multifocal presentation, CRMO, a designation introduced by Björkstén et al. in 1978.[3,5] Although it has been classified in various ways over time, the term CNO is now widely used according to the most recent nomenclature.[6-8]

To date, CNO remains still a poorly defined and heterogeneous condition. It is regarded as a diagnosis of exclusion, given the absence of standardized accepted diagnostic criteria and

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validated biomarkers.[9] Although the precise etiology remains unknown, accumulating evidence supports the central role of innate immune dysregulation and cytokine imbalance in disease pathogenesis.[1] The complex and unpredictable behavior of CNO poses ongoing challenges in diagnosis, management, and long-term care for both patients and physicians. Delayed or missed diagnoses are common and are often related to limited awareness of the disease and the fluctuating pain patterns it produces. Many patients are evaluated by multiple clinicians before reaching a definitive diagnosis, and these delays frequently lead to unnecessary or prolonged antibiotic treatments, excessive radiation exposure due to repeated imaging studies, and even multiple bone biopsies prior to establishing the correct diagnosis.[10-12]

In this review, we aim to summarize the current knowledge on CNO, to provide a practical approach for diagnosis and differential diagnosis in children, and to highlight recent advances in disease management.

Epidemiology

Although the true epidemiological data may remain uncertain due to the insidious nature of the disease and limited awareness, the incidence has been estimated in several reports to range between 0.4 and 2.3 per million.[7,13-15] A large cohort study from Germany comparing CNO and bacterial osteomyelitis (BOM) demonstrated that the incidence of CNO is likely underestimated and may be close to that of BOM.[16]

The average age at onset of pediatric CNO is between 7-12 years, with a modest predominance among females (female/male 1.5:1 to 4:1 in different series). While CNO appears to be reported more frequently in Western populations, especially in Europe and North America, cases have been documented in individuals of all racial and ethnic backgrounds.[14,17] The female predominance observed in CNO contrasts with infectious osteomyelitis, which is more frequent in males.[15,17-21] In contrast to the female predominance generally reported in the literature, a national Turkish cohort of 334 pediatric patients demonstrated a male predominance (56.3%) (in press; unpublished data). Consistently, three independent studies from Türkiye reported comparable male proportions (~53–56%).[22-24]

CNO can occur at any age, however disease onset before the age of two years should raise suspicion for a monogenic autoinflammatory condition such as Majeed syndrome or deficiency of the interleukin-1 receptor antagonist (DIRA).[8]

Pathophysiology and Genetics

The exact molecular pathogenic mechanism of CNO is poorly understood. However, recent advances in both genetic and molecular research have provided new insights into its underlying pathways. While a detailed discussion of the pathophysiology is beyond the scope of this review, a brief overview of the main mechanisms will be provided.

CNO is now recognized as an autoinflammatory bone disorders in which dysregulation of the innate immune system plays a central role. Studies have demonstrated dysregulated activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome, leading to an imbalance between pro- and anti-inflammatory cytokines; characterized by elevated levels of interleukin (IL)-1β, IL-6, and Tumor necrosis factor alpha (TNF-α), accompanied by a relative deficiency of IL-10.[25,26] This imbalance promotes recruitment of monocytes and neutrophils to the bone marrow, resulting in sterile inflammation and increased osteoclast activity.[8]

Findings from both human transcriptomic analyses and experimental models with *PSTPIP1* mutations suggest a persistent pro-osteoclastogenic environment that interferes with normal bone homeostasis and resolution

of inflammation.[27] Among the key mechanisms implicated, the receptor activator of nuclear factor-κB (RANK), its ligand (RANKL), and osteoprotegerin (OPG) axis has gained attention for its role in osteoclast differentiation and survival. Overexpression of RANKL or insufficient production of OPG enhances osteoclastogenesis and bone resorption, which may explain the characteristic osteolytic lesions observed in CNO.[25] This was demonstrated in an adult CNO study, supporting the role of osteoclast dysregulation in disease pathogenesis.[1,28]

In parallel, recent genomic studies have identified *P2RX7* variants that amplify inflammasome signaling and Filamin-binding LIM Protein 1 (*FBLIM1*) mutations that weaken IL-10-mediated regulatory feedback.[1,29,30] Together, these alterations link genetic susceptibility with innate immune hyperreactivity, creating recurrent cycles of inflammation, bone resorption, and repair that mimic bacterial osteomyelitis but occur in the absence of infection.[8]

Monogenic forms of CNO

A small subset of patients, particularly those presenting in infancy or with systemic features, may have monogenic autoinflammatory bone diseases. The best-known examples are Majeed syndrome (*LPIN2* variants) and DIRA (*IL1RN* variants) and pyogenic arthritis, pyoderma gangrenosum and acne syndrome, PAPA (*PSTPIP1* variants).[1,29] These disorders involve uncontrolled IL-1–mediated inflammation and typically present as severe, early-onset, and recurrent forms of osteomyelitis. Recognition of these entities is essential, as they may require targeted therapy aimed at IL-1 and TNF-α blockade rather than conventional anti-inflammatory regimens.[29]

Clinical Presentations

The cardinal feature of CNO is recurrent bone pain of insidious onset. CNO usually begins with a slow and subtle onset of recurring bone pain, tenderness, or localized swelling that may involve one or several sites of sterile inflammation. The clinical picture is highly variable; some patients experience isolated, short-lived disease, while others develop multiple or relapsing foci that can persist for years.[15] The pain often intensifies during nighttime and may cause limping or reduced mobility when weight-bearing bones are affected and mostly improves with nonsteroidal anti-inflammatory drug (NSAID) therapy.[31,32] The absence of infection or malignancy, combined with the waxing and waning pattern of symptoms, frequently contributes to diagnostic delay. Tenderness, swelling, and increased warmth may be observed over the affected bone; on the other hand, these findings may be absent depending on the thickness of the surrounding soft tissue.[18] Delays in diagnosis are common, as early, non-specific symptoms are frequently mistaken for benign conditions such as growing pains. Without appropriate treatment, CNO typically follows a prolonged, fluctuating course characterized by alternating phases of remission and relapse.[29,33]

Systemic features such as fever, malaise, fatigue, and weight loss are observed in about 15–20% of patients, yet most children with CNO remain clinically well except for symptoms related to bone pain[14,34] Inflammation can occur at any site of the skeleton; however, the metaphyseal regions of the long bones, clavicle, vertebral bodies, and pelvis are the most commonly involved sites.[35] Long bones of the lower extremities are affected about three times more often than those of the upper limbs, with the distal femur and proximal tibia being the most common sites. Other characteristic localizations include the clavicle, vertebrae, pelvis, and mandible. Involvement of the medial third of the clavicle is considered highly typical for CNO.[27,32] Lesions of the epiphysis or diaphysis may accompany metaphyseal lesions, but isolated epiphyseal or diaphyseal involvement without metaphyseal changes is uncommon. Spontaneous improvement can be observed in some cases.[36] Nearly 85% of cases present

with multifocal lesions, and the involvement is symmetrical in 25–40% of patients.[37] Although vertebral lesions occur less frequently, they are clinically significant because of potential complications such as fracture, spinal cord compression, kyphosis, or scoliosis. CNO tends to involve the thoracic vertebrae, and the preservation of intervertebral discs helps distinguish it from other conditions associated with vertebral destruction.[11,35,38] Pelvic lesions may occasionally present as unilateral sacroiliitis, while the small bones of the hands and feet are affected less commonly.[32,39]

Localized swelling of the soft tissue adjacent to the affected bone may sometimes mimic arthritis. However, in some series, arthritis has been reported in up to 40% of patients with CNO. It may occur adjacent to the bone lesion (60%) or at distant sites (40%), which can make it difficult to distinguish CNO from juvenile idiopathic arthritis (JIA).[6,16,34]

Extraosseous manifestations and associated inflammatory conditions

CNO can occur in association with other inflammatory conditions, and a positive family history of inflammatory or autoinflammatory diseases is common. Studies have shown that approximately 20% of patients have concomitant chronic inflammatory disorders such as JIA, spondyloarthropathies, inflammatory bowel disease (IBD), pyoderma gangrenosum, familial Mediterranean fever (FMF), and SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis).[1,16] Reported frequencies include inflammatory arthritis (10–41%), palmoplantar pustulosis (7–14%), psoriasis (4–22%), inflammatory bowel disease (4–22%), acne (4–22%), and FMF (approximately 10%) (Fig. 1).[1,16,40-42] The overlap between CNO and SAPHO syndrome has prompted some authors to suggest that CNO may represent a pediatric counterpart of SAPHO.[30] However, the typical anatomical sites of involvement differ between the two conditions. Patients with CNO who have concomitant inflammatory disorders may exhibit a more severe clinical phenotype. Therefore, in cases with an aggressive or refractory disease course, clinicians should carefully consider and screen for concomitant inflammatory or autoinflammatory diseases.[17,41,43]

Laboratory and Histopathological Findings

Routine laboratory tests usually provide non-specific findings, yet they remain essential for excluding alternative or secondary causes.[29] The initial diagnostic work-up in patients with suspected CNO typically includes basic laboratory tests — complete blood count (CBC), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) — as well as imaging studies and, when necessary, bone biopsy. Although these investigations are rarely diagnostic, they are useful in ruling out infection, malignancy, or metabolic bone disease[35] (Table I and Fig. 2).

CBC findings are usually within normal limits. A mild elevation in white blood cell count may occasionally be observed, whereas cytopenia is uncommon and should prompt evaluation for possible hematologic malignancy.[32] Mild elevations in inflammatory markers such as CRP and ESR are reported in nearly half of the patients, with frequencies ranging between

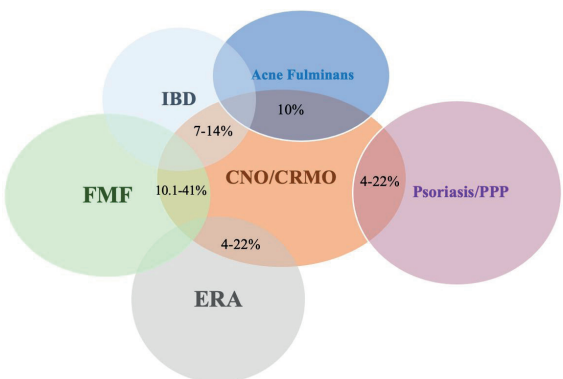

Fig. 1. Inflammatory disorders associated with CNO. (Figure modified after references 1 and 40)

CNO/CRMO: Chronic nonbacterial osteomyelitis / Chronic recurrent multifocal osteomyelitis, ERA: Enthesitis-related arthritis, FMF: Familial Mediterranean fever, IBD: Inflammatory bowel disease, PPP: Palmoplantar pustulosis.

Table I. Clues for differential diagnosis in chronic nonbacterial osteomyelitis*

Category	Red flag findings	Possible alternative diagnoses
Age onset	Onset <2 years	Monogenic AIDs
Symptoms and physical examination	High-grade fever, marked malaise, weight loss, night sweats, severe pain (can't bear weight, unable to walk), HSM, LAP	Bacterial osteomyelitis, malignancy, other inflammatory disorders and infections
Laboratory	Very high CRP or ESR, cytopenia, markedly elevated LDH or uric acid, low alkaline phosphatase, low phosphate, vitamin C deficiency	Infection, leukemia, lymphoma, hypophosphatasia, scurvy
Imaging	Solitary lesion, cortical destruction with periosteal reaction, soft tissue mass, or lack of multifocality,	Malignancy, bacterial osteomyelitis, scurvy
	localization at skull and diaphysis	
	periosteal elevation with subperiosteal hemorrhage	
Histopathology	Presence of atypical cells, granulomatous inflammation, or necrosis	Malignancy, infection, histiocytosis
Response to therapy	Absence of response to NSAIDs/anti-inflammatory treatments	Infection, neoplasm, metabolic bone disease

*May be incomplete.
AIDs: autoinflammatory diseases, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, HSM: hepatosplenomegaly, LAP: lymphadenopathy, LDH: Lactate dehydrogenase, NSAIDs: nonsteroidal anti-inflammatory drugs

49% and 80%. Markedly increased values (for example, threefold above the upper limit of normal) should raise suspicion for other underlying conditions.[29,44] Autoantibodies, including antinuclear antibodies (ANA) and HLA-B27, may rarely be detected in some individuals, but these lack diagnostic specificity.[16-18,29,37,45-47] Other useful laboratory tests are primarily aimed at differential diagnosis: lactate dehydrogenase (LDH) and uric acid for malignancies, alkaline phosphatase for hypophosphatasia, and vitamin C levels for scurvy. In CNO, these parameters are usually within normal limits. Since no serologic marker is disease-specific or reliable for monitoring, laboratory results should always be interpreted alongside the clinical and imaging context.[43]

Recent investigations have identified elevated levels of several cytokines and chemokines in CNO, such as TNF-α, IL-6, IL-12, monocyte chemoattractant protein-1 (MCP-1), C-C motif ligand 11 (CCL11), CCL5, collagen 1α, and the soluble IL-2 receptor (sIL-2R).[37,48,49] These mediators may eventually aid in distinguishing CNO from infectious or malignant mimickers and in assessing inflammatory activity. However, current evidence is preliminary and requires confirmation in larger, ethnically diverse cohorts using standardized analytic methods.[43] In addition, urinary N-telopeptide has been proposed as a possible biomarker of disease flares in patients receiving bisphosphonate therapy, but this observation also awaits independent validation.[50]

A bone biopsy may be warranted to exclude infection or malignancy, particularly in unifocal disease, atypical lesion sites, very early onset (< 2 years of age), or unexpected progression despite treatment.[1,35,51] When indicated, sampling should target the most active or symptomatic bone lesion. Histopathological findings in CNO/CRMO are not pathognomonic but rather demonstrate features of chronic inflammation.[27] Typical observations include bone marrow edema, vascular congestion, lymphoplasmacytic infiltration, and varying degrees of fibrosis or sclerosis. In long-standing lesions, osteonecrosis may occur, whereas biopsies from inactive sites may appear normal. Although non-specific, these features help confirm an inflammatory process and exclude other etiologies.[10,13,35,52,53]

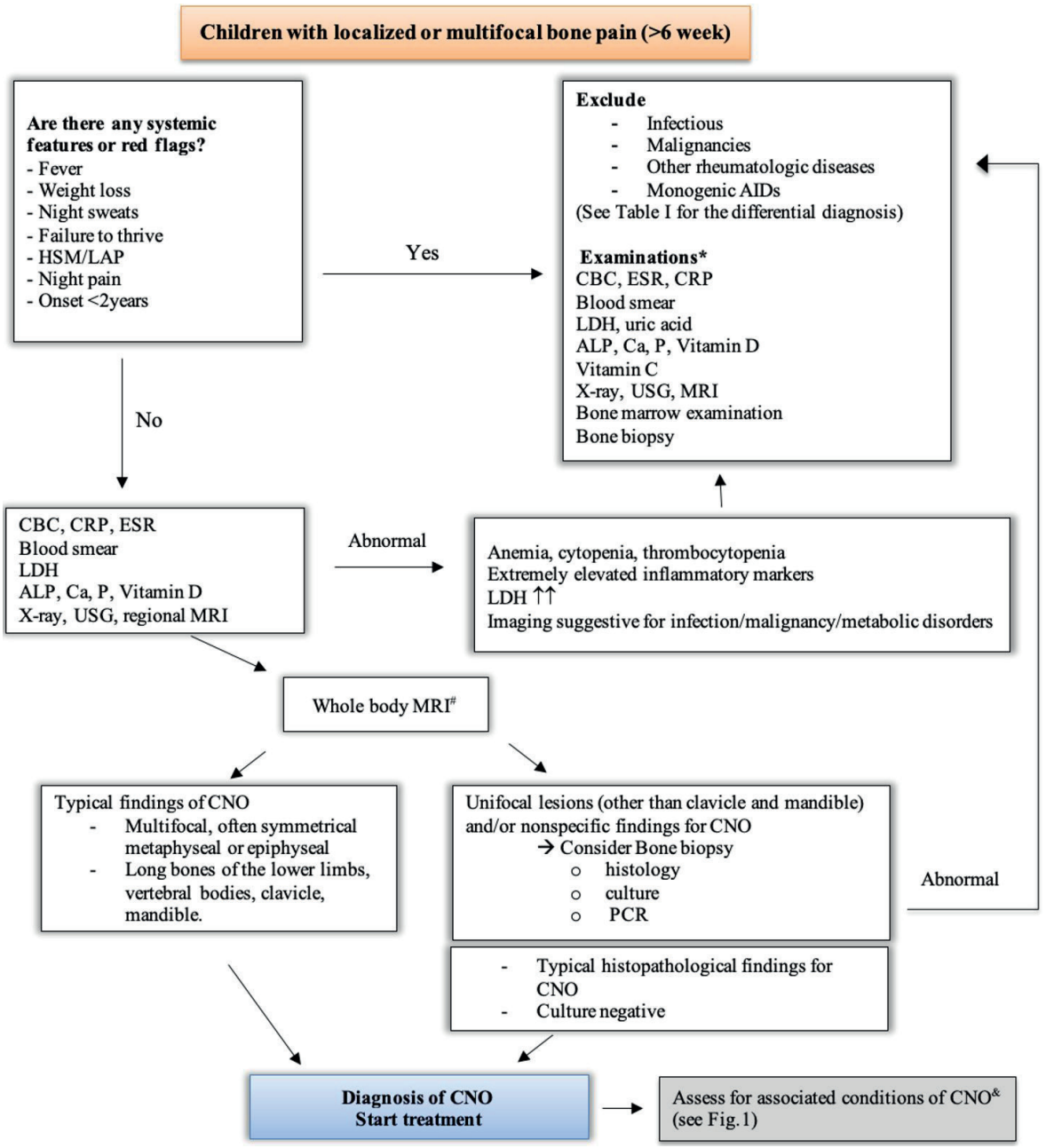

Fig. 2. Diagnostic approach to bone pain in children.

(Modified after references 13 and 35)

*Diagnostic tests should be performed and interpreted stepwise, based on clinical indication

#Gold standard for diagnostic imaging in CNO

&CNO is associated with psoriasis, PPP, acne, IBD, spondyloarthropathy/ERA and FMF

AID, auto-inflammatory disease; ALP, alkaline phosphatase; CBC, complete blood count; CNO, chronic nonbacterial osteomyelitis; CRP, C-reactive protein; ERA, enthesitis related arthritis; ESR, erythrocyte sedimentation rate; FMF, familial Mediterranean fever; GIS, gastrointestinal system; HSM, hepatosplenomegaly; IBD, inflammatory bowel disease; LAP, lymphadenopathy; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PPP, palmoplantar pustulosis; P, phosphate; PCR, polymerase chain reaction; USG, ultrasonography.

Radiologic Imaging in CNO

Imaging approach

CNO generally presents with non-specific clinical signs and/or laboratory tests, which underscores the importance of imaging techniques. Radiographs may reveal diagnostic or suspicious findings for CNO or may be unremarkable. The subsequent approach should involve either targeted or whole-body magnetic resonance imaging (WB-MRI). Presently, MRI has become the primary imaging modality for diagnosing CNO, monitoring treatment effectiveness and follow-up. In addition, WB-MRI may be crucial in treatment decisions with its capability to show disease burden including asymptomatic foci of osteitis.[11,54] Computed tomography (CT) has limited use due to radiation exposure and its inability to effectively demonstrate bone marrow lesions. However, in certain anatomical regions, including the pelvis, scapula, and spine, CT is superior to both radiographs and MRI in demonstrating CNO-related osteosclerosis.[33]

Lesion characteristics in imaging

Radiographs and CT

Radiographs and CT reveal round or ovoid osteolytic bone lesions centered at physeal lines which extend to both epiphysis and metaphysis of long bones (Fig. 3a). Sclerotic changes develop subsequently, progressing to hyperostosis and bony expansion, accompanied by a smooth or lamellated periosteal reaction in persistent chronic lesions (Fig. 3b). However, radiographic findings may be occult or normal at the early or healing phases of the disease.[11,33]

In addition to the initial work-up, radiographs are essential for follow-up of complications. Due to physitis, early physeal closure may occur through the formation of a physeal bridge or bar. Radiographs can demonstrate the characteristic "physeal tongue," which appears as a lytic or sclerotic tubular structure extending toward the metaphysis. Another point in follow-up imaging is treatment associated findings in patients who were treated with cyclic bisphosphonates (e.g., pamidronate), including fine sclerotic lines in the metaphysis known as zebra stripes, resulting from inhibited osteoclast activity.[39]

Magnetic resonance imaging

Whether focused or encompassing the whole body, CNO presents several unique characteristics on MRI. The hallmark of CNO on MRI is physitis related periphyseal osteitis that appears as hyperintense foci on fluid sensitive sequences (STIR or T2-weighted fat-saturated) and hypointense foci on T1-weighted images (Fig. 3c). Periosteal reaction, surrounding soft tissue edema and reactive synovitis may accompany the osteitis (Fig. 3d).[54] Lesions more commonly locate at the metaphysis or epi-/apophysis of a long bone (Fig. 3c). Diaphyseal involvement is less common (Fig. 3e). In flat and round bones, lesions affect the epi- or metaphyseal-equivalent regions of each bone that are in close proximity to the growth plates (i.e., apophyses of the iliac bones, endplates of the vertebrae, bones surrounding sacroiliac joints, Y-cartilage, ischiopubic synchondrosis) (Fig. 3f, 3g).[11,54] Pelvic bones including the proximal femurs and sacroiliac joints are the most commonly involved regions across the body. Long bones of the lower extremity (lower legs and feet > bones around the knee), upper extremities, and vertebral bodies are other sites that are usually involved in descending order. The clavicle, sternum, scapula, and mandible are other involved body parts (Fig. 3h).[39] In the spine, the thoracic and sacral vertebrae are the most commonly involved sites and osteitis is usually located focally at the superior endplate of the vertebra.[39,55] More importantly, the spine is the commonest site of pathological fracture in CNO and as high as half of cases with spinal disease resulted in vertebral deformities such as vertebra plana or scoliosis (Fig. 3f). [33]

After treatment, osteitis foci may fully resolve or heal with sclerosis. Vertebral height loss may persist without osteitis as a marker of previous disease. A diagnostic pitfall after

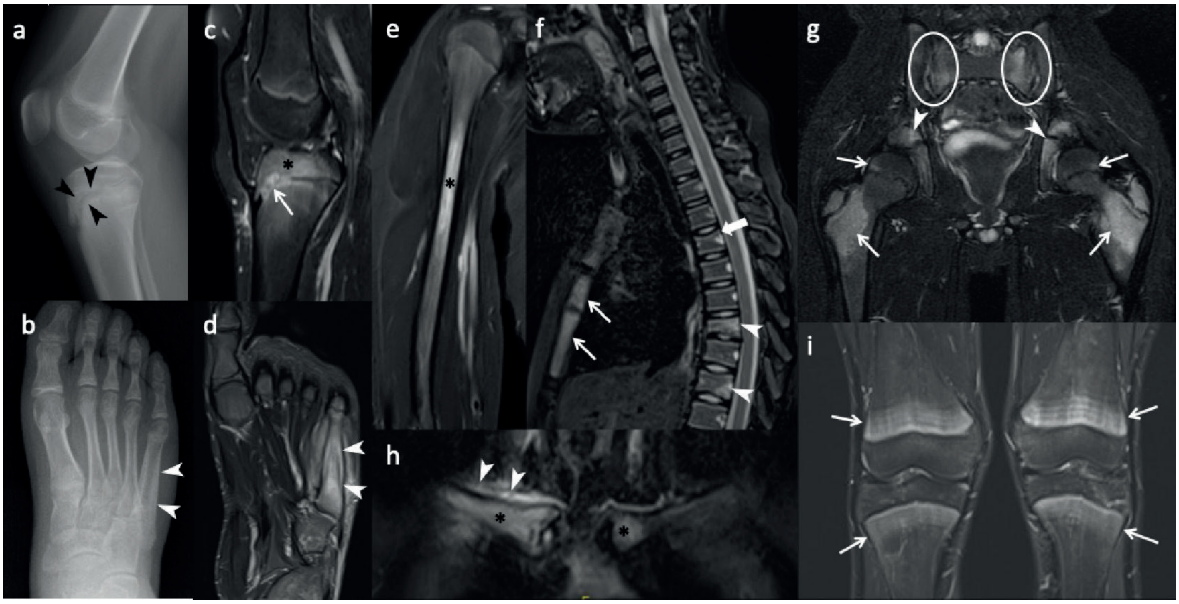

Fig. 3. Imaging findings of CNO patients. **(a)** Lateral view radiograph of the left knee in an 11-year-old girl reveals physeal enlargement with periphyseal sclerosis (arrowheads) consistent with physitis. **(b)** AP radiograph of the left foot in a 13-year-old boy shows diffuse solid periosteal reaction at the fifth metatarsal indicating the chronic phase of CNO (arrowheads). **(c)** Sagittal STIR image of knee obtained 15 days after radiograph of the same patient in a, shows hallmark lesion of CNO, physitis (arrow) and periphyseal osteitis (asterisk). **(d)** Axial STIR image of the foot two months before the same patient in image (b) shows diffuse fifth metatarsal osteitis (arrowheads) with smooth periosteal reaction and surrounding soft tissue edema. **(e)** Sagittal STIR image of humerus in a 13-year-old boy demonstrates diffuse diaphyseal osteitis (arrow) which is a rare type of involvement. **(f)** Sagittal STIR image of spine in a 11-year-old girl reveals foci of osteitis at T7 and T9 vertebrae (arrowheads) with a pathological fracture at the inferior endplate of T7 vertebra. Note the mild compression fracture at the superior end plate of T4 vertebra without osteitis indicating a sequel of a previous osteitis (thick arrow) and sternal osteitis surrounding synchondrosis (arrows). Nodular hyperintensities located at the midpoint of the posterior vertebrae are the entry sites of posterior internal vertebral venous plexus. **(g)** Coronal STIR image of pelvis in an 11-year-old boy shows typical periphyseal osteitis located at major trochanters, femoral heads (arrows) and surrounding triradiate cartilage (arrowheads) and sacroiliac joints consisted with sacroiliitis (circles), the latter two are anatomically metaphyseal-equivalent regions. **(h)** Coronal STIR image of a 13-year-old girl reveals clavicular involvement characterized by osteitis (asterisks) and periosteal (arrowheads) and soft tissue edema which is prominent on the right side. **(i)** Coronal STIR image of both knees in a 14-year-old boy who was treated with pamidronate shows a drug induced imaging pitfall as symmetrical metaphyseal bright bands (arrows) which have abrupt demarcation and include zebra stripes.

CNO, chronic nonbacterial osteomyelitis; STIR, short tau inversion recovery.

bisphosphonate treatment is the presence of bilateral symmetric bright metaphyseal bands on STIR. These high-signal bands can mimic disease relapse, and their abrupt demarcation in relation to the adjacent metadiaphysis can be a key feature for differentiating them from true osteitis (Fig. 3i).[54]

CNO mimickers

Normal variants of bone marrow, such as red marrow in the metaphysis during childhood and residual red bone marrow foci in the feet, should not be misinterpreted as osteitis (Fig. 4d). Focal periphyseal edema (FOPE) is another incidental finding located around the physis

during the physeal closure period (Fig. 4a). Bone contusions, physeal stress injuries, stress fractures, or reactions may result in or associated with osteitis, but history of trauma—either acute or chronic—and the location of these lesions can help differentiate them from CNO (Fig. 4b, 4c). Hematogenous osteomyelitis can also mimic osteitis in CNO, but in addition to the patient's history, physical examination, and laboratory findings, the presence of an abscess inside the bone and surrounding soft tissue, heterogeneous enhancement of bone marrow, and localized disease (as opposed to multifocal lesions) can aid in differentiation between these two entities (Fig. 4d, 4e). Neoplastic, infiltrative, or metastatic bone lesions, such as Ewing sarcoma, Langerhans cell histiocytosis, and leukemia, can pose diagnostic challenges; however, factors such as the patient's age, the presence of an extraosseous solid soft tissue component of the tumor, abrupt lesion contour, and lesion location and shape are key features to consider when evaluating these pathologies (Fig. 4f–h). Scurvy, as a metabolic condition,

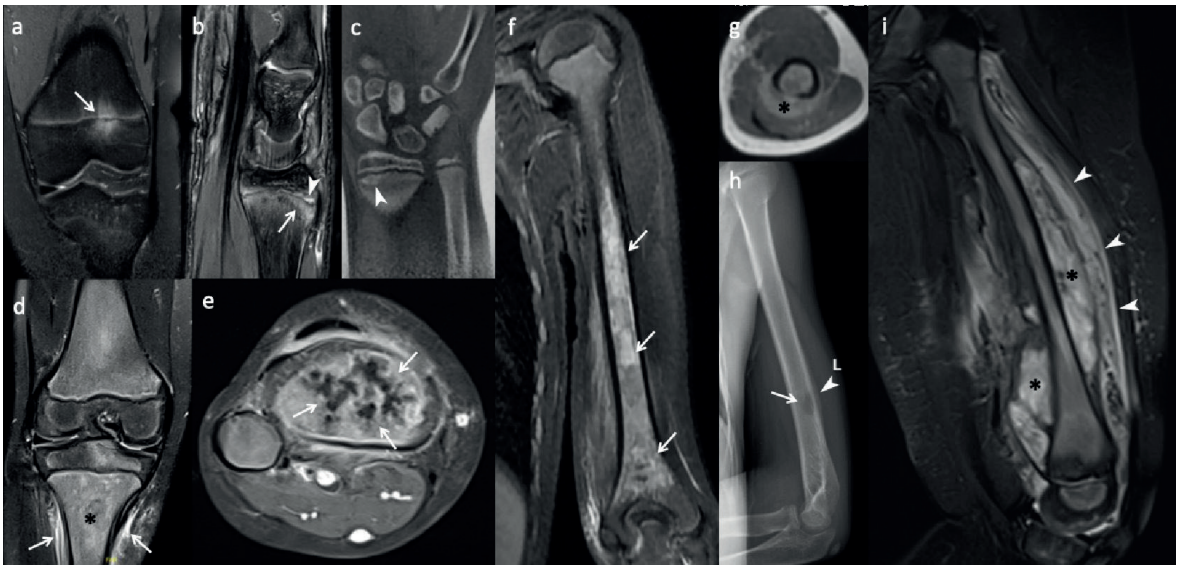

Fig. 4. CNO mimicker lesions of bones. **(a)** Coronal PD weighted fat-saturated image of a 13-year-old girl who is suffering from pain, shows focal periphyseal edema (FOPE) located at the distal femur (arrow). **(b)** Sagittal T2W fat-saturated MR image and **(c)** coronal ZTE sequence (CT-like image) reveal focal physeal enlargement of the distal radius at the dorsal side which is surrounded by osteitis consistent with physeal injury (type 1 Salter-Harris injury) in a gymnast. **(d)** Coronal PD weighted fat-saturated and **(e)** axial post-contrast T1W fat-saturated MR images of a 6-year-old girl who is suffering from pain at her right knee and has fever, show heterogeneous medullary signal intensities (asterisk) of proximal tibia metaphysis which also enhance heterogeneously (e, arrows), accompanied by periosteal reaction (d, arrows). Findings are consistent with osteomyelitis. In joint fluid and blood cultures methicillin-resistant *Staphylococcus aureus* (MRSA) has been isolated. Note the normal homogeneous medullary hyperintensity at the distal femur related to red bone marrow (d). **(f)** Coronal T2W fat-saturated and **(g)** axial post-contrast T1W fat-saturated images of the humerus in a 10-year-old boy reveal diametaphyseal heterogeneous hyperintense medullary lesion (f, arrows) and solid enhancing component (asterisk) with cortical destruction consistent with neoplasia, pathological diagnosis is Langerhans cell histiocytosis. **(h)** Lateral view humerus radiograph of the same patient shows focal lytic lesion (arrow) with wide zone transition at its superior border and periosteal reaction (arrowhead). **(i)** Coronal T2W fat-saturated MR image of a 3-year-old boy who is suffering from leg pain, hypertrophy and bleeding of the gingiva due to vitamin C deficiency demonstrates diffuse diametaphyseal osteitis-like hyperintensity accompanied by subperiosteal hemorrhage (asterisks) surrounded by soft tissue edema (arrowheads).

CNO, chronic nonbacterial osteomyelitis; CT, computed tomography; MR, magnetic resonance; PD, proton density; T2W, T2-weighted; ZTE, zero echo time.

is another mimicker that presents with metaphyseal osteitis. However, subperiosteal hemorrhages are not seen in CNO (Fig. 4i).[33,54]

Diagnosis and Classification Criteria

Diagnosis is challenging and typically relies on excluding other potential conditions. It is traditionally established through a combination of clinical evaluation, radiologic findings, histologic examination, and characteristic signs and symptoms.[3] Differential diagnoses of CNO are summarized in Table I.

Until recently, the absence of validated classification criteria for CNO posed a major limitation in both research and clinical practice. Earlier attempts to define such criteria were derived from small, single-center cohorts and lacked external validation, which limited their applicability and use in multicenter studies. Classification frameworks, in contrast to diagnostic criteria, are essential to delineate homogeneous patient populations, support epidemiologic investigations, and ensure consistency in evaluating disease features and treatment responses.[13] Two independent sets of classification/diagnosis criteria for CNO/CRMO were previously proposed both based on retrospective analyses encompassing patients with diverse clinical presentations—ranging from isolated inflammatory bone lesions to multifocal and relapsing disease.[10,37] However, the small sample sizes and absence of systematic comparison with alternative diagnoses, except for bacterial osteomyelitis, restricted their reliability. Moreover, neither set underwent prospective validation in independent cohorts. Consequently, universally accepted and externally validated classification criteria for CNO remained unavailable.[11,13] To address this gap, an international collaborative effort between the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR) recently resulted in the development and validation of new pediatric CNO classification criteria (Table II).[56] These criteria incorporate a weighted scoring system that integrates clinical, imaging, and laboratory domains. They represent an important advance and are expected to facilitate consistency in research and clinical trial settings. However, it should be emphasized that classification frameworks are primarily designed for research standardization rather than for routine diagnosis. Consequently, some patients with clinically evident CNO may not fulfill the required threshold for classification.[11,57] Recently, we evaluated the validation of this newly proposed classification criteria in our own patient cohort. The EULAR/ACR classification criteria for pediatric CNO demonstrated high specificity (97.9%) and sensitivity (92.7%), confirming their robustness and clinical applicability.[57] Multifocal and symmetric bone lesions, especially those involving the clavicle and mandible, were strongly associated with fulfillment of these criteria. Validation within a pediatric cohort further underscores their value for standardized disease classification and consistency across research studies.[57]

Fig. 2. provides an overview of the diagnostic algorithm for patients with CNO.

Treatment

Despite significant progress in understanding its clinical and immunopathologic spectrum, a standardized therapeutic protocol for CNO has not yet been established. Current management strategies are largely empirical and guided by disease severity, lesion distribution, and response to previous therapies.[1,30] Recently, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) reviewed consensus treatment protocols aimed at standardizing therapeutic approaches and prospectively capturing real-world data on treatment outcomes.[29,51]

NSAIDs represent the initial treatment of choice in patients without vertebral lesions and may lead to remission in some individuals. Nevertheless, disease relapses occur in over

Table II. EULAR/ACR classification criteria for pediatric CNO.[56]

Step 1, Verify entry criteria (all should be present):
1. Bone pain and/or musculoskeletal functional limitation ≥6 weeks;
2. Age of onset <18 years old;
3. Abnormal findings from radiograph and/or advanced imaging including MRI, CT, bone scintigraphy at non-arthritic bone sites*

Step 2, Verify exclusion criteria (none should be present):
1. Confirmatory evidence of mutually exclusive mimicker diseases**;
2. Platelet <100,000/mm^3;
3. Pathological LDH concerning malignancy***;
4. Complete and sustained clinical and laboratory response to antimicrobial treatment alone.

Step 3, Add the score: Add the highest value in each of the 9 domains below.
A score ≥ 55 is required to classify a patient as CNO.

Criteria domains / levels	Score
Bone biopsy	
Signs of inflammation[#] AND fibrosis	17
Signs of fibrosis only	11
Signs of inflammation only	9
No signs of inflammation or fibrosis in bone biopsy	0
Age at the onset of symptoms	
≥ 3 years old	17
< 3 years old	0
Sites of bone lesions based on imaging	
Clavicle and/or mandible	16
Sites other than clavicle, mandible, skull, or hand	9
Skull or hand without clavicle or mandible	0
Distribution pattern of bone lesions based on imaging	
Multifocal lesions (in ≥ 2 bones) with symmetrical pattern (bilateral involvement of at least one bone)	9
Multifocal without any symmetrical pattern bone involvement	7
Unifocal without whole body imaging such as WBMRI, PET/CT performed	3
Unifocal with whole body imaging performed	0

CNO, chronic nonbacterial osteomyelitis; CT, computed tomography; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PET/CT: positron emission tomography/computed tomography; WBMRI: whole body MRI.
*Typical imaging findings include but are not limited to lytic, sclerotic lesions with or without periosteal reaction, hyperostosis on radiograph or CT, bone marrow edema or hyperintensity in a fluid-sensitive sequence of MRI. Non-arthritic bone sites refer to bones whose joint-forming ends do not demonstrate imaging signs of arthritis including synovial thickening, enhancement and/or moderate to large joint effusions.
**Includes but not limited to primary or metastatic malignancy in bone, leukemia, lymphoma, neuroblastoma, infectious osteomyelitis, metabolic bone disease, vitamin C deficiency, hypophosphatasia, and monogenic bone diseases including Majeed or deficiency of interleukin-1 receptor antagonist (DIRA).
***Due to difference in laboratory assays across institutions, no absolute threshold is defined. Levels ≥ 700 IU or > 2 times of the upper normal limit may be considered pathological.
[#]Defined as the presence of immune cells including neutrophils, monocytes, lymphocytes and/or plasma cells.
[&]Axial arthritis is defined as imaging confirmation of inflammation within the sacroiliac joint or intervertebral joint.
[$]Cutaneous conditions include psoriasis, palmoplantar pustulosis, pyoderma gangrenosum, acne fulminans, and hidradenitis suppurativa.

Table II. Continued.[56]

Criteria domains / levels	Score
Coexisting conditions prior to the diagnosis of CNO	
Inflammatory bowel disease (IBD)	9
Cutaneous condition[$] without IBD	8
Axial arthritis[&] without cutaneous condition or IBD	5
None	0
Hemoglobin (normal range varies by age)	
≥ 10 g/dL	8
< 10 g/dL	0
Fever (oral/temporal temperature above 38 °C and not related to common infections)	
Absence of fever	8
Presence of fever	0
Erythrocyte sedimentation rate (Normal range: 0-20 mm/hr)	
<60 mm/hr	8
≥ 60 mm/hr	0
C-reactive protein (Normal range: 0-10 mg/L)	
< 30 mg/L	8
≥ 30 mg/L	0

CNO, chronic nonbacterial osteomyelitis; CT, computed tomography; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PET/CT: positron emission tomography/computed tomography; WBMRI: whole body MRI.
*Typical imaging findings include but are not limited to lytic, sclerotic lesions with or without periosteal reaction, hyperostosis on radiograph or CT, bone marrow edema or hyperintensity in a fluid-sensitive sequence of MRI. Non-arthritic bone sites refer to bones whose joint-forming ends do not demonstrate imaging signs of arthritis including synovial thickening, enhancement and/or moderate to large joint effusions.
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[$]Cutaneous conditions include psoriasis, palmoplantar pustulosis, pyoderma gangrenosum, acne fulminans, and hidradenitis suppurativa.

50% of patients within two years of starting therapy.[11,16,29,46] For refractory or multifocal cases, glucocorticoids, disease-modifying antirheumatic drugs (DMARDs) such as sulfasalazine and methotrexate (MTX), biologic agents targeting TNF-α, and bisphosphonates have also been reported to be effective in the treatment of CNO.[2]

In patients with vertebral involvement or insufficient response to NSAID monotherapy, CARRA recommends three main categories of systemic treatment: (1) conventional synthetic DMARDs, (2) bisphosphonates, and (3) TNF inhibitors, which can be administered alone or in combination with MTX to reduce anti-drug antibody formation.[51]

Despite the lack of head-to-head comparative trials and universally accepted treatment algorithms, most rheumatologists favor bisphosphonate therapy—either as monotherapy or in combination with other DMARDs—particularly in children with spinal involvement.[25,29,50,58,59] In addition, CARRA suggests that a short course of systemic glucocorticoids (up to six weeks) may be used

to manage acute disease flares alongside these systemic agents.[51]

Emerging biologic and targeted therapies, including IL-1 and IL-6 inhibitors, are currently under investigation for refractory cases and for monogenic autoinflammatory bone diseases. However, contrary to expectations, variable treatment responses have been reported in the literature with these drugs.[60,61] The limited efficacy observed may be attributed to pathophysiological heterogeneity and tissue-level differences in therapeutic response[1,30]

IL-17/IL-23 also are potential therapeutic targets for CNO. The Janus kinase (JAK) signaling pathway has emerged as a key regulator of innate and adaptive immune responses, orchestrating cytokine-mediated inflammation. Pharmacologic inhibition of JAKs has been shown to modulate the production of proinflammatory cytokines such as IL-6, IL-17, and IL-23.[30] Biologic agents targeting the IL-17 pathway, such as secukinumab, have been administered to patients with SAPHO syndrome, largely owing to their proven efficacy in psoriasis.[11,62,63] Nevertheless, further studies are required to establish their safety profile and clinical efficacy in this population.[11]

Prognosis and Outcome

CNO typically follows a relapsing–remitting course. Although outcomes vary among studies, the overall consensus is that CNO is not as benign as previously believed. With longer follow-up durations, patients initially thought to be in remission may experience disease flares.[17,18,43]

In a cohort of 178 patients followed for an average of four years, 57% remained non-remissive, and 26% developed permanent sequelae.[17] While in many cases the disease progresses initially and later subsides without lasting disability, several studies have documented persistent or severe disease courses in a subset of patients. Reported long-term complications include vertebral collapse or fracture leading to kyphosis, scoliosis, or neurological impairment; limb-length discrepancies secondary to growth plate involvement; extremity deformities (varus/valgus); recurrent clavicular lesions resulting in thoracic outlet syndrome; and mandibular involvement causing malocclusion or masticatory dysfunction.[7,18,43,51,53]

Long-term follow-up studies suggest that disease activity can persist for several years in a subset of patients. A longitudinal study in adults with CNO reported disease recurrence as late as 15 years after onset, emphasizing the importance of sustained follow-up and a coordinated transition to adult rheumatology care.[35,52]

Conclusion

CNO is an autoinflammatory bone disorder characterized by dysregulated cytokine activity. Clinical manifestations range from mild, localized pain to multifocal skeletal involvement. WB-MRI remains the gold standard for diagnosis and follow-up, yet CNO continues to be regarded as a diagnosis of exclusion owing to the absence of specific biomarkers. Early recognition is crucial to prevent complications such as vertebral fractures and chronic pain. Recent consensus treatment plans and translational research have improved understanding of disease pathophysiology, but further studies are needed to validate biomarkers for early diagnosis and differentiation from mimicking conditions, as well as long-term prognosis, and to refine long-term management strategies.

Author contribution

The authors confirm contribution to the paper as follows: Review conception and design: ÖB, AEY, YB, SO; literature review: ÖB, AEY; draft manuscript preparation: ÖB, AEY, YB, SO. 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

Full-text publication outcomes of oral abstracts presented at the Turkish National Pediatric Congresses

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ABSTRACT

Background. Scientific congresses are critical platforms for knowledge dissemination and collaboration. The scientific value of presented abstracts is best demonstrated through their subsequent publication as full-text articles in peer-reviewed journals. This study aimed to evaluate the publication rate and characteristics of oral abstracts presented at the Turkish National Pediatric Congresses (TNPC) between 2019 and 2023.

Methods. Abstract books of five consecutive congresses were reviewed. The publication status of each abstract was determined through systematic searches in Web of Science, PubMed, Scopus, Google Scholar and the TR Index utilizing the title, keywords from the title and author names. Parameters such as study design, collaboration type, index status and the impact factor of the journal, the year it was published, and time to publication were analyzed. Additionally, the subspecialty of each abstract and the publication rate for each subspecialty were evaluated.

Results. Among 268 oral abstracts, 111 (41.8%) were published as full-text articles. Of these, 66 (59.5%) were published in journals indexed in the Science Citation Index Expanded. Approximately one-third (32.4%) of the articles were published in Q1 or Q2 ranked journals. The average impact factor was 1.72 ± 1.26 and the mean time to publication was 1.6 ± 1.17 years. The most common study design published was retrospective (51.3%), and the majority were single-center studies (88.3%). The highest publication rates were observed in the fields of rheumatology, adolescent medicine, and infectious diseases.

Conclusion. A significant portion of the papers presented at TNPC congresses are published in peer-reviewed scientific journals. The fact that more than one-third of the published studies appear in high-impact journals demonstrates the academic quality of the papers presented at the congresses and the effectiveness of the selective evaluation process. The findings provide valuable contributions to the monitoring and development of academic productivity in the field of pediatrics in Türkiye.

Key words: Publication rate, scientific congress, pediatric abstracts, Türkiye, bibliometric analysis.

Scientific congresses represent essential venues for sharing emerging research, offering investigators the opportunity to present preliminary results to the academic community and for networking for future collaborations. While such presentations are valuable for fostering dialogue and early feedback, their lasting scientific contribution depends largely

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on subsequent full-text publication.[1] This transition not only facilitates peer validation and wider dissemination, but also ensures that the research becomes a citable part of the scholarly record, enabling further inquiry and application. Additionally, presentations of research with stronger scientific and methodological quality also encourages higher-quality submissions to future congresses. Assessing the rate at which conference abstracts are converted into full-text publications is therefore of critical importance, as it reflects not only the scientific quality and methodological rigor of the presented research but also the academic influence and credibility of the conferences themselves.[2] Reported publication rates following conference presentations vary across medical specialties, typically ranging from 34% to 59%.[3]

The Turkish National Pediatric Society (TNPS), founded in Ankara in 1958 by Prof. Dr. İhsan Doğramacı, has played a leading role in advancing pediatric healthcare in Türkiye for over six decades. With 24 branches across various provinces, the Society has made significant contributions to the improvement of child health through education, advocacy, and scientific exchange. As part of its mission, TNPS has organized 68 Turkish National Pediatric Congresses (TNPCs), which bring together thousands of healthcare professionals annually. These congresses provide a forum for the presentation of current issues in pediatric health and the latest scientific developments by both nationally and internationally recognized experts. In addition to promoting high-quality, evidence-based education, the congresses foster professional networking among pediatricians. Each year, approximately 50 oral abstracts are presented, offering pediatricians across the country an opportunity to share their research with a broader academic audience.

TNPS also publishes two academic journals in collaboration with the Hacettepe University Institute of Child Health and the International Children's Center. Among them, *The Turkish Journal of Pediatrics* (TJP), published bimonthly since 1958, is indexed in the Science Citation Index-Expanded. As the editorial board of TJP, we recognized that, despite the rigorous peer-review process used for oral abstract selection at TNPCs, limited data exist regarding the proportion of these abstracts that are ultimately published as full-text articles and the characteristics of those publications.

This study aims to address this gap by evaluating the publication rate of oral abstracts presented at TNPCs and analyzing the associated characteristics of the resulting full-text publications over a five-year period (2019-2023).

Materials and Methods

Study design and data collection

The study included five TNPCs held between 2019 and 2023. Oral abstracts were identified from official congress abstract books. A master list of all oral abstracts was compiled; poster abstracts were not evaluated. Abstracts from the past two congresses (2024 and 2025) were not included in the analysis, as an adequate time interval is required for the studies to progress to full-text publication.

Search strategy

Each abstract was searched in PubMed, Web of Science, Scopus, Google Scholar and TR Index using author names, abstract titles, and title keywords. Both English and Turkish titles were used in the search. Each year was evaluated independently by two researchers. Publications matching the abstracts were counted as "converted abstracts".

Variables analyzed

The following data were collected: Pediatric subspecialty category, year of presentation, study design (retrospective, prospective or cross-sectional), collaboration (single-center, multicenter, international), time to publication (years), journal indexing status (Science Citation

Index Expanded [SCIE], Social Sciences Citation Index [SSCI], Emerging Sources Citation Index [ESCI], TR Index (also known as TR Dizin), and others [journals not indexed in any of the aforementioned databases]) and for those indexed in the Web of Science, journal impact factor and quartile (Q) category of the journal at the time of publication, as reported by Clarivate Journal Citation Reports.

Statistical analysis

Descriptive statistics were used. Numerical variables were presented as mean ± standard deviation (SD), and categorical data as frequency and percentage. All analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Out of 268 oral abstracts presented between 2019 and 2023, a total of 111 (41.8%) were subsequently published as full-text articles in peer-reviewed journals. The year-by-year distribution of publication rates and related characteristics is presented in Table I. The highest annual conversion rate was observed in 2019 (50.0%), and the lowest in 2023 (29.1%).

Fig. 1. illustrates the distribution of time from abstract presentation to publication, stratified by presentation year. The majority of publications occurred within 3 years for all cohorts.

Among the published abstracts, 61.3% (n=68) appeared in journals indexed in SCIE or SSCI, while 17.1% (n=19) were published in journals indexed in ESCI. Publications in journals indexed in TR Index constituted 13.5% (n=15) of the total of published articles. The mean time to publication was 1.6 ± 1.17 years, with a range from 0 to 6 years. Most of the published studies were retrospective in design (51.3%) and conducted in a single center (88.3%), while only three (2.7%) were the result of international collaborations.

The mean journal impact factor was 1.72 ± 1.26 (range: 0.04–4.84). One study published in *The Lancet* in 2020 (impact factor: 99.7) was excluded from the impact factor analysis due to its outlier status. Approximately one-third (32.4%) of the articles were published in Q1 or Q2 ranked journals.

Subspecialties with the highest number of abstracts submitted included Infectious Diseases (n=32), Neonatology (n=24), and Social Pediatrics (n=23). Table II presents the distribution of abstracts and publication rates by pediatric subspecialty. The highest conversion rates were observed in Pediatric Rheumatology: 100% (5/5) and Adolescent Medicine: 71.4% (5/7).

Discussion

Since its establishment, the TNPS has organized annual national pediatric congresses that have evolved into cornerstone events in the field. These meetings bring together leading experts from Türkiye and abroad to present the latest research and clinical advancements. Although the abstracts submitted to TNPS congresses have the potential to significantly influence pediatric practice, no prior systematic evaluation has assessed how many of these presentations successfully undergo peer review and achieve full-text publication. This study demonstrates that nearly half of the oral abstracts presented at TNPCs were subsequently published as full-text articles, a rate that aligns with findings from other international congresses. A 2018 Cochrane review examining 425 studies and 307,028 scientific meeting abstracts reported a mean full-text publication rate of 46.4%.[1] In contrast, two studies from other Turkish medical societies in 2014 and 2015, found much lower publication rates of 11% and 21.9%,[4,5] suggesting that the publication outcomes of TNPC abstracts compare favorably within the national context.

Table I. Annual publication rates and characteristics of abstracts.

Year	Published / total abstracts, n (%)	Study design, n (%)	Collaboration level, n (%)	Time to publication (years), mean ± SD (min–max)	Journal indexing status, n	Quartile (Q), n	Impact factor, mean ± SD (min–max)
2019	30 / 60 (50.0%)	Retrospective: 13 (43.3%) Cross-sectional or Prospective: 17 (56.7%)	Single-center: 28 (93.3%) Multicenter: 1 (3.3%) International: 1 (3.3%)	2.26 ± 1.4 (0–6)	SCIE: 22 SSCI: 0 ESCI: 2 Other: 1 TR Index: 5	Q1: 5 Q2: 5 Q3: 10 Q4: 4	2.0 ± 1.2 (0.1–4.8)
2020	29 / 63 (47.6%)	Retrospective: 11 (37.9%) Cross-sectional or Prospective: 18 (62.1%)	Single-center: 24 (82.8%) Multicenter: 3 (10.3%) International: 2 (6.9%)	1.62 ± 1.1 (0–4)	SCIE: 17 SSCI: 1 ESCI: 4 Other: 3 TR Index: 4	Q1: 2 Q2: 6 Q3: 5 Q4: 10	1.75 ± 1.5 (0.04–4.84)
2021	17 / 38 (44.7%)	Retrospective: 11 (64.7%) Cross-sectional or Prospective: 6 (35.3%)	Single-center: 13 (76.5%) Multicenter: 4 (23.5%) International: 0	1.58 ± 1.06 (0–4)	SCIE: 7 SSCI: 0 ESCI: 4 Other: 3 TR Index: 3	Q1: 2 Q2: 1 Q3: 2 Q4: 6	1.38 ± 1.08 (0.2–3.5)
2022	19 / 52 (36.5%)	Retrospective: 10 (52.6%) Cross-sectional or Prospective: 9 (47.4%)	Single-center: 19 (100%) Multicenter: 0 International: 0	1.47 ± 0.68 (0–3)	SCIE: 7 SSCI: 1 ESCI: 7 Other: 1 TR Index: 3	Q1: 4 Q2: 2 Q3: 2 Q4: 7	1.44 ± 1.34 (0.1–4.3)
2023	16 / 55 (29.1%)	Retrospective: 12 (75%) Cross-sectional or Prospective: 4 (25%)	Single-center: 14 (87.5%) Multicenter: 2 (12.5%) International: 0	0.9 ± 0.68 (0–2)	SCIE: 13 SSCI: 0 ESCI: 2 Other: 1 TR Index: 0	Q1: 2 Q2: 7 Q3: 1 Q4: 4	1.77 ± 0.93 (0.1–3.1)
Total	111 / 268 (41.8%)	Retrospective: 57 (51.35%) Cross-sectional or Prospective: 54 (48.65%)	Single-center: 98 (88.29%) Multicenter: 10 (9.0%) International: 3 (2.7%)	1.6 ± 1.17 (0–6)	SCIE: 66 SSCI: 2 ESCI: 19 Other: 9 TR Index: 15	Q1: 15 Q2: 21 Q3: 20 Q4: 31	1.72 ± 1.26 (0.04–4.84)

Impact factors and quartile categories pertain only to articles published in journals indexed in the Web of Science and have those parameters reported in the Journal Citation Reports. TR Index is also known as TR-Dizin; *One study published in *The Lancet* in 2020 (Impact Factor: 99.7) was excluded from impact factor analysis due to being an outlier; ESCI: Emerging Sources Citation Index, SCIE: Science Citation Index Expanded, SSCI: Social Sciences Citation Index.

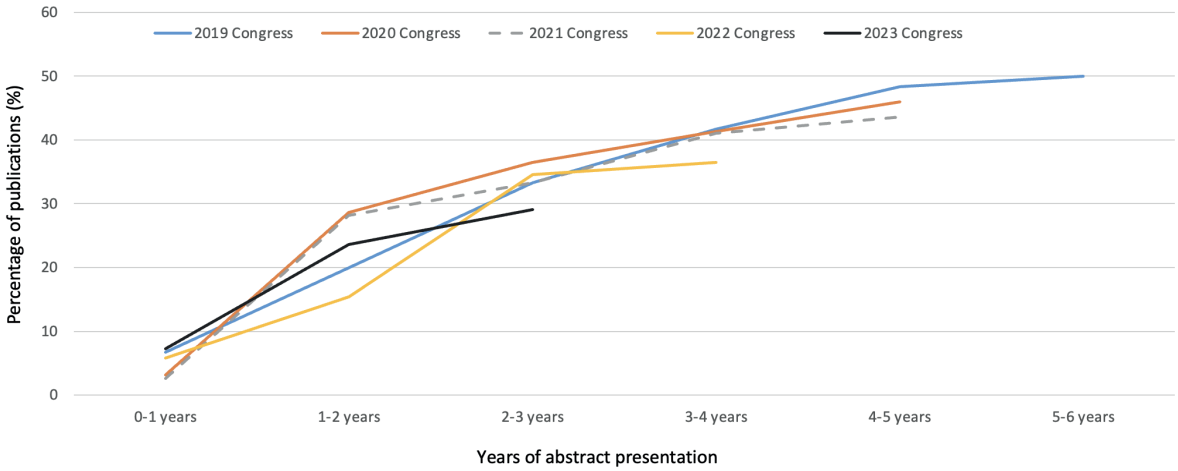

Fig. 1. Time from abstract presentation to publication by year.

Table II. Number of abstracts and full-text publication rates by pediatric subspecialty.

Subspecialty*	Total number of abstracts, n (column %)	Publication rate, n (row %)
Adolescent health	7 (2.6)	5 (71.4)
Allergy	9 (3.4)	2 (22.2)
Cardiology	14 (5.2)	5 (35.7)
Developmental pediatrics	14 (5.2)	7 (50.0)
Emergency medicine	6 (2.2)	2 (33.3)
Endocrinology	13 (4.9)	6 (46.2)
Gastroenterology	16 (6.0)	5 (31.3)
General pediatrics	9 (3.4)	4 (44.4)
Genetics	5 (1.9)	2 (40.0)
Hematology	9 (3.4)	2 (22.2)
Immunology	5 (1.9)	2 (40.0)
Infectious diseases	32 (11.9)	18 (56.3)
Intensive care	14 (5.2)	6 (42.9)
Metabolism	15 (5.6)	4 (26.7)
Neonatology	24 (9.0)	10 (41.7)
Nephrology	14 (5.2)	6 (42.9)
Neurology	14 (5.2)	4 (28.6)
Non-pediatric specialty	8 (2.9)	2 (25.0)
Oncology	7 (2.6)	2 (28.6)
Pulmonology	5 (1.9)	2 (40.0)
Rheumatology	5 (1.9)	5 (100.0)
Social pediatrics	23 (8.6)	11 (47.8)
Total	268 (100)	111 (41.8)

*Presented in alphabetical order.

Despite the relatively high publication rate, it is important to recognize that more than half of the abstracts were not published in peer-reviewed journals. The reasons for non-publication remain unclear; it is not known how many were submitted and subsequently rejected versus never submitted at all. A prior study in 2003, on orthopedics meetings found that 16% of abstracts were submitted but rejected, while 36% were never submitted. The most commonly cited reasons for non-submission included lack of time, ongoing nature of the project, and difficulties in collaboration with co-authors.[6] These findings highlight the need to explore and address the barriers that prevent abstracts from being developed into full manuscripts.

The mean time to publication in our study was 1.6 years, consistent with previous reports in the literature. For example, a study of abstracts presented at the Urological Society of Australia and New Zealand's annual meetings reported a mean time to publication of 1.3 years, with 80% published within two years.[7] In our study, the longest observed time to publication was 6 years. Similar trends have been observed across various medical specialties, where publication timelines generally range from 1 to 2 years. This delay likely reflects the time required for manuscript preparation, submission, peer review, and editorial processing.[8] The peak in publication rates in 2019 and the decline observed in 2023 may further support this observation.

Similar to the literature, in our study retrospective and single-center studies dominated both the study design and level of collaboration, likely due to their feasibility and ease of data access. However, previous studies have shown that multicenter and international studies are more likely to be published and have greater impact,[8]emphasizing the importance of promoting collaborative research efforts in future congress submissions.

Subspecialties with the highest number of submitted abstracts included Infectious Diseases, Neonatology, and Social Pediatrics—consistent with the common thematic priorities of general pediatric congresses. It is noteworthy that each subspecialty also maintains its own national society, which may draw high-quality submissions to specialty-specific meetings and thereby limit the number of top-tier abstracts submitted to general pediatric congresses.

This study has several limitations. First, we analyzed only oral abstracts and did not assess the study designs of those that were not published. Previous research has indicated that abstracts presenting randomized controlled trials and those selected for oral presentation are more likely to be published,[3] but we were unable to evaluate this factor within the unpublished group. Second, our full-text search was limited to journals indexed in Medline and TR Index. Therefore, it is possible that some publications were missed, although each abstract was independently evaluated by two reviewers to minimize this risk. Another possible reason for some being missed could be that the title of the article, the keywords, or some of the authors may have appeared differently in the publication. Additionally, we were not able to evaluate the reasons for non-publication.

In conclusion, the fact that nearly half of the abstracts were published—over one-third of them in Q1 or Q2 ranked journals—and the relatively short time to publication suggest that the studies presented orally at TNPCs are of high scientific quality and are maturing into full publications in a timely manner. TNPCs contribute meaningfully to the national pediatric research output. These findings highlight the importance of monitoring academic productivity and identifying potential barriers to publication, thereby contributing to the continued development of pediatric research in Türkiye.

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Ethical approval

This study did not require ethics committee approval as it involved the analysis of publicly available data from published conference abstract books and did not include human participants or identifiable personal data.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: SA, AD, GEÜ, EH; Data collection: SA, MPK, ÖB, YY, LAY ; analysis: SA, interpretation of results: all authors; draft manuscript preparation: SA. 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

Dose-specific childhood vaccine refusal in Balıkesir, Türkiye (2024): a population-based surveillance analysis

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ABSTRACT

Background. Vaccine hesitancy has intensified since COVID-19. In Türkiye, a performance-based family medicine system provides free vaccines. Before May 2024, physicians could remove refusals from metrics tied to pay deductions, obscuring true rates. A new policy mandating documentation created a natural experiment. We used population-based data to quantify these previously hidden dose-specific refusal rates across the childhood schedule.

Methods. We conducted a population-based ecological analysis of monthly dose-specific refusals among children aged 0–59 months in Balıkesir Province, in 2024. Refusals were extracted from Performance Exception Forms. Rates were calculated per 1,000 target children (Wilson 95% confidence intervals [CI]s), using populations derived from Turkish Statistical Institute counts. To quantify the policy's impact, we fitted an interrupted time-series regression with a fixed breakpoint at May 2024. This model estimated the baseline level and slope (January-April) and compared them to the immediate level shift and new monthly slope post-reform (May–December).

Results. Of 3,584 missed-dose exceptions, 3,002 (83.8%) were refusals. The aggregate refusal rate was 3.9 per 1,000 (January-April) versus 21.6 per 1,000 (May–December), while the rate of on-schedule vaccinations decreased from 99.3% to 97.5%. Segmented regression indicated a baseline of 2.6 per 1,000 and a post-policy level increase of 13.7 per 1,000 (p=0.005); pre- and post-policy monthly slopes were not significant. Refusals concentrated in booster and later-scheduled doses (18–48 months), whereas primary-series doses showed lower, comparatively stable rates. Notably, refusal for the second measles-mumps-rubella dose (MMR-II, 48 months) rose toward year-end, reaching 47.4 per 1,000 in December (95% CI, 35.1–63.6).

Conclusions. Mandatory documentation exposed substantial under-ascertainment of parental refusal in performance-based records. Refusal is disproportionately clustered at booster and later-childhood visits, with MMR-II approaching herd-immunity margins. Programmatically, pediatric booster encounters are key leverage points for targeted counseling, and sustained, transparent surveillance as enabled by the new policy, is essential for early signal detection and response.

Key words: booster doses, childhood immunization, health policy, interrupted time-series, surveillance, vaccine hesitancy.

Childhood immunization is the cornerstone of public health, known for preventing millions of deaths globally each year.[1] However, a new trend among parents has emerged. Vaccine hesitancy, defined as the delay in acceptance, or refusal of vaccination despite service availability, has been declared a top-ten global health threat by the World Health Organization

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(WHO), contributing to resurgences of diseases like measles.[2] In the post-COVID-19 era, vaccine hesitancy has intensified globally. European research, for instance, highlights a decline in vaccination coverage that has occurred alongside growing parental concerns about routine childhood immunizations.[3] On a wider scale, global meta-analyses estimate that over 21% of parents exhibit hesitancy regarding routine childhood vaccines, though the prevalence varies significantly across regions.[4]

Türkiye's vaccination landscape has undergone a significant transformation over the past decade, shaped by both policy reforms and evolving public attitudes. While the country has made well-documented progress—reducing zero-dose prevalence from 3.2% in 1993 to 0.9% in 2018, despite persistent regional inequities[5] —a paradoxical trend has emerged. During this same period, vaccine hesitancy has surged, escalating from rare events to over 23,000 families by 2018, a trend potentially linked to intensified public debate and a 2015 legal decision on parental consent.[6,7]

This trend unfolded within Türkiye's national immunization programme which provides vaccines free of charge through an easy-to-access nationwide, performance-based family medicine system. All health facilities are connected through an integrated information technology (IT) infrastructure, enabling the vaccine tracing system to track immunizations administered in any setting—including hospitals and private clinics—beyond the family physician (FP) network.[8] However, if system records indicate that a child is unvaccinated, the FP is required to document an explanation to avoid pay deductions. Thus, the performance-based system mandates FPs to certify their non-accountability for every unmet preventive service -including missed vaccinations- in a monthly performance exception form.[9] Despite this accountability mechanism, the system's financial incentives created a surveillance blind spot. Until May 2024, FPs could record a missed dose as "parental refusal" to remove it from the performance metrics used to calculate pay deductions, meaning that many refusals never reached the national surveillance database. The new regulation implemented in May 2024 reversed this, closing the systemic gap by making all such events visible to the national system and mandating that physicians obtain a wet-signed parental document for each refusal as the condition for avoiding a performance deduction.

This policy change created a natural experiment to address the gap in systematic documentation. While national surveys like the Turkish Demographic Health Survey[10] provide some population estimates (e.g., 3.4% unvaccinated among children aged 24-35 months in 2018), these figures represent multiple reasons for non-vaccination and not solely explicit refusal. Conversely, recent community-based studies in Türkiye have suggested substantially higher rates of vaccine hesitancy, with some regions reporting hesitancy rates exceeding 15%, highlighting the discrepancy between survey-based estimates and administratively flawed surveillance data.[11,12] Earlier attempts to quantify refusal through FP reporting documented comparatively low rates[13], indicating a notable gap in the systematic documentation of refusal rates.

Therefore, this study aims to quantify dose-specific vaccine refusal rates among children aged 0–59 months in Balıkesir (2024) and to test the hypothesis that the May 2024 mandatory documentation policy created an immediate, significant increase in recorded refusals, thereby exposing the true, previously under-ascertained burden.

Materials and Methods

Study design

Adopting an ecological cross-sectional approach, we examined monthly dose-specific refusals of vaccines included in Türkiye's national immunization programme among children aged 0–59 months in 2024.

Study population, data collection, and variables

The study population comprised children aged 0–59 months residing in Balıkesir, a province in the Marmara Region of Türkiye. By December 2024, the province had approximately 1.2 million residents, with an estimated 55,000 falling within the target age band.[14] Missed vaccine data were collected from the publicly available anonymized 'family medicine practice performance exception forms' published monthly by the Balıkesir Provincial Health Directorate from January 2024 to December 2024.[15] Free-text reasons for missed vaccination were coded and cross-validated by the authors, then grouped into four standard categories (vaccine refusal, migration, logistics, and other), enabling the identification of explicit refusals linked to specific doses. The 12 monthly files were then merged into a single dataset.

Because the study focused on doses routinely delivered in the family medicine system, hepatitis B dose I (administered at birth in hospitals) and the tetanus-diphtheria (Td) booster (Td-R) given at age 13 through school services were excluded. The national immunization schedule is outlined in Table I.

Estimating monthly target populations

Monthly target population numbers were derived by disaggregating annual single-age population counts according to observed birth distributions, thereby addressing seasonal variation (e.g., peaks in January and summer). Monthly live-birth counts for each province (2019-2023) were obtained from Turkish Statistical Institute (TURKSTAT) birth statistics (Supplementary Table S1).[16] For each calendar month, we divided the corresponding birth count by that year's total births to derive within-year monthly proportions (e.g., January 2020: 932/11,444 = 0.081), presented in Supplementary Table S2. Single-year age populations at the provincial level were retrieved from the 2024 TURKSTAT address-based population registration system dated 31 December 2024 (Supplementary Table S3).[14] Because monthly birth statistics for 2024 were not yet available, we projected the 2024 monthly birth distribution by applying the 2023 proportions to the 2024 annual birth estimate. The monthly target population calculation method is further exemplified in the Supplementary Tables S3 and S4.

Table I. National immunization schedule for vaccines by the Ministry of Health of Türkiye (2024)

Vaccine	Birth	1 Mo	2 Mo	4 Mo	6 Mo	12 Mo	18 Mo	24 Mo	48 Mo	13 Yr
Hepatitis B	I	II			III					
BCG			I							
DTaP-IPV-Hib			I	II	III		R			
PCV			I	II		R				
MMR*						I			II	
DTaP-IPV									R	
OPV					I		II			
Td										R
Hepatitis A							I	II		
Varicella						I				

*Balıkesir does not need an extra dose of MMR at 9 months. Hepatitis B I and Td are excluded from the study.
BCG: Bacille Calmette-Guérin vaccine, DaPT-IPV: Quadrivalent diphtheria and tetanus toxoid with acellular pertussis + inactivated polio vaccine, DaPT-IPV-HIB: Pentavalent Diphtheria and tetanus toxoid with acellular pertussis + inactivated polio vaccine + Haemophilus influenzae type b pediatric dose vaccine, Hepatitis A: Hepatitis A pediatric dose vaccine, Hepatitis B: Hepatitis B pediatric dose vaccine, MMR: Measles mumps rubella vaccine, Mo: At the end of months, OPV: Oral polio vaccine, PCV: Pneumococcal conjugate vaccine, R: Rappel (Booster), Td: Tetanus-diphtheria vaccine, Varicella: Varicella vaccine, Yr: At the end of the year.

Measurements and analysis

Dose-specific vaccine refusal rates were computed by dividing the monthly vaccine refusal counts by the corresponding projected monthly target population numbers, expressed per thousand individuals; illustrative example of this calculation is provided in Supplementary Tables S5-S7. Robust 95% confidence intervals (CIs) were generated with the Wilson method, which is widely regarded as more reliable for low proportions. Temporal trends were visualized using raw monthly rates to explicitly display month-to-month variability. To quantify the policy-related change, we fitted an interrupted time-series regression with a fixed break at May 2024. Model 1 assessed the aggregate trend, while Model 2 was fitted to the full disaggregated panel dataset (18 vaccine types X 12 months; N=216) to estimate vaccine-specific effects with sufficient degrees of freedom. Given the short pre-intervention window, these models were specified primarily to estimate the baseline level (January-April) and the immediate level shift post-reform (May-December), while treating slope estimates descriptively. Statistical analyses were conducted using R software version 4.2.1.

Ethics approval

This study constitutes a secondary analysis of publicly available, anonymized, and aggregated data. The datasets are made accessible through the official website of the Ministry of Health in accordance with applicable regulations and legislation[17]; specific data links are available in the Supplementary Table S8. Given the use of non-identifiable administrative surveillance data that are publicly disclosed, this research is exempt from formal ethics committee approval.

Results

In 2024, 3,584 unmet vaccine-dose exceptions were reported in Balıkesir. Before the May policy change (January–April), 423 exceptions occurred alongside a 99.3% on-schedule vaccination rate; refusals accounted for 60.0% (n=254) of these exceptions, followed by 'other' reasons (21.5%, n=91) and migration (18.4%, n=78). Post-policy (May–December), exceptions increased to 3,161 while the on-schedule rate slightly decreased to 97.5%. Recorded refusals increased to 2,748, comprising 86.9% of post-reform exceptions. Other reasons included 'other' (7.4%, n=234), migration (5.3%, n=169),

Table II. Childhood vaccine refusal counts and rates (per thousand target children) by age milestone and period

Month	January - April 2024			May - December 2024		
	Refusal count	Projected	Rate (‰)	Refusal count	Projected	Rate (‰)
1 Mo	11	3,273	3.4	104	6,798	15.3
2 Mo	40	9,944	4.0	326	20,394	16.0
4 Mo	24	6,777	3.5	228	13,616	16.7
6 Mo	27	11,176	2.4	363	19,706	18.4
12 Mo	46	10,166	4.5	494	21,469	23.0
18 Mo	47	11,929	3.9	566	20,772	27.2
24 Mo	13	3,523	3.7	207	7,794	26.6
48 Mo	46	7,707	6.0	460	16,658	27.6
Total	254	64,497	3.9	2,748	127,209	21.6

Mo: At the end of months.
Periods: The data are stratified into two periods reflecting a change in surveillance policy: January–April 2024 (Four months before mandatory inclusion of refusal data in performance evaluations) and May–December 2024 (Eight months after mandatory inclusion began). Hepatitis B I and Tetanus-diphtheria vaccine Rappel are excluded.
Projected: Projected target population count for the specific age milestone during the specified period.
Rate (‰): Refusal rate calculated per 1,000 projected target children (Refusal count / Projected × 1,000).

Table III. Dose-specific monthly vaccine refusal rates per thousand, May-December 2024

Schedule	Vaccine	May 24	Jun 24	Jul 24	Aug 24	Sep 24	Oct 24	Nov 24	Dec 24
1 Mo	Hepatitis B II	17.3 (10.1-29.4)	9.4 (4.8-18.4)	14.4 (8.3-25.1)	13.5 (7.9-23.0)	14.9 (8.9-24.8)	25.3 (16.6-38.3)	13.6 (7.6-24.1)	14.6 (8.4-25.4)
6 Mo	Hepatitis B III	24.3 (16.0-36.9)	15.0 (8.6-26.0)	11.2 (6.1-20.5)	18.4 (11.0-30.6)	13.4 (7.5-23.8)	25.3 (16.3-39.2)	17.6 (10.7-28.9)	22.9 (14.7-35.4)
2 Mo	BCG I	12.2 (6.6-22.3)	17.3 (10.1-29.4)	8.2 (4.0-16.9)	14.4 (8.3-25.1)	13.5 (7.9-23.0)	14.9 (8.9-24.8)	28.9 (19.5-42.6)	14.8 (8.5-25.7)
2 Mo	DTaP-IPV-Hib I	11.0 (5.8-20.7)	17.3 (10.1-29.4)	9.4 (4.8-18.4)	16.8 (10.1-28.1)	14.6 (8.7-24.3)	14.9 (8.9-24.8)	31.3 (21.4-45.4)	14.8 (8.5-25.7)
4 Mo	DTaP-IPV-Hib II	11.2 (6.1-20.5)	17.1 (10.0-29.0)	14.6 (8.4-25.4)	22.6 (14.2-36.0)	10.6 (5.6-20.0)	18.1 (11.0-29.6)	17.7 (11.1-28.1)	22.3 (14.6-33.9)
6 Mo	DTaP-IPV-Hib III	23.2 (15.1-35.5)	15.0 (8.6-26.0)	12.3 (6.9-22.0)	18.4 (11.0-30.6)	14.6 (8.4-25.4)	25.3 (16.3-39.2)	17.6 (10.7-28.9)	21.7 (13.7-34.0)
18 Mo	DTaP-IPV-Hib R	24.6 (16.3-36.9)	21.8 (14.0-33.8)	14.9 (8.9-24.9)	37.5 (26.4-53.0)	39.4 (28.3-54.6)	29.1 (19.5-43.3)	33.5 (23.6-47.5)	22.9 (14.9-35.1)
48 Mo	DTaP-IPV R	32.2 (23.0-44.9)	18.7 (12.3-28.4)	22.8 (15.7-33.0)	22.4 (15.4-32.7)	26.1 (18.1-37.5)	28.4 (19.6-41.0)	29.4 (20.4-42.2)	48.5 (36.1-64.9)
2 Mo	PCV I	11.0 (5.8-20.7)	18.6 (11.1-31.1)	9.4 (4.8-18.4)	16.8 (10.1-28.1)	14.6 (8.7-24.3)	14.9 (8.9-24.8)	31.3 (21.4-45.4)	14.8 (8.5-25.7)
4 Mo	PCV II	11.2 (6.1-20.5)	17.1 (10.0-29.0)	14.6 (8.4-25.4)	24.0 (15.2-37.6)	10.6 (5.6-20.0)	18.1 (11.0-29.6)	17.7 (11.1-28.1)	21.3 (13.8-32.6)
12 Mo	PCV R	25.7 (17.2-38.3)	26.3 (17.6-39.2)	13.9 (8.3-23.1)	25.3 (17.2-37.0)	24.0 (15.8-36.5)	25.8 (17.1-38.8)	25.5 (16.9-38.3)	18.8 (11.4-30.7)
6 Mo	OPV I	23.2 (15.1-35.5)	15.0 (8.6-26.0)	12.3 (6.9-22.0)	18.4 (11.0-30.6)	14.6 (8.4-25.4)	25.3 (16.3-39.2)	17.6 (10.7-28.9)	21.7 (13.7-34.0)
18 Mo	OPV II	22.3 (14.5-34.3)	20.6 (13.1-32.4)	14.9 (8.9-24.9)	37.5 (26.4-53.0)	37.1 (26.4-51.9)	27.9 (18.5-41.8)	34.7 (24.5-48.8)	22.9 (14.9-35.1)
12 Mo	MMR I	26.8 (18.1-39.6)	25.2 (16.7-37.8)	13.9 (8.3-23.1)	25.3 (17.2-37.0)	24.0 (15.8-36.5)	25.8 (17.1-38.8)	25.5 (16.9-38.3)	17.5 (10.5-29.2)
48 Mo	MMR II	31.2 (22.2-43.8)	17.8 (11.6-27.4)	22.0 (15.0-32.0)	22.4 (15.4-32.7)	27.0 (18.9-38.5)	27.3 (18.7-39.7)	29.4 (20.4-42.2)	47.4 (35.1-63.6)
12 Mo	Varicella I	25.7 (17.2-38.3)	26.3 (17.6-39.2)	13.9 (8.3-23.1)	25.3 (17.2-37.0)	25.2 (16.7-37.8)	25.8 (17.1-38.8)	25.5 (16.9-38.3)	17.5 (10.5-29.2)
18 Mo	Hepatitis A I	23.5 (15.4-35.6)	20.6 (13.1-32.4)	13.9 (8.1-23.6)	37.5 (26.4-53.0)	39.4 (28.3-54.6)	27.9 (18.5-41.8)	32.4 (22.7-46.2)	22.9 (14.9-35.1)
24 Mo	Hepatitis A II	32.3 (22.7-45.7)	26.7 (18.8-37.9)	19.4 (12.9-29.2)	20.1 (13.2-30.6)	27.7 (19.1-40.0)	37.5 (26.5-52.7)	27.9 (19.0-40.9)	24.1 (15.8-36.5)

BCG: Bacille Calmette-Guérin vaccine, DaPT-IPV: Quadrivalent diphtheria and tetanus toxoid with acellular pertussis + inactivated polio vaccine, DaPT-IPV-HIB: Pentavalent diphtheria and tetanus toxoid with acellular pertussis + inactivated polio vaccine + Haemophilus influenzae type b pediatric dose vaccine, Hepatitis A: Hepatitis A pediatric dose vaccine, Hepatitis B: Hepatitis B pediatric dose vaccine, MMR: Measles mumps rubella vaccine, Mo: At the end of months, OPV: Oral polio vaccine, PCV: Pneumococcal conjugate vaccine, R: Rappel (Booster), Varicella: Varicella vaccine.

and logistical issues (0.3%, n=10). Overall, parental refusal (n=3,002) constituted 83.8% of all yearly exceptions, establishing it as the primary driver of missed doses, far exceeding other factors. Dose-specific refusal details are presented in Table II. Vaccine-group-specific monthly refusal counts and refusal rates are summarized in Supplementary Tables S9 and S10. Correspondingly, the aggregate refusal rate rose from 3.9 per 1,000 (95% CI: 3.4–4.4) in the first four months to 21.6 per 1,000 (95% CI: 20.8–22.4) in the subsequent eight-month period. This increase was consistent across all age-specific vaccination schedules.

Monthly refusal rates during the May-December 2024 period revealed dose-specific variations (Table III). Primary-series vaccines such as Bacille Calmette-Guérin (BCG) I, pneumococcal conjugate vaccine (PCV) I, and diphtheria and tetanus toxoid with acellular pertussis, inactivated polio vaccine, and Haemophilus influenzae type b vaccine (DTaP-IPV-Hib) I generally exhibited lower refusal rates than their corresponding boosters. Refusal rates peaked for DTaP-IPV-Hib rappel (booster) dose (R) (39.4‰ in September) and particularly for diphtheria and tetanus toxoid with acellular pertussis and inactivated polio vaccine (DTaP-IPV) R (48.5‰ in December). Temporal trends had variations across vaccines; refusal rates for measles, mumps, and rubella vaccine (MMR) II and the DTaP-IPV R booster showed increases towards the end of the year, peaking in December at 47.4‰ (95% CI: 35.1–63.6) and 48.5‰ (95% CI: 36.1–64.9), respectively. Conversely, rates for some early doses, such as Hepatitis B II and BCG I, remained comparatively stable, varying between 8.2‰ and 28.9‰.

Fig. 1 illustrates the monthly temporal trends in dose-specific refusal rates throughout 2024. A visual shift occurs across all vaccine groups starting in May 2024, coinciding with the implementation of the mandatory refusal reporting system and revealing higher rates thereafter. Post-May, later doses within a series and boosters regularly attracted more refusals than initial doses, whereas month-to-month volatility persisted. End-of-the-year surge for the 48-month boosters (DTaP-IPV R and MMR II) is particularly pronounced.

Grouping refusals by scheduled age (Fig. 2) yields a similar hierarchy: the 18-, 24-, and 48-month milestones generally attracted the highest rates once routine mandatory reporting began, whereas vaccines scheduled in early infancy were refused less frequently. When several vaccines were co-administered at a single visit, their monthly trajectories tended to align with one another.

Finally, segmented-regression (Model 1) output quantifies the regulatory effect (Fig. 3). Prior to May, the baseline level was beta coefficient (β) = 2.6‰. After the reform, the level increased significantly to β = 16.3‰, a net rise of 13.7 per mille points ($p = 0.005$). The within-period slopes, which test whether rates continued to climb from the beginning to the end of each segment, were 0.5‰ and 0.2‰ per month, respectively, and neither reached statistical significance. Complete parameters for Model 1 and the vaccine-type-specific Model 2 are presented in the Supplementary Table S11.

Discussion

This study provides the first comprehensive quantification of vaccine refusal rates using systematically documented health system data from Türkiye. Following the implementation of the policy, vaccine refusals were documented at a rate of 2.1%. This represented a substantial increase in refusals, suggesting that previous underreporting rather than a genuine escalation was the cause, as evidenced by the stable pre- and post-policy slopes. Refusal rates were higher for booster and later-scheduled doses compared to primary series vaccinations. Vaccine refusals accounted for 83.8% of all documented vaccination exceptions, underscoring their major contribution to immunization gaps.

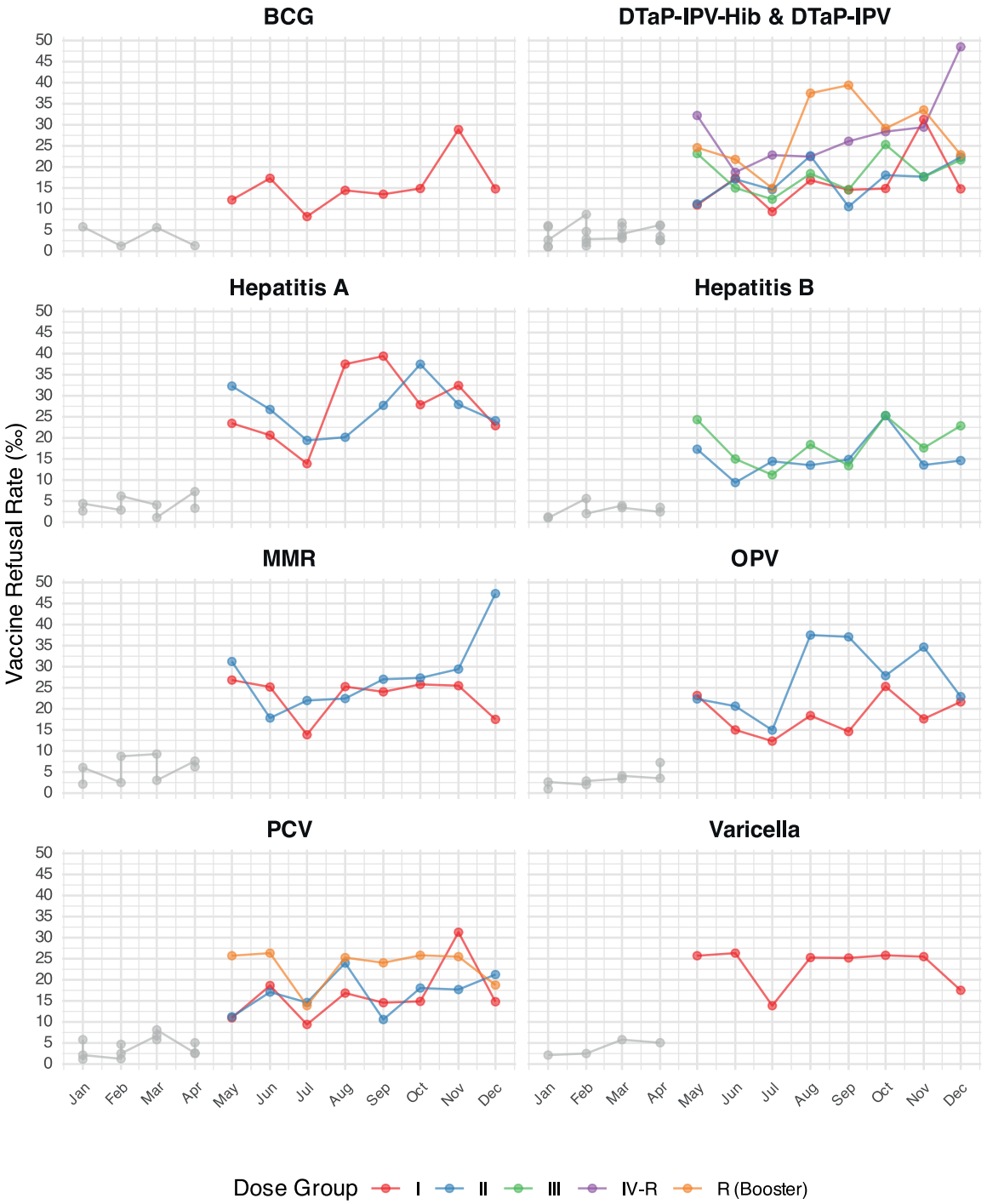

Fig. 1. Monthly childhood vaccine refusal rates by vaccine and dose group, 2024.

BCG: Bacille Calmette-Guérin vaccine, DaPT-IPV: Quadrivalent diphtheria and tetanus toxoid with acellular pertussis + inactivated polio vaccine, DaPT-IPV-HIB: Pentavalent diphtheria and tetanus toxoid with acellular pertussis + inactivated polio vaccine + Haemophilus influenzae type b pediatric dose vaccine, Hepatitis A: Hepatitis A pediatric dose vaccine, Hepatitis B: Hepatitis B pediatric dose vaccine, IV-R: DTaP-IPV, MMR: Measles mumps rubella vaccine, OPV: Oral polio vaccine, PCV: Pneumococcal conjugate vaccine, R: Rappel (Booster), Varicella: Varicella vaccine.

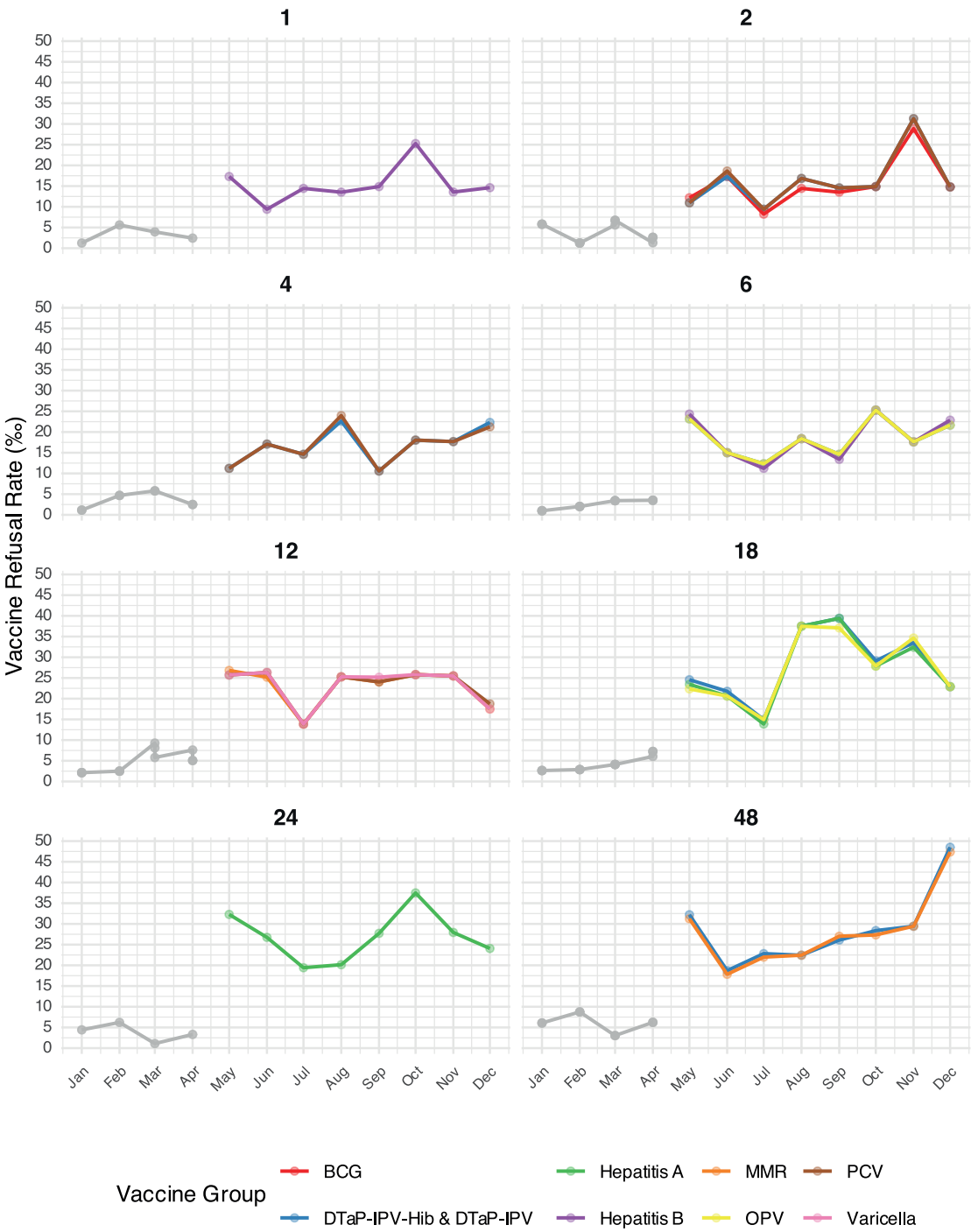

Fig. 2. Monthly childhood vaccine refusal rates by scheduled age milestone, 2024

BCG: Bacille Calmette-Guérin vaccine, DaPT-IPV: Quadrivalent diphtheria and tetanus toxoid with acellular pertussis + inactivated polio vaccine, DaPT-IPV-HIB: Pentavalent diphtheria and tetanus toxoid with acellular pertussis + inactivated polio vaccine + Haemophilus influenzae type b pediatric dose vaccine, Hepatitis A: Hepatitis A pediatric dose vaccine, Hepatitis B: Hepatitis B pediatric dose vaccine, MMR: Measles mumps rubella vaccine, OPV: Oral polio vaccine, PCV: Pneumococcal conjugate vaccine, Varicella: Varicella vaccine.

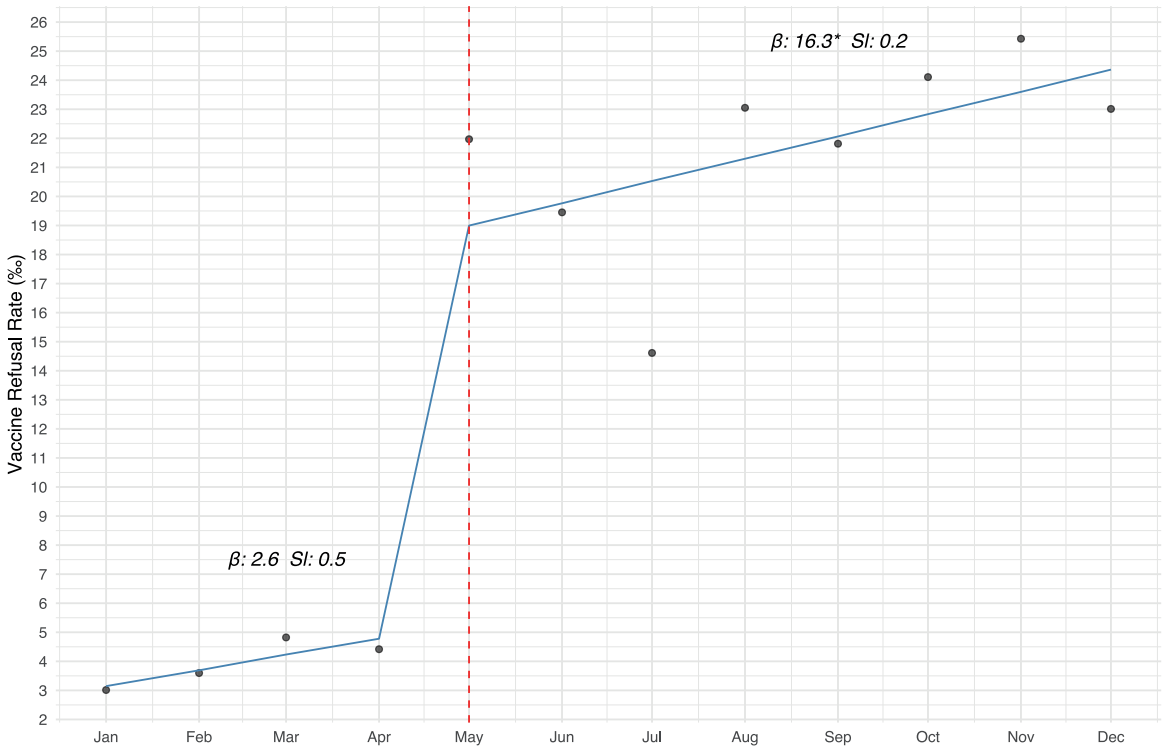

Fig. 3. Segmented regression of monthly vaccine refusal rates before and after the May 2024 policy reform

β = baseline level for the segment (‰), Sl = within-segment slope (‰ per month), "*" = $p < 0.05$ (significant); values without * are not significant, Red dashed line = May 2024 policy reform (model join-point), Estimates derived from Model 1 (segmented regression, for details see Supplementary material).

Our study reveals markedly higher vaccine refusal rates in Balıkesir during May-December 2024 (aggregate 21.6‰) compared to previous family medicine-based surveillance studies in Türkiye, which typically reported rates between 2‰–6‰.[7,13,18,19] Pre-policy (January-April) rates (3.9‰) aligned with these earlier estimates. The sharp May increase suggests that mandatory reporting uncovered substantial pre-existing refusal previously underrepresented in performance-based data. As pre-policy records might be systematically unreliable, extending the baseline backward was unfeasible; however, this sharp level shift itself serves to quantify the magnitude of the previous surveillance gap. Post-May rates[11,12] converge with community-based surveys, indicating higher underlying refusal, and highlighting the importance of systematic surveillance over voluntary reporting systems.[20]

From a health management perspective, the May 2024 reform exposed flaws in Türkiye's performance-based financing (PBF) system. International evidence suggests that PBF incentives alone are often costly and unreliable, supporting verifiable data over pay-based exemptions.[21] While intended to improve quality, performance mechanisms undermined data authenticity when clinicians faced pressure without support, triggering resistance regarding feasibility.[22] This tension highlights broader challenges: immunization monitoring faces indicator overload and reporting burden, yet disease threats demand stable surveillance.[23] Patients need trustworthy protection, providers reasonable accountability, and administrators reliable systems. Navigating these competing interests requires the system to evolve, prioritizing the overriding benefit of public health.

Regarding international contextualization, our documented 2.1% vaccine dose refusal rate demands evaluation within contemporary global vaccination challenges. Our findings align closely with the Netherlands (approximately 2%)[24] while remaining substantially below rates reported in Austria (2.7–5.9%)[25], Brazil (2.7%)[26], and Pakistan (22%).[27] WHO European Region surveillance data demonstrate concerning regional patterns, with MMR second-dose coverage declining from 92% to 91% between 2019–2024[28], while more than half of member states now fail to meet the 95% herd immunity elimination target, with some countries reporting coverage below 82%.[29] While direct comparisons have limitations due to methodological differences, within this regional context, our refusal rate of 2.1%, appears relatively well-contained. Nevertheless, even modest increases in these rates could erode existing herd immunity margins and compromise disease elimination efforts.

While unmet vaccination reasons in Canada and Brazil primarily involve access barriers or vaccine shortages, our study identified refusal as the predominant factor.[30,31] For instance, timely vaccination rates for free vaccines in Austria have been reported to range from 6.3% to 48.8% by vaccine type[25], whereas our analysis indicates that post-policy timely vaccination coverage in Türkiye remains over 97.5%. This high rate of on-schedule vaccination suggests that transportation and vaccine logistics challenges have been relatively resolved, reinforcing that refusal is the most significant remaining challenge, particularly following post-COVID-19 trends in hesitancy.[3] Our findings further demonstrate that refusal rates were consistently higher for booster and later-scheduled doses compared to the primary series. This pattern carries particular public health significance for measles-containing vaccines, where our data revealed 2.7% refusal for 48-month vaccinations after May, escalating to 4.7% for MMR II by December 2024. Given that coverage rates exceeding 95% are critical for maintaining measles elimination status[32], these refusal trends approach thresholds that could compromise herd immunity, potentially creating outbreak-susceptible populations not only in Balıkesir but likely across other Turkish regions. This concerning trajectory likely reflects several interconnected factors identified in prior literature, including parents' diminished perception of disease risk as children age[33], accumulated concerns about safety and potential side effects from previous doses[34], and the emergence of vaccine fatigue[35] following repeated immunization encounters. Moreover, Turkish qualitative research reveals that vaccine refusal often clusters with broader rejection of healthcare services[36], suggesting systematic mistrust that extends beyond vaccination decisions. This pattern may be further amplified in vulnerable populations, as specialized clinic studies demonstrate a fourfold increase in refusal among younger siblings of children with autism spectrum disorder[37], indicating how specific family experiences can cascade into broader immunization hesitancy.

This study's major strength lies in providing the first systematic, population-based quantification of dose-specific vaccine refusal rates using comprehensive health system surveillance data, unlike previous survey-based approaches. The interrupted time-series regression analysis enabled the precise assessment of temporal trends following policy implementation. However, several limitations warrant consideration. The ecological study design and single province setting limit the generalizability of our findings to the broader Turkish population. Additionally, denominators were based on projections, which could affect rate precision, though they were anchored to known annual population data. The data also lacked sociodemographic details, preventing an analysis of refusals across different strata. Future individual-level research is suggested to explore these factors and validate the findings nationally. Furthermore, the exclusion of hospital-administered Hepatitis B I and Td vaccines may underestimate the complete picture of refusal patterns across all delivery

settings. Finally, while the four-month baseline might be sufficient to detect the substantial level shift, the limited statistical power for trend analysis warrants cautious interpretation of slope estimates.

Vaccine refusals constitute a substantial proportion of immunization gaps, making their resolution critical for improving coverage. This study highlights the importance of the post-May regulatory reform in Türkiye, which enabled more systematic detection of vaccine refusals. In an era of declining vaccine confidence, comprehensive surveillance systems become indispensable for enabling early trend detection, rapid misinformation response, and tailored interventions for at-risk populations.[38] Enhanced interventions targeting refusals should leverage integrated healthcare approaches, as other research suggests that postnatal care utilization and maternal education strongly correlate with vaccine acceptance—making these more effective than vaccination-only strategies.[39]

While our analysis suggests overall stability during the post-May period, refusal rates for certain later doses approached critical herd immunity thresholds. This pattern raises legitimate concerns about the potential impact of increasing vaccine hesitancy, particularly within the Balıkesir region. Enhanced interventions are needed for later doses, and nationwide long-term surveillance is essential to determine broader patterns, as refusal rates likely vary across Türkiye's diverse socioeconomic regions. Future nationwide surveillance should incorporate sociodemographic stratification to identify regional variations and enable geographically targeted public health responses.

Supplementary materials

Supplementary materials for this article are available online at https://doi.org/10.24953/turkjpediatr.2026.6792.

Ethical approval

This study constitutes a secondary analysis of publicly available, anonymized, and aggregated data. The datasets are made accessible through the official website of the Ministry of Health in accordance with applicable regulations and legislation; specific data links are available in the supplementary material. Given the use of non-identifiable administrative surveillance data that are publicly disclosed, this research is exempt from formal ethics committee approval.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: SK, MT; data collection: SK; analysis and interpretation of results: SK, MT; draft manuscript preparation: SK, MT. 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

Problematic social media use and eating behaviors in adolescence: gender-based differences

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ABSTRACT

Background. Adolescence is a key period for shaping eating behaviors. Social media, central to identity formation and peer interaction, may influence diet through appearance-related mechanisms, with possible gender differences. This study investigated associations between social media use, addiction, and disorder with eating behaviors among Turkish adolescents, focusing on the mediating role of appearance-related social media consciousness.

Methods. A cross-sectional survey was conducted with 487 high school students aged 14–18 years in Manavgat, Antalya, Türkiye. Measures included the Social Media Addiction Scale for Adolescents (SMASA), Social Media Disorder Scale (SMDS), Appearance-Related Social Media Consciousness Scale (ASMC), Scale of Effects of Social Media on Eating Behavior (SESMEB) and Eating Habits Questionnaire for Adolescents (EHQA). Non-parametric tests were used due to non-normal data distributions; gender-stratified multiple regression models identified independent predictors of unhealthy eating habits. Simple mediation analyses (PROCESS Model 4) were performed to test indirect effects, as mediation models allow evaluation of whether ASMC explains the pathway between social media–related variables and unhealthy eating.

Results. Female adolescents reported longer daily social media use than males (median = 3.0 vs. 2.0 hours, $p < 0.05$). Across genders, healthy eating (EHQA) was negatively correlated with ASMC and SESMEB (all $p < 0.01$). Regression analyses showed that SMDS, ASMC, and SESMEB were significant predictors of unhealthy eating among females, while ASMC and SESMEB predicted unhealthy eating among males. Mediation analyses showed partial mediation in females in both models (SMASA → ASMC → EHQA; SMDS → ASMC → EHQA), with both direct and indirect effects being significant. In males, direct effects were non-significant, whereas indirect effects were significant.

Conclusions. Problematic social media use was associated with unhealthy eating among adolescents. In females, both direct and indirect (appearance-related social media consciousness-mediated) effects were observed, whereas in males the association was indirect only. Gender-specific psychological mechanisms should be considered in developing interventions to promote healthier digital engagement and eating behaviors in adolescence.

Key words: adolescent behavior, body image, feeding behavior, social media.

Non-communicable diseases (NCDs) account for approximately 74% of global deaths each year, largely driven by modifiable behaviors such as unhealthy dietary patterns, which increase the risk of cardiovascular disease, diabetes, and cancer.[1] To reduce this burden, the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) emphasize the importance of promoting healthy eating early in life and recognize adolescence as

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a critical period for shaping long-term health trajectories.[2]

Adolescence is marked by rapid physical and neurocognitive development and increased sensitivity to social influences. It is also a formative stage when lifelong health behaviors, including dietary patterns, are established. Evidence links adolescent habits such as frequent ultra-processed food intake, irregular meals, and breakfast skipping to increased risk of non-communicable diseases in adulthood.[3,4] While adolescence provides a critical window for establishing healthy dietary behaviors, this potential is increasingly challenged by a digitally mediated world. Social networking platforms now serve not only as channels of communication but also as key spaces for identity formation, peer interaction, and lifestyle modeling, including food-related decisions.[5] This evolving digital and social landscape aligns with broader global vulnerabilities highlighted by the 2025 Second Lancet Commission on Adolescent Health and Wellbeing, which identifies health and optimal nutrition as one of the core domains of adolescent wellbeing. The Commission notes that adolescents are growing up amid the long-term impacts of coronavirus disease 2019, accelerating climate crises, geopolitical conflicts, and pervasive commercial and digital pressures, underscoring the need to strengthen healthy dietary behaviors during this developmental period.[6]

Social media may negatively affect adolescents' healthy eating behaviors; developmentally vulnerable youth are particularly susceptible to persuasive digital food marketing, often delivered through appealing content by influencers and celebrities.[7] As adolescents gain greater autonomy, they encounter food environments, both offline and online, that often promote convenience, impulsivity, and the consumption of calorie-dense, nutrient-poor products rather than supporting healthy choices. This tension is especially evident in digital spaces saturated with persuasive food content and peer-driven trends. Major global health organizations have called for policy interventions to limit the digital marketing of unhealthy foods to children and adolescents; in 2020, WHO, UNICEF, and the Lancet Commission jointly issued a global call to action to protect young people from exposure to harmful products such as tobacco, alcohol, and sugar-sweetened beverages.[8,9] Additionally, the Lancet Commission on Adolescent Health and Wellbeing has identified adolescent nutrition as a "hidden crisis," urging integrated strategies to monitor and improve young people's eating behaviors worldwide.[10,11] Recent national data indicate that 91.3% of Turkish children aged 6–15 use the internet and 66.1% specifically use social media, underlining the importance of addressing the potential impact of digital environments on adolescent eating behaviors in Türkiye as well.[12]

Although the link between social media use and adolescent eating behaviors is increasingly recognized, the psychosocial mechanisms remain unclear. Gender differences are evident; female adolescents tend to engage with appearance-focused content and are more sensitive to idealized body images, while male adolescents more often follow performance- or status-oriented content. These distinct patterns may influence dietary behaviors through different psychological pathways.[13]

This study aims to examine the associations between social media use, social media addiction, and social media disorder with eating behaviors among Turkish adolescents. In addition, the study investigates whether appearance-related social media consciousness serves as a mediating mechanism in these associations and whether these pathways differ by gender. Based on these aims and the existing theoretical and empirical literature, the following hypotheses were formulated:

H1. Higher levels of social media use, social media addiction, and social media disorder will be associated with poorer eating behaviors among adolescents.

H2. Appearance-related social media consciousness will mediate the associations between social media addiction and social media disorder and unhealthy eating behaviors.

H3. These direct and indirect pathways will differ by gender, with stronger appearance-related mechanisms expected among female adolescents.

Materials and Methods

Study design and ethical considerations

This cross-sectional study was conducted between February and May 2024 in one private and one public high school located in Manavgat, Antalya, Türkiye. Ethical approval was obtained from the appropriate institutional ethics committee (protocol-decision number: 230077-118, date: 20/10/2023) and permission to conduct the research was granted by the national educational authority. All study procedures were performed in accordance with the Declaration of Helsinki.

Sample size

An a priori power analysis was performed using G*Power 3.1 for a multiple regression model that included three theoretically relevant predictors (social media addiction, social media disorder, and appearance-related social media consciousness) and four additional predictors (age, body mass index [BMI] percentile, daily social media use, and social media's influence on eating behaviors). Assuming a small-to-medium effect size ($f^2 = 0.05$), $\alpha = 0.05$, and power = 0.95, the required minimum sample size was 348 participants. To account for potential non-response or unusable data, a 20% attrition margin was applied, increasing the target sample size to approximately 435 participants. The final analytic sample of 487 adolescents exceeded both the calculated minimum sample size and the attrition-adjusted target, demonstrating that the study was sufficiently powered for the planned correlation, regression, and mediation analyses.

Participants

The study included high school students aged 14–18 years from one private and one public high school. These two schools were intentionally selected to ensure representation of students from different socioeconomic backgrounds. In coordination with the administrations of both schools, suitable classes from the 9th, 10th, 11th, and 12th grades were included, and all students in these classes were invited to participate. However, no quota-based or proportional sampling procedures were implemented to ensure balanced participation across schools or classrooms; therefore, the distribution of participants reflects the naturally occurring class and school sizes.

Participation was voluntary, and students who were absent or declined participation were classified as non-respondents and were not replaced. A detailed information and voluntary participation form and the parental/guardian consent form were signed prior to participation. Participants were included if they were aged 14–18 years, enrolled in grades 9–12 of the study school, able to read and understand Turkish, present during the data collection session, and provided assent along with parental/guardian consent. Exclusion criteria encompassed diagnosed cognitive or learning disabilities preventing completion of the instruments, acute or significant chronic medical or psychological conditions that may interfere with assessments, and refusal, withdrawal, or absence on the survey day.

Data collection procedures and tools

Data collection was carried out through a structured, self-administered questionnaire distributed in classroom settings under the direct supervision of a trained researcher. The questionnaire included demographic items (age, sex), daily internet and social media use (hours/day), and nutrition-related non-scale items such as the number of main meals and snacks consumed per day. Daily screen time variables (internet use and social media use,

hours/day) were obtained entirely through self-report, as participants manually stated their average usage; no device-based analytics (e.g., iOS Screen Time or Android Digital Wellbeing) were used. Height and weight were self-reported by students, and BMI percentiles were calculated using age- and sex-specific reference values based on the Centers for Disease Control and Prevention (CDC) growth charts, and weight-status categories were defined using CDC BMI percentile cut-offs: <5th percentile (underweight), 5th–<85th percentile (healthy weight), 85th–<95th percentile (overweight), ≥95th percentile (obesity), and ≥120% of the 95th percentile or ≥35 kg/m² (severe obesity).[14]

Social Media Addiction Scale for Adolescents (SMASA)

The SMASA was developed by Özgenel, Canpolat, and Ekşi (2019) to assess adolescents' levels of problematic social media use. The scale consists of 9 items rated on a 5-point Likert scale ranging from 1 (never) to 5 (always), with total scores ranging from 9 to 45. Higher scores indicate greater addiction tendencies. The scale was constructed based on DSM-5 criteria for behavioral addictions and demonstrated a unidimensional structure. It explained 56.8% of the total variance, and the internal consistency coefficient (Cronbach's alpha) was reported as 0.904, indicating excellent reliability.[15]

The Social Media Disorder Scale (SMDS)

The SMDS was originally developed by Van den Eijnden et al. (2016) and adapted into Turkish by Erzen and Odacı (2021) to measure problematic social media use among adolescents. The Turkish version consists of 13 dichotomous (yes/no) items grouped under three subdimensions: strain, insistence, and escape. Total scores range from 0 to 13, with higher scores indicating a greater risk of disordered social media use. Confirmatory factor analysis supported the three-factor structure, and the internal consistency coefficient (Cronbach's alpha) was reported as 0.81, demonstrating acceptable reliability.[16,17]

The Appearance-Related Social Media Consciousness Scale (ASMC)

In this study, adolescents' awareness and concern regarding their appearance on social media were assessed using the ASMC. The scale was originally developed by Choukas-Bradley et al. (2020) and later adapted into Turkish by Kurtuluş et al. and validated by Yıldırım et al. (2022). The ASMC consists of 13 items and employs a 7-point Likert scale, ranging from 1 (never) to 7 (always). Total scores range between 13 and 91, with higher scores indicating greater sensitivity to how one's appearance is perceived in online contexts and a higher degree of investment in maintaining online attractiveness. Psychometric analysis of the Turkish version demonstrated strong internal consistency, with a reported Cronbach's alpha coefficient of 0.89, indicating high reliability.[18,19]

The Scale of Effects of Social Media on Eating Behavior (SESMEB)

In this study, the SESMEB, developed by Keser et al. (2020), was employed to assess the influence of social media on adolescents' eating behaviors. The SESMEB comprises 18 items, each rated on a 5-point Likert scale ranging from 1 (never) to 5 (always), yielding total scores between 18 and 90. Higher scores indicate a greater perceived impact of social media on eating behaviors. The SESMEB exhibited excellent internal consistency, with a Cronbach's alpha coefficient of 0.928, indicating high reliability.[20]

The Eating Habits Questionnaire for Adolescents (EHQA)

In this study, adolescents' eating behaviors were assessed using the EHQA, which was originally developed by Bester and Schnell (2004) based

on the Eating Attitudes Test (EAT-26) and the Eating Behavior Test (EBT-16). The Turkish adaptation and validation of the scale were conducted by Yılmaz and Şişman (2021). The EHQA originally comprised 64 items rated on a 4-point Likert scale (1 = always to 4 = never), with higher scores reflecting healthier eating habits. Items with item–total correlations below 0.30 were removed stepwise, resulting in a 44-item scale with four factors: body image perception, external factors, nutrition, and exercise behavior. The internal consistency of the 44-item version was satisfactory, with a Cronbach's alpha coefficient of 0.84.[21,22]

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics version 30 (IBM Corp., Armonk, NY, USA) and the PROCESS macro (version 4.2) developed by Hayes. A two-tailed significance level of $p < 0.05$ was adopted.[23]

The distribution of continuous variables was examined using the Shapiro–Wilk test together with skewness / kurtosis statistics. Since these indicators suggested deviations from normality, nonparametric procedures were employed for group comparisons. Descriptive statistics were summarized as medians and interquartile ranges (IQR) for continuous variables, and as frequencies and percentages for categorical variables. Gender-based comparisons of age, BMI percentiles, internet use, social media use, social media–related scale scores and eating behavior outcomes were conducted using the Mann–Whitney U test. Differences in categorical BMI status (underweight, healthy weight, overweight, obesity) were examined using the chi-square (χ^2) test. Spearman's rho correlation coefficients were used to examine the associations among social media use and the total scores of SMASA, SMDS, ASMC, SESMEB, and EHQA, with results reported separately for female and male adolescents.

Multiple linear regression analyses were conducted to identify predictors of unhealthy eating habits, including social media use and the total scores of SMASA, SMDS, ASMC, and SESMEB, with analyses stratified by gender. Prior to the main analyses, data were examined for normality, linearity, and multicollinearity assumptions. Variance inflation factor (VIF) and tolerance values were inspected to assess multicollinearity, and all predictors fell within acceptable ranges (VIF = 1.03–2.20; tolerance = 0.45–0.96; acceptable thresholds: VIF < 5, tolerance > 0.40), indicating no multicollinearity concerns. Independent variables were selected a priori based on the theoretical framework and previous literature linking social media use and social media–related cognitive processes with adolescent eating behaviors. To ensure comparability across models, the same set of predictors was applied to both female and male adolescents, and no automated variable selection procedures (e.g., stepwise methods) were used. Values represent unstandardized regression coefficients (B), standardized coefficients (β), p-values, and 95% confidence intervals (CIs). Model performance was summarized using explained variance (R^2) and the F statistic for overall model significance.

Simple mediation analyses were conducted using PROCESS Model 4 (Hayes, 2022) to examine whether Appearance-Related Social Media Consciousness mediated the associations of Social Media Addiction (Model 1) and Social Media Disorder (Model 2) with unhealthy eating habits. All mediation analyses were performed separately for female and male adolescents. For each model, unstandardized coefficients (B), standardized coefficients (β), p-values, and 95% CIs were reported. Indirect effects were estimated using 5,000 bootstrap resamples with bias-corrected CIs. Direct, indirect, and total effects, as well as model summary statistics (R^2 and F values), were provided. To enhance interpretability, the key mediation pathways for both Model 1 and Model 2 were visualized using path diagrams created via the Confluence diagramming interface.

Results

Gender-based comparisons of demographic, anthropometric, social media, and eating behavior variables are presented in Table I. A total of 487 adolescents participated in the study, including 245 females and 242 males. Age did not differ significantly between females and males ($p = 0.088$). BMI percentiles were higher among males ($p < 0.001$), and weight status categories differed significantly by gender ($\chi^2 = 21.911$, $p < 0.001$). The number of main meals per day differed between groups ($p < 0.001$), whereas the number of snacks per day did not ($p = 0.562$). Daily internet use was similar across genders ($p = 0.142$). Daily social media use differed significantly between groups ($p = 0.037$). Females scored higher on SMASA, SMDS, ASMC, and SESMEB (all $p < 0.001$). Total EHQA scores also differed significantly between genders ($p < 0.001$). Gender-based differences were also observed across EHQA subscales, including body image perception ($p < 0.001$), external factors ($p < 0.001$), nutrition ($p = 0.014$), and exercise behavior ($p < 0.001$).

Gender-stratified correlations are presented in Table II. Among females, social media use, SMASA, SMDS, ASMC, and SESMEB were all positively correlated with one another (all $p < 0.01$), and each showed negative correlations with EHQA ($p < 0.05$ to $p < 0.01$). Among males, similar positive associations were observed among social media use, SMASA, SMDS,

Table I. Gender-based comparison of demographic, anthropometric, social media, and eating behavior variables

	Female	Male	p value*
Age, years	15.0 (14.0-16.0)	15.0 (14.0-16.0)	0.088
BMI percentiles	52.0 (27.5-73.0)	67.5 (41.5-87.0)	<0.001
Weight status			<0.001
Underweight	10 (4.1%)	6 (2.5%)	
Healthy weight	202 (82.4%)	166 (68.6%)	
Overweight	28 (11.4%)	45 (18.6%)	
Obesity	5 (2.0%)	25 (10.3%)	
Number of main meals per day	3 (2-3)	3 (2-3)	<0.001
Number of snacks per day	1 (1-2)	1 (1-2)	0.562
Internet use, hours/day	4.0 (3.0-5.0)	4.0 (3.0-5.0)	0.142
Social media use, hours/day	3.0 (2.0-4.0)	2.0 (1.0-4.0)	0.037
SMASA, total score	23.0 (18.0-27.0)	20.0 (17.0-25.0)	<0.001
SMDS, total score	7.0 (5.0-10.0)	6.0 (4.0-8.0)	<0.001
ASMC, total score	53.0 (37.0-69.0)	35.0 (23.0-51.0)	<0.001
SESMEB, total score	35.0 (29.0-42.0)	31.0 (22.0-39.0)	<0.001
EHQA, total score	121.0 (107.5-132.0)	128.0 (117.0-138.3)	<0.001
EHQA, body image perception	44.0 (32.5-52.0)	50.5 (43.0-55.0)	<0.001
EHQA, external factors	42.0 (37.0-47.0)	45.5 (40.0-51.0)	<0.001
EHQA, nutrition	29.0 (25.0-31.0)	27.0 (24.0-30.3)	0.014
EHQA, exercise behavior	9.0 (6.0-10.0)	7.0 (5.0-9.0)	<0.001

Values are presented as median (interquartile range) for continuous variables and n (%) for categorical variables (weight status).
*Weight status categories were compared using the chi-square (χ^2) test, and the p values for the comparisons of other variables were derived from the Mann–Whitney U test (for continuous variables).
ASMC: Appearance-Related Social Media Consciousness, EHQA: Eating Habits Questionnaire for Adolescents, SESMEB: Scale of Effects of Social Media on Eating Behavior, SMASA: Social Media Addiction Scale for Adolescents, SMDS: Social Media Disorder Scale.

Table II. Correlations between social media use and eating behavior by gender

	SMU	SMASA	SMDS	ASMC	SESMEB	EHQA
SMU, hours/day	------	0.353**	0.332**	0.322**	0.300**	-0.145*
SMASA, total score	0.368**	------	0.697**	0.395**	0.472**	-0.307**
SMDS, total score	0.259**	0.670**	------	0.348**	0.413**	-0.352**
ASMC, total score	0.044	0.203**	0.372**	------	0.344**	-0.456**
SESMEB, total score	0.052	0.331**	0.353**	0.384**	------	-0.355**
EHQA, total score	-0.013	-0.169**	-0.203**	-0.374**	-0.451**	------

Upper triangle (above the diagonal) shows results for female adolescents; lower triangle (below the diagonal) shows results for male adolescents. *p < 0.05; **p < 0.01 (Spearman's rho correlation)
ASMC: Appearance-Related Social Media Consciousness, EHQA: Eating Habits Questionnaire for Adolescents, SESMEB: Scale of Effects of Social Media on Eating Behavior, SMASA: Social Media Addiction Scale for Adolescents, SMDS: Social Media Disorder Scale, SMU: social media use.

Table III. Multiple regression analysis of predictors of unhealthy eating habits by gender

Predictors	Female					Male				
	B	β	p	%95 CI		B	β	p	%95 CI	
Age, years	-0.753	-0.051	0.358	-2.364	0.858	1.713	0.108	0.052	-0.017	3.442
BMI percentile	-9.758	-0.279	**<0.001**	-13.478	-6.039	-5.252	-0.228	**<0.001**	-7.775	-2.729
SMU, hours/day	0.506	0.062	0.279	-0.412	1.423	0.469	0.057	0.322	-0.462	1.401
SMASA, total score	0.065	0.026	0.741	-0.321	0.450	-0.252	-0.096	0.203	-0.641	0.137
SMDS, total score	-1.051	-0.203	**0.008**	-1.827	-0.276	0.155	0.029	0.711	-0.669	0.979
ASMC, total score	-0.295	-0.373	**<0.001**	-0.388	-0.203	-0.242	-0.260	**<0.001**	-0.352	-0.132
SESMEB, total score	-0.250	-0.172	**0.005**	-0.422	-0.077	-0.498	-0.368	**<0.001**	-0.657	-0.339
Model Summary Statistics:	R^2: 0.362, F: 19.175					R^2: 0.313, F: 15.246				

Values represent unstandardized regression coefficients (B), standardized coefficients (β), p-values, and 95% confidence intervals (CIs). Separate multiple linear regression models were conducted for female and male adolescents. R^2 represents the coefficient of determination, and F indicates the overall significance of the regression model. Regression assumptions—including residual normality, homoscedasticity, and multicollinearity—were assessed prior to analysis. All tolerance and VIF values fell within acceptable limits, confirming the absence of multicollinearity.
ASMC: Appearance-Related Social Media Consciousness, BMI: body mass index, SESMEB: Scale of Effects of Social Media on Eating Behavior, SMASA: Social Media Addiction Scale for Adolescents, SMDS: Social Media Disorder Scale, SMU: social media use, VIF: variance inflation factor.

ASMC, and SESMEB (all p < 0.01), while EHQA was negatively correlated with SMASA, SMDS, ASMC, and SESMEB (all p < 0.01), but not with social media use.

Multiple regression analyses examining predictors of unhealthy eating habits by gender are summarized in Table III. For female adolescents, BMI percentile, SMDS, ASMC, and SESMEB were significant predictors of EHQA scores (all p < 0.01), while age, SMU, and SMASA were not significant. The overall model was significant (R^2 = 0.362, F = 19.175). For male adolescents, BMI percentile, ASMC, and SESMEB were significant predictors (all p < 0.001), whereas age, SMU, SMASA, and SMDS were not. The overall model was significant (R^2 = 0.313, F = 15.246).

Mediation analyses examining the indirect effects of SMASA and SMDS on unhealthy eating habits through appearance-related social media consciousness are presented in Table IV and illustrated in Fig. 1 and Fig. 2, which visually depict these mediation pathways, showing standardized and unstandardized coefficients,

significance levels, and the distinction between full and partial mediation across female (pink) and male (blue) adolescents.

Model 1 (SMASA → EHQA via ASMC): For females, SMASA significantly predicted ASMC ($p < 0.001$), and ASMC significantly predicted EHQA ($p < 0.001$). The total effect of SMASA on EHQA was significant ($p < 0.001$), and the indirect effect (95% CI: –0.582 to –0.236) was also significant. The direct effect remained significant ($p = 0.010$), indicating partial mediation. The model accounted for 10.1% of the variance ($R^2 = 0.101$, $F = 27.377$). For males, SMASA significantly predicted ASMC ($p = 0.002$), and ASMC significantly predicted EHQA ($p < 0.001$). The total effect was significant ($p = 0.006$), as was the indirect effect (95% CI: –0.325 to –0.050), while the direct effect was non-significant ($p = 0.076$), indicating full mediation. The model explained 3.1% of the variance ($R^2 = 0.031$, $F = 7.740$).

Model 2 (SMDS → EHQA via ASMC): For females, SMDS significantly predicted ASMC ($p < 0.001$), and ASMC significantly predicted EHQA ($p < 0.001$). Both the total effect ($p < 0.001$) and indirect effect (95% CI: –1.045 to –0.395) were significant, while the direct effect remained significant ($p < 0.001$), indicating partial mediation. The model explained 14.4% of the variance ($R^2 = 0.144$, $F = 40.788$). For males, SMDS significantly predicted ASMC ($p < 0.001$), and ASMC significantly predicted EHQA ($p < 0.001$). The total effect ($p = 0.001$) and indirect effect (95% CI: –0.983 to –0.385) were significant, whereas the direct effect was non-significant ($p = 0.218$), indicating full mediation. The model accounted for 4.2% of the variance ($R^2 = 0.042$, $F = 7.827$).

Table IV. Mediation models of social media addiction / disorders and unhealthy eating habits via appearance-related social media consciousness

Model / Paths	Female					Male				
	B	β	p	%95 CI		B	β	p	%95 CI	
MODEL 1: Social Media Addiction → Unhealthy Eating Habits										
Social Media Addiction → Mediator	1.299	0.407	**<0.001**	0.965	1.633	0.563	0.200	**0.002**	0.168	0.959
Mediator → Unhealthy Eating Habits	-0.306	-0.386	**<0.001**	-0.416	-0.195	-0.314	-0.337	**<0.001**	-0.420	-0.208
Total Effect	-0.804	-0.318	**<0.001**	-1.118	-0.490	-0.463	-0.177	**0.006**	-0.848	-0.077
Direct Effect	-0.407	—	**0.010**	-0.754	-0.060	-0.286	—	0.076	-0.658	0.086
Indirect Effect	-0.397	—	**sign.**	-0.582	-0.236	-0.177	—	**sign.**	-0.325	-0.050
Total Model Summary Statistics:	R^2: 0.101, F: 27.377					R^2: 0.031, F: 7.740				
MODEL 2: Social Media Disorder → Unhealthy Eating Habits										
Social Media Disorder → Mediator	2.417	0.370	**<0.001**	1.675	3.159	2.182	0.378	**<0.001**	1.558	2.807
Mediator → Unhealthy Eating Habits	-0.286	-0.361	**<0.001**	-0.387	-0.185	-0.306	-0.329	**<0.001**	-0.419	-0.193
Total Effect	-1.961	-0.379	**<0.001**	-2.591	-1.332	-1.098	-0.205	**0.001**	-1.879	-0.325
Direct Effect	-1.271	—	**<0.001**	-1.919	-0.623	-0.431	—	0.218	-1.223	0.361
Indirect Effect	-0.690	—	**sign.**	-1.045	-0.395	-0.667	—	**sign.**	-0.983	-0.385
Total Model Summary Statistics:	R^2: 0.144, F: 40.788					R^2: 0.042, F: 7.827				

Values represent unstandardized path coefficients (B), standardized coefficients (β) when available, p-values, and 95% confidence intervals (CIs). Some β and p-values are not reported ("—" or "sign.") because PROCESS Model 4 does not compute standardized coefficients or exact significance levels for specific indirect paths under bootstrapping procedures. R^2 represents the coefficient of determination and F indicates the overall model significance. Predictors: Social Media Addiction and Social Media Disorder; Mediator: Appearance-Related Social Media Consciousness; Outcome: Unhealthy Eating Habits.

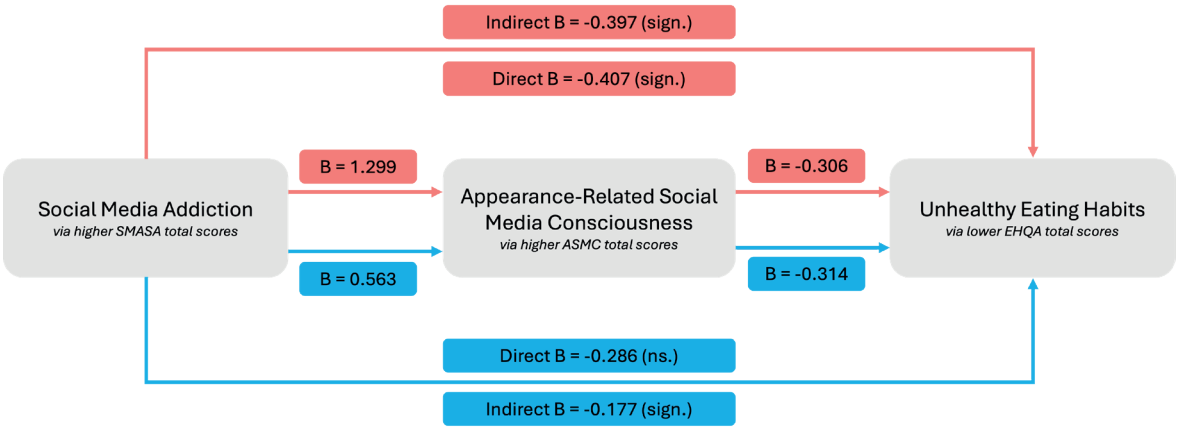

Fig. 1. Mediation model for Social Media Addiction → ASMC → Unhealthy Eating Habits (Model I)

Standardized and unstandardized coefficients (B), direct and indirect effects, and significance levels (sign./ns.) are displayed for female (pink) and male (blue) adolescents. C

ASMC: Appearance-Related Social Media Consciousness, EHQA: Eating Habits Questionnaire for Adolescents, SMDS: Social Media Disorder Scale.

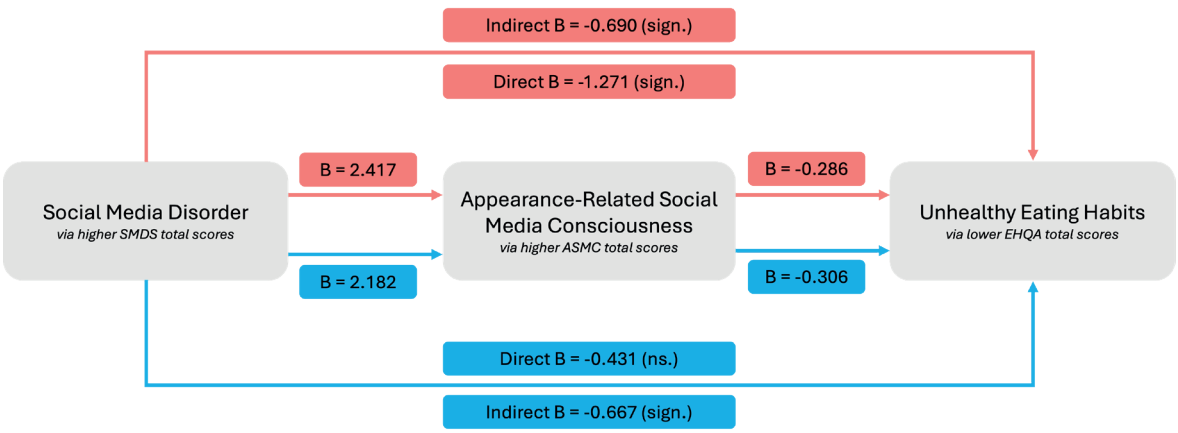

Fig. 2. Mediation model for Social Media Disorder → ASMC → Unhealthy Eating Habits (Model II)

Standardized and unstandardized coefficients (B), direct and indirect effects, and significance levels (sign./ns.) are displayed for female (pink) and male (blue) adolescents. C

ASMC: Appearance-Related Social Media Consciousness, EHQA: Eating Habits Questionnaire for Adolescents, SMDS: Social Media Disorder Scale.

Discussion

This study provides important insights into gender differences in the associations between social media use and adolescents' eating behaviors. Our findings show that female adolescents report significantly higher levels of social media use, addiction, and disorder compared to males, and these characteristics are linked to less healthy eating patterns. Appearance-related social media consciousness emerged as both a negative correlate of healthy eating and a mediating factor in the statistical pathways connecting social media addiction and disorder with eating behaviors. Notably, the mediating role of appearance-related consciousness differed by gender.

Although overall internet use was similar across genders, female adolescents reported higher daily social media use as well as higher levels of social media addiction and disorder compared to male adolescents. This pattern aligns with our findings and is consistently supported by

previous research.[24-27] Evidence from large-scale international datasets further reinforces this trend. For instance, the Health Behaviour in School-Aged Children study conducted in collaboration with the WHO across 42 countries reports that female adolescents exhibit markedly higher rates of intensive and problematic social media use.[28] In parallel, a longitudinal four-wave study spanning 18 months found that female adolescents consistently maintained higher levels of active social media use at all measurement points compared to their male counterparts.[29] Moreover, results from the Generation R Study showed that female adolescents were 36–58% more likely than males to be social media users, highlighting a persistent and robust gender difference in digital engagement patterns.[30]

Appearance-based social media consciousness refers to individuals' ongoing preoccupation with how they appear to others on social media and is strongly associated with body dissatisfaction.[18] Consistent with this conceptualization, female adolescents in our study demonstrated markedly higher levels of appearance-related social media preoccupation. This preoccupation was positively associated with social media use duration, addiction, and disorder; however, the association with use duration emerged only among girls, underscoring a gender-specific pattern. These results are consistent with prior research demonstrating that girls tend to engage more intensively with appearance-focused social media content, and are additionally supported by studies linking social appearance anxiety with social media addiction.[31-33] Such patterns can be interpreted through *objectification theory*, which posits that gendered socialization fosters an externalized perspective of the body, particularly among female adolescents. This self-objectification leads individuals to perceive themselves as objects continually evaluated by others. Social media platforms, where others' gaze is perpetually present, facilitate this process by enabling content curation, sharing, and peer feedback in the form of likes and comments, thus reinforcing appearance-focused evaluations.[34] Consequently, the greater salience of social media dynamics among female adolescents may be associated with increased appearance-related awareness, reflecting a potential reciprocal alignment between social media engagement and body image concerns rather than a directional causal process.[35,36] These associations can also be explained through the *social comparison theory*. Accordingly, female adolescents are prone to upward comparisons on social media—contrasting themselves with those perceived as superior—and internalizing the appearance ideals these figures portray. This process is linked to negative body image and heightened body dissatisfaction among female adolescents.[37] Consistently, Ioannou et al.[36] reported that increased social media use is associated with greater body dissatisfaction, potentially due to intensified cognitive preoccupation with appearance in digital contexts.[38] Notably, findings from recent research also show that Turkish girls report lower satisfaction with their bodies compared to boys, further supporting this gender-specific vulnerability.

Adolescence is a period when eating behaviors become increasingly complex, with social media–related factors adding to body dissatisfaction.[39] Gender differences emerge not only in social media use but also in its impact on eating behaviors, highlighting the importance of examining psychosocial mediators from a gender-specific perspective.[20] Compared to males, female adolescents experience the impact of social media on eating behaviors more strongly, a finding consistent with previous literature.[40-42] Among female adolescents, longer social media use appears to be associated with less healthy eating behaviors. Spending more than two hours per day on social media has been associated with higher SESMEB scores compared to spending less time, but this finding has been demonstrated only in female students.[40,42] This result is consistent with the present study, which showed a positive

association between social media use and SESMEB scores only among female adolescents.

Although numerous studies have demonstrated the association between social media use and eating behaviors, mediators have typically focused on body dissatisfaction.[43-45] During adolescence—a period marked by heightened appearance sensitivity and identity formation—exposure to social media content such as *fitspiration* or *thinspiration* contributes to the internalization of unrealistic beauty ideals and the normalization of restrictive eating behaviors. These processes appear particularly pronounced among female adolescents who interact more frequently with beauty- and diet-related content.[46] Female adolescents also share appearance- and food-focused social media content more than males, which conceptually links to eating behaviors.[47]Appearance-based rejection sensitivity has also been identified as a mediator in the relationship between social media addiction and disordered eating.[45] Moreover, recent multi-path mediation research has highlighted that excessive social media use can predict both restrained eating and emotional overeating through appearance and weight esteem. While these indirect pathways emerged for both outcomes, gender differences were observed: appearance esteem mediated the link between social media use and emotional overeating only among females, whereas the pathway to restrained eating did not differ by gender.[48] In another serial mediation framework, Foster et al.[49] demonstrated that Snapchat use was associated with greater appearance-based social comparisons, which in turn were linked to a stronger drive for thinness and to patterns of problematic, compensatory eating behaviors. This further supports the notion that social media influences eating behaviors primarily through appearance-oriented cognitive mechanisms rather than through direct exposure alone.[49] Our findings align with this literature. Mediation analyses revealed that ASMC significantly mediated the relationship between social media addiction and disorder and eating behaviors among female adolescents, while for male adolescents, this mediation was only partially significant and limited to social media disorder. Direct effects were significant only among female adolescents. Additionally, ASMC mediated the association between social media use duration and eating behaviors in female but not in male adolescents. This pattern is consistent with evidence from Zaharia and Gonta[50], who identified similar appearance-based mediating pathways connecting social media engagement to compensatory eating behaviors.

The mechanisms linking social media participation, including use, addiction, and disorder, to eating behaviors can be explained through several psychological and sociocultural frameworks. Social Cognitive Theory suggests that adolescents internalize body ideals and dietary patterns via observational learning and reinforcement, amplified by constant exposure to peers, influencers, and digital celebrities.[51] Similarly, the Tripartite Influence Model shows how media, peers, and family jointly shape body image concerns and disordered eating, with social media merging these influences in a highly visual, interactive environment.[52] Uses and Gratifications Theory further explains that adolescents turn to social media to fulfill needs for self-expression, validation, and social comparison, making them more receptive to appearance- and food-related content.[53] Interactive features such as likes, comments, and filters intensify feedback loops that reward idealized appearance and restrictive eating, fostering emotional vulnerability and maladaptive behaviors like emotional eating, food restriction, or bingeing. In the context of influencer-driven digital food marketing, these processes normalize impulsive, unhealthy eating habits among youth and enable the rapid peer-driven spread of behaviors through the contagion effect.[54] Moreover, body dissatisfaction, long recognized as a key predictor of disordered eating, has become increasingly salient on visual platforms. The Perfect Storm framework posits that these interactive features intersect with developmental vulnerabilities,

such as heightened peer sensitivity and identity formation, creating a high-risk environment for body image concerns and maladaptive eating.[55] Excessive social media engagement and addiction can further disrupt adolescents' biological, psychological, and social functioning, undermining healthy lifestyle habits.[56]

Our findings indicate that when compared with females, male adolescents appear more advantaged in adopting healthy eating behaviors. Although previous literature has generally associated male gender with lower diet quality, cultural differences may influence these outcomes and should be considered.[57-58] A recent systematic review highlighted that the determinants of dietary habits differ by gender: females are more strongly influenced by external motivators (e.g., the ideal of thinness), whereas males are more driven by internal motivators (e.g., pleasure, improving physical performance).[59] In Türkiye, research has shown that female adolescents report higher levels of emotional and external eating, which are associated with lower mindful eating.[60] Additionally, the prevalence of disordered eating behaviors has been found to be higher among female adolescents than male adolescents.[61]

This study has several limitations. First, its cross-sectional design prevents causal inferences regarding the associations among social media use, appearance-related mechanisms, and eating behaviors. Second, all behavioral variables including screen time, anthropometric indicators, and eating habits were self-reported, which may introduce recall bias and common-method variance. Third, although one private and one public high school were selected to reflect socioeconomic diversity, the study was conducted within a single district and participation was not balanced across schools or classrooms, potentially limiting representativeness. Fourth, because students were nested within classes and schools, their responses may not have been fully independent, and clustering effects could have influenced the precision of regression estimates. Fifth, although the models included key social media variables, appearance-related social media consciousness, and basic demographics (age, BMI percentile, gender), other important confounders such as socioeconomic status, parental education, physical activity, sleep, and mental health were not measured and therefore could not be controlled for. Finally, the mediation analyses relied on unstandardized PROCESS outputs, which do not report standardized indirect effects or p-values, limiting the granularity of interpretation. Future studies should incorporate longitudinal designs, objective digital-behavior metrics, and more comprehensive confounder assessments to strengthen causal inference.

In conclusion, this study underscores the pivotal role of appearance-related social media consciousness in shaping the pathways through which various social media dynamics, including use, addiction, and disorder, shape adolescents' tendencies toward both healthy and unhealthy eating behaviors. Notably, these mechanisms were more pronounced among female adolescents, highlighting gender-specific vulnerabilities in the digital environment. Our findings emphasize the need for tailored interventions that promote media literacy, critical engagement with appearance-focused online content, and body awareness to support healthier digital habits and eating patterns. Furthermore, the results point to important implications for policymakers and educators, who should consider regulating digital food and appearance-related marketing and developing gender-sensitive prevention programs to mitigate the adverse effects of social media on adolescent health.

Ethical approval

This study was approved by the Muğla Sıtkı Koçman University Medical and Health Sciences Ethics Committee with the date 20/10/2023 and numbered 230077-118 (protocol-decision). Additionally, permission to conduct the research was granted by the Turkish

Ministry of National Education on 13/11/2023. Participation was voluntary, and informed consent was obtained from all students prior to data collection.

Author contribution

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

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

The relationship between early feeding skills and general movements of preterm infants in the neonatal intensive care unit

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ABSTRACT

Background. Early feeding skills and general movements (GMs) are negatively affected by hypotonia due to prematurity. Interventions for feeding skills can be guided by understanding the relationship between feeding skills and GMs. In the light of this, the study focused on understanding the relationship between early feeding skills and preterm infants' GMs in the neonatal intensive care unit (NICU).

Methods. Participants in this cross-sectional study were forty infants with a postmenstrual age of 34–37 weeks who were hospitalized in the NICU at Abant İzzet Baysal University Training and Research Hospital. The data consisted of demographic characteristics (birth weight, gestational age, date of birth, age, and sex), feeding skills, assessed with the Early Feeding Skills Assessment Tool, and GMs, assessed with the General Movement Assessment.

Results. A strong correlation was found between the Oral-Motor Function subscale of the Early Feeding Skills Assessment Tool and the Upper Limbs subscale of the General Movements Motor Optimality Score (rho=0.74, p=0.001). Among the demographic characteristics, only maternal age was associated with feeding skills. A weak correlation was determined between the Physiologic Stability subscale of the Early Feeding Skills Assessment Tool and maternal age (rho=0.34 p=0.03).

Conclusions. This study reveals the relationship between feeding skills and general movement of preterm infants at NICU. GMs of upper extremity were found to positively affect feeding skills. This process may be accelerated by interventions to improve the GMs of upper extremity during the transition to oral feeding.

Key words: infant, movement, premature, upper extremity.

Preterm infants face substantial feeding challenges as a result of the immaturity of their oral–motor, neurological, and gastrointestinal systems. Approximately 80% experience oral feeding difficulties during their hospitalization in the neonatal intensive care unit (NICU).[1] Such difficulties not only delay hospital discharge, but may also adversely affect growth trajectories and neurodevelopment if not promptly identified and addressed. Moderate and late preterm infants generally present with less severe medical complications than those born very preterm; however, they still face a greater risk of adverse neurodevelopmental outcomes when compared with term infants.[2] Late preterm infants also show a high prevalence of feeding

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problems due to factors such as immature brain development, incoordination of the suck-swallow-breathing, lower oromotor tone, gastrointestinal dysmotility, immature suction pressure, higher incidence of gastroesophageal reflux and disturbed sleep–wake cycles. These issues often lead to several problems: hypoglycemia, hyperbilirubinemia, prolonged nasogastric tube feeding, delayed achievement of oral feeding independence, and reduced breastfeeding rates.[3-5] These infants are also at risk for hypothermia, respiratory morbidities, infection, intraventricular hemorrhage (IVH), and periventricular leukomalacia (PVL).[4] This population is often affected by incomplete coordination of suck–swallow–breathe, which may be further disrupted by comorbidities such as gastroesophageal reflux, necrotizing enterocolitis (NEC), or respiratory instability.[1,6]

The acquisition of feeding skills is a complex process that requires the coordination of three actions: sucking, swallowing and breathing.[7] Additionally, the coordination of multiple sensory-motor systems is necessary to avoid serious adverse effects such as coughing, gagging, apnea, bradycardia, hypoxia, tachypnea, increased energy expenditure, and aspiration.[8-10] The development of the coordination among these three actions in preterm infants is a dynamic process and typically does not begin until the postmenstrual age (PMA) of 32 to 34 weeks.[11] Feeding is one of the first coordinated motor skills an infant requires;[12] therefore, difficulties in this area are considered an early marker of brain changes associated with atypical motor and neurological development.[13-15] Sucking ability may seem "natural" for healthy term infants, but this is not the case for premature infants.[16] Moreover, achieving independence in oral feeding is challenging, as it requires the integration of the lips, jaw, cheeks, tongue, palate, pharynx, and larynx to establish coordinated sucking, breathing, and swallowing.[17] In preterm infants, it is common to see disruptions in the coordination of these actions, as well as abnormal feeding behaviors such as atypical jaw or tongue movements, leading to inadequate nutrition.[18] Early sucking and feeding skills predict infant neurodevelopmental outcome.[19] In addition, preterm infants with feeding difficulties have been reported to be at risk for delayed cognitive and language development in long-term follow-up.[20]

Feeding and swallowing of the upper gastrointestinal tract and are controlled by specific brain regions and cranial nerves. The coordination of these movements is regulated by central pattern generators (CPGs). These neuronal networks, typically located in the spinal cord or brainstem, autonomously coordinate the activity of multiple muscles into movement series without requiring segmental sensory or supraspinal input.[21]

General movements (GMs) are generated and controlled by the discharge of CPGs, in the same way that breathing, sucking, and swallowing are.[22,23] Prechtl's General Movements Analysis is a widely used predictive tool, whose assessments are based on visual perception of age-specific normal or abnormal spontaneous GMs.[24] This assessment method is considered a highly sensitive and reliable tool for evaluating the immature nervous system.[25] The three main chronological periods of GMs are known as 'Preterm' (up to about 36 weeks of gestational age), 'Writhing' (up to about 8 weeks of postterm age) and, 'Fidgety' movements (9 to about 20 weeks of postterm age).[26] In both preterm and term periods, GMs are defined as variable, whole-body movements characterized by a fluid sequence of arm, leg, neck, and trunk motions. Throughout this period, GMs emerge and disappear with varying intensity, speed, and range of motion.[24] Reduced variation and diversity in GMs are strongly associated with cerebral palsy, a condition that originates from CPGs located in the spinal cord and brainstem.[22,23,27]

To the best of our knowledge, no study has evaluated the relationship between preterm infants' feeding skills and their GMs during the writhing period, which are considered the

earliest spontaneous movements. However, one study, Nieuwenhuis et al., reported that the development of sucking patterns in preterm infants during the fidgety period depends on the quality of fidgety movements themselves. Uncoordinated sucking patterns were associated with abnormal fidgety movements, suggesting that uncoordinated sucking, swallowing, and breathing may indicate underlying neurological dysfunction.[28] In the light of this important discovery, this study aimed to investigate the relationship between early GMs, and feeding skills in preterm infants between 34 and 37 weeks PMA.

Materials and Methods

This cross-sectional study included 40 preterm infants with a PMA of 34–37 weeks who were hospitalized in the Neonatal Intensive Care Unit of Abant İzzet Baysal University Training and Research Hospital between November 2022 and December 2024. Ethical approval was given by the Clinical Research Ethics Committee of Bolu Abant İzzet Baysal University (approval number: 2022/266, approval date: 25.10.2022). Informed consent was obtained from the parents of all participating infants. The three data sources were demographic information (birth weight, gestational age, date of birth, age, and sex), feeding skills measured using the Early Feeding Skills Assessment Tool (EFS), and GMs, evaluated using the General Movement Assessment.

Participants

Samples of preterm infants who admitted to the Neonatal Intensive Care Unit of Abant İzzet Baysal University Training and Research Hospital and fulfilled the inclusion criteria were recruited through continuous convenience sampling. There were 40 infants who had a postmenstrual age of 34-37 weeks in this study following the acquisition of written informed consent from their parents. Requirements for inclusion were as follows: postmenstrual age of between 34 and 37 weeks, no requirement for ventilation assistance, a history of preterm birth, and the capacity to engage in oral feeding. Infants were excluded if they had congenital malformations, genetic disorders, or metabolic diseases.

Measurements

Assessments were conducted in a quiet environment where the average noise level did not exceed 45 dB. Records were made of the infants' gestational age, birth weight, corrected age, and sex. The following information was also documented: time to transition to oral feeding, hospitalization duration and the presence of morbidities such as intracranial hemorrhage (ICH), PVL, congenital malformation, respiratory distress syndrome, sepsis, hypoglycemia, hyperbilirubinemia, patent ductus arteriosus (PDA), and NEC.

Early feeding skills assessment tool

The feeding skills of all infants were assessed using the EFS by one researcher (S.A.T.) during a 5-minute bottle-feeding session. A new bottle and a rubber bottle nipple were used for each newborn. These sessions were conducted at least two hours after the previous feeding. During feeding, infants were positioned in a 30-degree reclined supine angle in the arms of the nurse.[29] It is a valid and reliable tool for assessing feeding skills in preterm infants, based on the observation of feeding behavior.[30] The Turkish version consists of 19 items across five subscales: breathing regulation, oral-motor function, swallowing coordination, feeding engagement, and physiological stability. Each item is rated using a three-point Likert scale, with specific response options for each item. The ranges for the subscales are as follows: breathing regulation subscale, 5-15 points, oral-motor function subscale 4-12 points, swallowing coordination subscale, 4-12 points, feeding engagement subscale, 2-6 points and physiological stability subscale, 4-12 points. The total EFS score ranges from 19 to 57, with higher scores indicating more mature feeding skills.

Turkish version of the EFS has a high test-retest reliability with an ICC of 0.95.[31]

General movements assesment

In general, general movements (GMs) maintain a similar appearance from the early fetal period until the second month of term age. From term age onward, these movements are referred to as "writhing movements." At 6–9 weeks post-term age, these movements are gradually replaced by fidgety GMs. Spontaneous movements in infants were assessed observationally using the General Movements Assessment (GMA), developed by Prechtl. This involved making short (three- to five-minute) video recordings of each infant, which were used by a GM Trust-certified evaluator (S.A.T.) to calculate the General Movement Optimality Score–Revised (GMOS-R).[26]

This detailed assessment employs a semi-quantitative approach using a standardized scale to detect minimal changes in movement quality. A score was assigned to each movement criterion, such as amplitude, speed, range in space, initiation, and termination of GMs.

The General Movement Optimality Score–Revised (GMOS-R) ranges from 0 to 38, with higher scores indicating better movement quality. The scoring is distributed as follows: Upper extremities 0–16 points, lower extremities 0–16 points, neck and trunk 0–4 points, sequencing 0–2 points.[32,33]

Statistical analysis

The sample size was calculated using the G*Power 3.1.9.2 software. Post hoc analysis was performed with a correlation coefficient of 0.59 between the total scores of the EFS and the General Movements Motor Optimality Score, an alpha level of 0.05, and a total sample size of 40. These parameters resulted in a study power of 0.98.

Statistical analysis was conducted using the SPSS (Statistical Package for Social Sciences) software (version 20.0). The Shapiro-Wilk test was used to assess the normality of data distribution. Descriptive statistics were presented as mean ± standard deviation and median (interquartile range, IQR) for continuous variables, and as numbers and frequencies for binary and categorical variables. Comparisons between two independent groups (presence vs. absence of respiratory distress syndrome or sepsis) were performed using the Mann-Whitney U test. Categorical variables were compared using Fisher's exact test. The Spearman correlation test was performed to examine the relationship between the EFS and the General Movements Motor Optimality Score in preterm infants. The strength of correlation coefficients was classified as < 0.50 (weak correlation), 0.50-0.70 (moderate), or > 0.70 (strong).[34] A p-value of <0.05 was considered statistically significant for all analyses.

Results

The study included preterm infants with a mean gestational age of 33.52±1.50 weeks, and for 30% of these the age was 34 weeks. ICH was detected in one case, located in the left ventricle, with a severity of Grade 3. Periventricular leukomalacia was observed in two cases, both bilateral, with a severity of Grade 1. The mean duration to achieve full oral feeding was 14.33±10.31 days, and the mean hospitalization duration was 19.90±16.15 days. The clinical characteristics of the preterm infants are summarized in Table I.

The mean scores of Feeding Skills and General Movements Quality of Preterm Infants are presented in Table II. The EFS showed a mean score of 13.03±2.29 for the Respiratory Regulation subscale, 9.23±2.24 for Oral-Motor Function, 10.95±1.82 for Swallowing Coordination, 4.43±0.78 for Engagement, and 10.78±1.34 for Physiologic Stability. The total score for this assessment was 48.40±7.11. For the General Movements Motor Optimality Score, the mean scores for the four subscales were as follows: for the Upper Limbs, 15.60±2.58, for the Lower Limbs, 15.13±3.08, for Neck

Table I. Clinical profile of preterm infants (N=40).

Variables	
Maternal age, years, mean±SD	35.53±1.19
Mode of delivery, n (%)	
Cesarean Section	40 (100)
Vaginal birth	0 (0)
Sex, n (%)	
Female	23 (57.5)
Male	17 (42.5)
Gestational age, weeks, mean±SD	33.52±1.50
Gestational age categories, n (%)	
30 weeks	2 (5)
31 weeks	3 (7.5)
32 weeks	2 (5)
33 weeks	11 (27.5)
34 weeks	12 (30)
35 weeks	7 (17.5)
36 weeks	3 (7.5)
Birth weight, grams, mean±SD	2101.35±382.69
Birth weight categories, n (%)	
LBW (< 2500 gram)	1 (2.5)
Very LBW (< 1500 gram)	31 (77.5)
Extremely LBW (< 1000 gram)	8 (20)
Time to transition to oral feeding, days, mean±SD	14.33±10.31
Hospitalization duration, days, mean±SD	19.90±16.15
Periventricular leukomalacia, n (%)	2 (5)
Congenital malformation, n (%)	0 (0)
Respiratory distress syndrome, n (%)	27 (67.5)
Sepsis, n (%)	29 (72.5)
Hypoglycemia, n (%)	3 (7.5)
Hyperbilirubinemia, n (%)	36 (90)
Patent ductus arteriosus, n (%)	4 (10)
Necrotizing enterocolitis, n (%)	0 (0)

LBW: low birth weight, SD: standard deviation.

and Trunk, 3.15±0.83, and for the Sequence of General Movements, 1.70±0.46. The total score for this assessment was 35.65±6.04. In the global assessment, 31 infants (77.5%) were classified as having a Poor Repertoire, while 9 (22.5%) were classified as normal. Preterm infants without respiratory distress syndrome demonstrated significantly higher scores in oral-motor function (p=0.02), engagement (p=0.003), physiologic stability (p=0.007), and total score (p=0.01) compared to those with respiratory distress syndrome. Additionally, the upper limb subscale of the General Movements Motor Optimality Score was significantly higher in infants without respiratory distress (p=0.02) (Table II).

Weak, moderate, and strong correlations were observed between the subscales of the EFS and the General Movements Motor Optimality Score (rho=0.34 to 0.74, p<0.05) (Table III). The lowest correlation was between the Physiologic Stability subscale of the EFS and the Neck and Trunk subscale of the General Movements Motor Optimality Score (rho=0.34, p=0.02). The highest correlation was observed between the Oral-Motor Function subscale of the EFS and the Upper Limbs subscale of the General Movements Motor Optimality Score (rho=0.74, p=0.001). A moderate correlation was found between the total score of the EFS and the total score of the General Movements Motor Optimality Score (rho=0.59, p=0.001).

Correlation analyses showed several significant associations between the EFS and clinical variables in preterm infants (Table IV). Maternal age showed a weak positive correlation with Physiologic Stability (rho=0.34, p=0.03). Time to transition to oral feeding demonstrated significant negative correlations with all subscales, including Respiratory Regulation (rho=–0.43, p=0.005), Oral-Motor Function (rho=–0.52, p=0.001), Swallowing Coordination (rho=–0.49, p=0.003), Engagement (rho=–0.46, p=0.003), Physiologic Stability (rho=–0.54, p=0.001), and the total score (rho=–0.58, p=0.001). Similarly, length of hospital stay was strongly and negatively correlated with all subscales and the total score (rho range=–0.54 to –0.70, all p=0.001) (Table IV).

Correlation analyses revealed several significant associations between the General Movements Motor Optimality Score and clinical variables in preterm infants (Table V). Maternal age was positively correlated with Neck and Trunk scores (rho=0.40, p=0.009). Gestational age showed a positive correlation with the Sequence of General Movements (rho=0.35, p=0.02). Time to transition to oral feeding was negatively correlated with Upper Limbs (rho=–0.40, p=0.01), Lower Limbs (rho=–0.51, p=0.001), Total Score (rho=–0.43, p=0.005), and Global Assessment (rho=–0.34, p=0.02). Similarly, length of hospital stay demonstrated negative correlations with Upper Limbs (rho=–0.40, p=0.009), Lower Limbs (rho=–0.53, p=0.001), Total Score (rho=–0.43, p=0.005), and Global Assessment (rho=–0.33, p=0.03) (Table V).

Discussion

This study included preterm infants transitioning to oral feeding. A strong positive correlation was found between oral motor function and upper extremity GMs; in other words, the better the general movements of the upper extremities, the better the feeding skills. Better feeding skills are more likely to lead to the development of independent feeding skills in the future. This finding suggests that rehabilitation interventions aimed at developing preterm infants' oral feeding, and generally improving their overall feeding skills should target upper extremity GMs. Additionally, it is known that GMs are directly linked to development of feeding skill and play a crucial role in early feeding skills. Therefore, the most effective interventions for preterm infants are

Table II. Feeding skills and general movements quality of preterm infants, and their comparison between infants with and without respiratory distress syndrome and sepsis.

Variables	Mean±Standard Deviation (N=40)	Respiratory Distress Syndrome			Sepsis		
		Presence (n=17)	Absence (n=23)	P*	Presence (n=11)	Absence (n=29)	P*
		Median (IQR)			Median (IQR)		
Early Feeding Skills Assessment Tool							
Respiratory regulation	13.03±2.29	13 (10.5-14)	15 (10-15)	0.09	14 (12-15)	13 (10-14)	0.14
Oral-motor function	9.23±2.24	8 (6.5-10)	10 (10-12)	**0.02**	9 (8-12)	8 (6-10)	0.29
Swallowing coordination	10.95±1.82	12 (10-12)	12 (10-12)	0.20	12 (10-12)	11 (10-12)	0.36
Engagement	4.43±0.78	4 (4-5)	5 (4-5)	**0.003**	4 (4-5)	4 (4-5)	0.80
Physiologic stability	10.78±1.34	10 (9-11)	12 (11-12)	**0.007**	11 (10-12)	12 (9-12)	0.64
Total	48.40±7.11	49 (49-50.5)	53 (46-55)	**0.01**	50 (46-54)	50 (40-55)	0.33
General Movements Motor Optimality Score							
Upper limbs	15.60±2.58	15 (12-17)	18 (14-18)	**0.02**	17 (15-18)	14 (12-18)	0.32
Lower limbs	15.13±3.08	16 (10-16)	16 (16-18)	0.05	16 (13 -17)	16 (11-18)	0.97
Neck and trunk	3.15±0.83	3 (2-4)	3 (3-4)	0.40	3 (3-4)	3 (3-4)	0.60
Sequence of general movements	1.70±0.46	2 (1-2)	2 (1-2)	0.94	2 (1-2)	2 (1-2)	0.81
Total	35.65±6.04	37 (26-39)	38 (32-42)	0.05	38 (34-40)	36 (28-42)	0.80
Global assessment, n (%)							
Poor repertoire	31 (77.5)	16 (51.6)	15 (48.4)	0.05$^{\beta}$	23 (74.2)	8 (25.8)	0.68$^{\beta}$
Normal	9 (22.5)	1 (11.1)	8 (88.9)		6 (66.7)	3 (33.3)	

*Mann–Whitney U test; the significance level was set at p<0.05; $^{\beta}$Fisher's exact test; the significance level was set at p<0.05. Bold values indicate statistical significance.

Table III. The relationship between the early feeding skills assessment tool and the general movements motor optimality score in preterm infants (N=40).

Variables		Early Feeding Skills Assessment Tool					
		Respiratory regulation	Oral-motor function	Swallowing coordination	Engagement	Physiologic stability	Total score
General Movements Motor Optimality Score	Upper limbs	0.62	0.74	0.38	0.43	0.51	0.68
		(0.001)**	(0.001)**	(0.01)*	(0.005)**	(0.001)**	(0.001)**
	Lower limbs	0.51	0.67	0.37	0.48	0.48	0.61
		(0.001)**	(0.001)**	(0.01)*	(0.002)**	(0.002)**	(0.001)**
	Neck and trunk	0.36	0.45	0.20	0.42	0.34	0.36
		(0.02)*	(0.003)**	(0.20)	(0.007)**	(0.02)*	(0.02)*
	Sequence of general movements	0.17	0.13	0.11	0.06	0.12	0.90
		(0.29)	(0.39)	(0.49)	(0.70)	(0.42)	(0.58)
	Total score	0.53	0.69	0.31	0.48	0.43	0.59
		(0.001)**	(0.001)**	(0.05)	(0.001)**	(0.005)**	(0.001)**

Data was expressed as rho (p); Spearman correlation test: the significance level was set as *p<0.05 and **p<0.01.

Table IV. Correlation values of the early feeding skills assessment tool regarding the maternal age, gestational age, and birth weight, time to transition to oral feeding, length of hospital stay in preterm infants (N=40).

Variables	Early Feeding Skills Assessment Tool					
	Respiratory regulation	Oral-motor function	Swallowing coordination	Engagement	Physiologic stability	Total score
Maternal age	0.07	0.13	0.13	0.18	0.34	0.11
	(0.64)	(0.41)	(0.42)	(0.24)	(0.03)*	(0.47)
Gestational age	-0.01	0.07	-0.06	-0.06	0.05	-0.001
	(0.91)	(0.62)	(0.69)	(0.68)	(0.72)	(0.99)
Birth weight	-0.15	0.07	-0.13	-0.03	-0.09	-0.04
	(0.34)	(0.64)	(0.42)	(0.85)	(0.56)	(0.80)
Time to transition to oral feeding	-0.43	-0.52	-0.49	-0.46	-0.54	-0.58
	(0.005)**	(0.001)**	(0.001)**	(0.003)**	(0.001)**	(0.001)**
Length of hospital stay	-0.54	-0.57	-0.61	-0.55	-0.66	-0.70
	(0.001)**	(0.001)**	(0.001)**	(0.001)**	(0.001)**	(0.001)**

Data was expressed as rho (p); Spearman correlation test: the significance level was set as *p<0.05 and **p<0.01.

those that take a holistic approach even as they look at their overall development and assisting in all functional areas.

The American Academy of Pediatrics (AAP) emphasizes that competence in oral feeding is a requirement for discharge from the NICUs.[35] Before transitioning to oral feeding, preterm infants should be fed by tube to ensure sufficient nutrient intake. This is an important process, as it directly affects weight gain, and has a significant impact on long-term neurodevelopmental outcomes.[36] In the United States, the prevalence of pediatric feeding disorders fluctuates form 2.7% and 4.3%, with more than 50% of cases occurring in preterm infants.[37] Getting to know that, preterm infants frequently show a feeding problems and require proper care. In order to manage oral feeding difficulties and minimize their effects, it is important to execute an evaluation

Table V. Correlation values of the general movements motor optimality score regarding the maternal age, gestational age, birth weight, time to transition to oral feeding, length of hospital stay in preterm infants (N=40).

Variables	General Movements Motor Optimality Score					
	Upper limbs	Lower limbs	Neck and trunk	Sequence of general movements	Total score	Global assessment
Maternal age	0.26	0.21	0.40	0.05	0.24	0.19
	(0.09)	(0.19)	(0.009)**	(0.75)	(0.12)	(0.22)
Gestational age	0.10	0.18	0.05	0.35	0.14	0.16
	(0.52)	(0.24)	(0.74)	(0.02)*	(0.38)	(0.30)
Birth weight	0.002	0.18	-0.007	0.14	0.13	0.23
	(0.98)	(0.26)	(0.96)	(0.38)	(0.42)	(0.14)
Time to transition to oral feeding	-0.40	-0.51	-0.25	-0.10	-0.43	-0.34
	(0.01)*	(0.001)**	(0.11)	(0.51)	(0.005)**	(0.02)*
Length of hospital stay	-0.40	-0.53	-0.23	-0.02	-0.43	-0.33
	(0.009)**	(0.001)**	(0.14)	(0.86)	(0.005)**	(0.03)*

Data was expressed as rho (p); Spearman correlation test: the significance level was set as *p<0.05 and **p<0.01.

during hospitalization, intervention as early as possible and ensure active management.[38] There's no clear direction for the timing of oral feeding starts. A few studies suggest to start oral feeding before 33 week while others suggest a later time[39] The current study focused on infants who started oral feeding between 34 and 37 weeks PMA, because those with more mature oral feeding skills have shown to feed a higher feeding volumes.[29] Ecevit et al. assessed oral feeding skills with NeoSAFE and reported that feeding skills were similar in late preterm, early-term, and full-term infants. Late preterm infants appear to similar oral motor abilities with their term counterparts.[29]

There is still debate in the literature on the influence of gestational age, birth weight, and postmenstrual age on the initiation of oral feeding, sucking ability, and overall feeding process. Some researchers determine that these demographic factors have a significant impact on feeding development, while others disagree.[40,41] This discrepancy may be due to differences in the age ranges of infants across studies. Our study focused on preterm infants at age of PMA 34–37 weeks, and found no significant impact on early feeding skills for maternal age, gestational age, or birth weight. In contrast, the factor of maternal age was observed to influence physiological stability during feeding. It is important to remember that the transition to oral feeding is influenced by a range of other factors, including continuous positive airway pressure support, mechanical ventilation, and neonatal morbidities including bronchopulmonary dysplasia, NEC, and IVH.[42]

The EFS has been shown to be a valid and reliable instrument for evaluating oral feeding skills and readiness for oral feeding transition in preterm infants. Girgin et al. used the scale with preterm infants with similar demographic characteristics to the ones in the present study (gestational age, postmenstrual age, and birth weight) and found similar EFS scores.[31]

In the moderate to late preterm population, adequate follow-up is often lacking, which limits the understanding of potential long-term effects on neurodevelopment.[43] Regular monitoring becomes particularly important when there are frequent poor repertoire patterns in GMs, as these abnormal patterns are often associated with a wide range of neurodevelopmental alterations.[44] Compared with previous studies, the present study identified a higher proportion of poor repertoire (PR) patterns among moderate to late preterm infants.[45] This discrepancy may be attributable to differences

in NICU care conditions. The global evidence suggests that there are considerable variations in prenatal, perinatal, and postnatal care practices across countries. Unfortunately, these variations may substantially influence neurodevelopmental outcomes in infants at high risk for neurodevelopmental impairments. Therefore, to reduce this inequality, it is important to improve the quality of neonatal intensive care. Such improvements, as well as earlier detection of cerebral palsy and the systematic implementation of early intervention strategies, are likely to a reduce the prevalence of cerebral palsy and improve long-term neurodevelopmental trajectories in this vulnerable population.[46]

In the first months after birth, both sucking patterns and GMs may serve as early indicators of future neurological impairments. However, inconsistent results have been reported across studies on the relationship between these two factors during the fidgety period. Yardımcı Lokmanoğlu et al., examining the relationship between sucking patterns and fidgety movements, reported only a weak correlation between sucking and the Motor Optimality Score-Revised total score, fidgety movements, observed movement patterns, and age-adequate movement repertoire subcategories.[47] On the other hand, Nieuwenhuis et al. reported a clear association between normal and abnormal sucking patterns in preterm infants and the quality of fidgety movements. Other studies also found such an interconnection, including the regulation or generation of fidgety movements. Additionally, the coordination of these motor activities was found to be highly dependent on CPGs, as evidenced by their association with other subcategories of the Motor Optimality Score (MOS).[28] These findings are further supported by the present study, which shed light on the relationship between feeding skills and general movements during the writhing period. This finding provides evidence for the argument that motor and oral motor skills positively influence each other's development, and highlights the interconnected nature of early neuromuscular control in preterm infants.[48] At the age of 2, children with definite feeding difficulties and those at risk for feeding difficulties had generally lower cognitive, language, and motor scores.[49] These feeding difficulties may be due to early hypotonia, which may disrupt the development of oral-motor skills.[50] Early feeding behaviors are significant predictors of motor outcomes at ages 4-5. Therefore, it is important to identify extremely preterm infants with early feeding difficulties due to the risk of poor motor outcomes in later childhood. This highlights the need for screening for early diagnosis and intervention.[51]

It is important to note that wide variations in hospital practices contribute to differences in the levels of care provided to late preterm infants.[52] Aliaga et al. revealed that these differences in care practices influence both the duration of birth hospitalization and the risk of readmission.[53] These findings underscore the importance of standardizing care for late preterm infants across clinical settings to reduce variability in outcomes and minimize readmission rates. Furthermore, such standardization would facilitate consistency in outcome measurement and enhance the reliability of assessments in future research.[52]

In preterm infants, delays in discharge, which manifested as prolonged hospitalization and higher postmenstrual age at discharge, were likewise associated with poorer feeding performance at term-equivalent age.[54] Assessment of oral feeding levels in late preterm infants during their first feeding may help identify those at risk for difficulties that could delay hospital discharge. Lau et al. demonstrated that such difficulties in this age group not only influence the length of hospital stay, but also increase the likelihood of readmissions, further reporting that feeding skills are a significant predictor of hospitalization duration.[55] Similarly, Crowe et al. highlighted that feeding difficulties negatively impact the achievement of full oral feeding and prolong hospitalization.[56] Correspondingly,

the present study revealed that feeding skills were associated with the duration of both hospitalization and transition to oral feeding. Furthermore, GMs were also found to be related to these outcomes. Taken together, these results suggest that the quality of both feeding skills and GMs may play a protective role, by shortening hospital stay and accelerating the transition. From a clinical perspective, these findings highlight the importance of systematically assessing both oral feeding performance and general movement quality in preterm infants during hospitalization. Early identification of impairments in these domains may guide the implementation of targeted, evidence-based interventions. The aim of these should be to support neurodevelopmental progress, optimize feeding readiness, and ultimately improve discharge outcomes and reduce healthcare burden.

It is known that early medical factors in preterm infants are linked to feeding performance at term-equivalent age.[54] In particular, GM trajectories during the NICU stay have been shown to be negatively influenced by presence of ICH, younger gestational age, the requirement for respiratory support, patent ductus arteriosus, and the presence of infection.[57] In line with the literature, this study found that better GMs were associated with higher maternal age, gestational age and birth weight. This study has the potential to assist health care professionals in the early identification of infants with morbidities who are at increased risk of adverse developmental trajectories, even prior to hospital discharge. Preterm infants at term equivalent age have lower feeding skill scores and greater difficulty with arousal, tongue positioning, suck-swallow-breathe discoordination, and completing feedings.[58] In these circumstances, careful monitoring of additional morbidities may provide a practical means of tracking neurodevelopmental risk and guiding timely referral to appropriate early intervention services.

Our study is notable as the first to reveal the relationship between early feeding skills and writhing movements, among the earliest general movement repertoires in life. Unlike previous studies, which examined the relationship between sucking patterns and fidgety movements in infants with a corrected age of 9-16 weeks.[28,47] our study focused on preterm infants at the age of 34-37 weeks PMA. This sample is an important age group, however, we acknowledge that this limited age range makes it difficult to generalize the results to all preterm age infants. An important contribution of this study is highlighting the role of morbidities in preterm infants in the NICU, and demonstrating the interrelationships between length of hospital stay, time to transition to oral feeding, GMs, and feeding skills. Early-life stress is another factor that negatively impacts oral feeding skills and their development,[59,60] however, the scope of this study did not include accounting for stress responses when deciding on feeding times. The study sample is relatively small and heterogeneous in terms of gestational age, and the number of very preterm infants is also small. Differences in the development of early feeding skills among very preterm infants are well documented, therefore, this heterogeneity limits the generalizability of the findings.[61] Indeed, infants born at the earliest gestational ages are at the most significant risk for adverse outcomes during the neonatal period. Gestational age is a key determinant of both neonatal survival and morbidity.[62] Feeding performance in very preterm infants is often delayed and inconsistent due to immature neural and oro-motor structures. Even at 40 weeks PMA, compared with term infants, preterm infants exhibit significantly less mature feeding behaviors, including more frequent nasogastric feeding, longer feeding durations, and increased episodes of coughing, choking, and fussing during feeding.[54,63,64] PMA at the time of assessment is critical, as feeding skills and GMs mature progressively with increasing PMA, and earlier assessments may underestimate eventual abilities.[54,63] In

addition, even when at term age, preterm infants continue to demonstrate more problems than their term infant counterparts, including poor arousal, poor tongue positioning, suck-swallow-breathe discoordination, inadequate sucking bursts, tonal abnormalities, tongue discoordination during sucking, and difficulty in regulating breathing.[55] From this perspective, it is recommended that preterm infants be followed longitudinally, including at term age, and evaluated within a broad developmental framework.[58]

One of the limitations of our study is the lack of a healthy term infant control group for comparison with preterm infants in the GMs and feeding skills. Such a comparison could yield a more precise understanding of the specific effects of prematurity on feeding skills and motor development.

In conclusion, this study highlights the importance of GMs in the feeding performance of premature infants. GMs, especially upper extremity GMs are associated with feeding skills. A comprehensive evaluation of premature infants in this regard is critical. This evaluation should include their GMs, in addition to assessing feeding disorders, which are among the most common causes of morbidity in preterm infants in NICU. This approach enables healthcare professionals to adopt a more in-depth, multidimensional perspective in the evaluation and treatment of these infants. For such infants, we hypothesize that effective, evidence-based interventions to improve oral feeding skills can to shorten hospitalization and reduce the risk of hospital readmission.

Ethical approval

The study was approved by Clinical Research Ethics Committee of Bolu Abant İzzet Baysal University (date: October 25, 2022, number: 2022/266).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: SAT; data collection: SAT, ST, ST, MD, analysis and interpretation of results: SAT, SYY, TBO, ST, ST, MD; draft manuscript preperation: SAT, SYY, TBO, ST, ST, MD. 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

Prognostic significance of serum apelin-13 and galectin-3 concentrations as potential indicators of severity and mortality in pediatric acute respiratory distress syndrome

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ABSTRACT

Background. The predictive and prognostic significance of apelin and galectin-3 as biomarkers in pediatric acute respiratory distress syndrome (PARDS) and lung injury has remained limited. This study examined the association between serum apelin-13 and galectin-3 levels, PARDS severity, and patient outcomes.

Methods. The study included children aged 1 month to 18 years diagnosed with PARDS on admission to a pediatric intensive care unit, alongside age- and sex-matched outpatient controls. PARDS was diagnosed and classified by severity according to Second Pediatric Acute Lung Injury Consensus Conference (PALICC-2) guidelines, based on oxygenation indices for non-invasive and invasive ventilation. Exclusion criteria included prior transplants, chronic lung disease, cyanotic congenital heart disease, prolonged ventilation, and other major conditions. After informed parental consent, 3 mL of peripheral venous blood was collected from all participants. Serum samples for apelin-13 and galectin-3 were stored at −80°C and analyzed using commercial enzyme-linked immunosorbent assay (ELISA) kits. Demographic, clinical, and laboratory data were systematically recorded for analysis.

Results. The study and control groups were comparable in age and gender. Patients had significantly lower hemoglobin, hematocrit, red blood cell, calcium, and phosphorus levels, and higher neutrophil counts, C-reactive protein, and liver enzymes. Apelin-13 levels did not differ significantly between groups, wheras median galectin-3 levels were significantly higher in patients (p=0.003). Apelin-13 levels were significantly lower and galectin-3 levels significantly higher with increasing PARDS severity. Severe PARDS was associated with lower PaO2/FiO2 ratios, arterial pH, and higher ventilator pressures. Mortality was 36.4% in severe and 22.7% in moderate PARDS. Serum galectin-3 level was the sole independent predictor of mortality (OR: 1.20, 95% CI 1.02–1.39, p=0.02).

Conclusion. Although the apelin/APJ system's role in acute lung injury is known, its diagnostic and prognostic value in PARDS requires further study. Galectin-3 levels correlate with disease severity and outcomes, highlighting the need for larger, age- and phenotype-homogenized studies to confirm its role as an independent mortality predictor.

Key words: apelin-13, biomarkers, galectin-3, pediatric acute respiratory distress syndrome (PARDS), prognosis.

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Pediatric acute respiratory distress syndrome (PARDS) remains a major cause of mortality and long-term morbidity in all age groups, from infants to adolescents, despite recent trends in the development of new diagnosis algorithms and attempts to standardize management over the past decade.[1] The incidence of PARDS was 3.2% in pediatric intensive care unit patients and 6.1% in pediatric patients on mechanical ventilation.[2] In 2015, the Pediatric Acute Lung Injury Consensus Conference (PALICC) introduced diagnostic criteria for PARDS that differed from those used for adults.[3] Despite research that has significantly advanced our understanding of the pathophysiology of PARDS, lung protection, and oxygenation[4,5], the latest update (Second International Guidelines for the Diagnosis and Management of PARDS [PALICC-2]) pointed out that supportive therapies, in addition to the diagnosis and definitive treatment of PARDS, are still not sufficiently standardized globally, particularly in settings with limited resources.[1,6]

PARDS is a heterogeneous clinical syndrome, and the lack of adherence to recommended principles in its diagnosis and management across individual pediatric intensive care units (PICUs) remains problematic.[7,8] Investigating the prognostic and predictive value of biomarkers that may help determine disease severity and outcomes could enhance the identification and management of patients with PARDS.[1] Apelin serves as an endogenous ligand for the G protein-coupled receptor APJ. The apelin/APJ system is proposed to mitigate pulmonary arterial hypertension within the respiratory system and possesses an intrinsic anti-injury mechanism against acute lung injury and acute respiratory distress.[9] Galectin-3, a ß-galactoside-binding lectin, is predominantly expressed by endothelial and alveolar macrophages and has been demonstrated to activate the host's inflammatory response through the induction of cytokine release.[10] Recent studies suggest that it plays a role in regulating the inflammatory and pulmonary responses, especially in PARDS that develops after coronavirus disease (COVID-19).[11,12] The predictive and prognostic significance of apelin-13 and galectin-3 as biomarkers in PARDS and lung injury has remained limited. This study examined the association between serum apelin-13 and galectin-3 levels, PARDS severity, and patient outcomes.

Methods

This observational cohort study obtained approval from the Ankara Training and Research Hospital Ethics Committee and was performed in accordance with the Declaration of Helsinki. The research was conducted between December 2023 and May 2025 in a pediatric intensive care unit at a tertiary care hospital. The study group was made up of children aged 1 month to 18 years diagnosed with ARDS upon their admission to the PICU. The control group was selected from children who had no chronic diseases, were not receiving medication, had no underlying lung disease and had no recent infection or lung disease. The control group comprised age and sex-matched volunteers who underwent blood tests in the pediatric outpatient department for various reasons, including young children seeking approval for kindergarten, adolescents undergoing routine blood checks prior to internships, and healthy children aged 9-12 months receiving routine hemogram and ferritin assessments. PARDS was diagnosed according to PALICC-2.[1] In children receiving non-invasive ventilation (facemask interface with continuous airway positive pressure/positive end-expiratory pressure ≥ 5 cm H2O), a PaO_2/FiO_2 ratio ≤ 300 or SpO_2/FiO_2 ratio ≤ 250 indicated PARDS. For those on invasive mechanical ventilation, an oxygenation index (OI = mean airway pressure x FiO_2/PaO_2) ≥ 4 was used to define PARDS. Four hours following diagnosis, the severity of PARDS was categorized as follows: mild PARDS was defined as 4≤OI<8, moderate as 8≤OI<16, and severe as ≥16. Exclusion criteria included having a solid organ transplant, hematopoietic stem cell transplant, lung cancer, a positive human immunodeficiency virus (HIV) test,

a history of respiratory failure or pulmonary edema from heart failure, exacerbation of chronic lung disease, being ventilator dependent, having cyanotic congenital heart disease, or being on ventilators for more than seven days prior to $PaO_2/FiO_2 \leq 300$. Parental consent was obtained after informing them that the laboratory samples collected from the children would be utilized and presented anonymously for scientific purposes, and that the research involved no invasive procedures.

The demographic data, baseline complete blood count (CBC), and laboratory parameters of both patients and controls were collected, while patients' vital parameters, mechanical ventilation values, and arterial blood gas variables were recorded during the intensive care period. The Pediatric Risk of Mortality (PRISM III) score, a widely used severity-of-illness scoring system in PICUs, was included to assess the risk of mortality and to adjust for disease severity in the analysis. We obtained 3 mL of peripheral venous blood from patients at the first hour and controls for baseline laboratory tests and serum samples that were separated from the same sample for apelin-13 and galectin-3 levels were stored at −80 °C. The samples were then prepared according to the manufacturer's recommendations using commercial enzyme-linked immunosorbent assay (ELISA) kits. The normal ranges for apelin-13 and galectin-3 were 1.4-94.8 ng/mL and 19.75-1600, respectively.

Statistical analysis

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) software version 19.0. The normal distribution of variables was assessed through visual methods, including histograms and probability plots, as well as analytical methods (Kolmogorov-Smirnov test and the Shapiro-Wilk test). Laboratory and clinical parameters that followed a normal distribution were presented as mean ± standard deviation, whereas those that did not conform to normality were reported as median and interquartile ranges. Given the further reduction in sample size after age stratification, serum apelin-13 and galectin-3 levels were summarized using medians and interquartile ranges Categorical variables were represented as numerical values and percentages. The chi-square test was used to compare categorical variables between the control and study groups. Independent samples t-test or Mann-Whitney test was used to compare continuous variables, depending on normal distribution. For the comparison of variables among three PARDS severity classes, One-way ANOVA was employed for normally distributed continuous variables, whereas the Kruskal-Wallis test was utilized for non-normally distributed variables. Spearman's correlation was used to assess the association between apelin-13 and galectin-3 levels and baseline characteristics, as well as clinical and ventilatory parameters of PARDS. A univariate logistic regression analysis was conducted to assess the relationship between study parameters and mortality. In the context of multivariate analysis, variables identified in univariate analysis were subsequently included in logistic regression analysis to ascertain the independent predictors of mortality. Variables were selected for multivariate logistic regression based on clinical relevance and univariate analysis results. Parameters with $p<0.10$ in univariate analysis were considered candidates and were entered into the multivariate model using the enter method (forced entry), rather than an automated stepwise approach. Model performance was evaluated by the Omnibus test of model coefficients for overall goodness-of-fit and by the Nagelkerke R^2 to assess the explanatory power of the multivariate logistic regression model. The Omnibus test demonstrated a statistically significant overall model fit ($\chi^2 = 31.49$, $p<0.001$). The model showed good explanatory power with a Nagelkerke R^2 of 0.80. Discrimination was acceptable, and model convergence was achieved without instability. A receiver operating curve (ROC) analysis was performed to evaluate the diagnostic performance of galectin-3 for pediatric acute respiratory distress syndrome (PARDS). A p value of 0.05 was used for statistical significance.

Power analysis

A post-hoc power analysis was performed using G*Power (version 3.1.9.4) to assess the difference in galectin-3 levels between PARDS patients and controls. The analysis yielded an effect size of 0.86, corresponding to a statistical power of 98.9% (1-β error probability) at a two-tailed $\alpha = 0.05$.

Results

Among the 44 patients, the etiology of PARDS was bronchopneumonia in 20 (45.5%), viral pneumonia in 17 (38.6%), sepsis in 5 (11.4%), and ventilator-associated pneumonia in 2 (4.6%). The age and gender distributions were comparable between groups (Table I). Mean values for hemoglobin (p<0.001), hematocrit (p<0.001), red blood cells (p<0.001), calcium (p<0.001), and phosphorus (p=0.003) were significantly lower and absolute neutrophil count (p<0.001), C-reactive protein (p<0.001), and liver function enzymes (p=0.005) were significantly higher in patients than in controls. The median serum apelin-13 level did not differ significantly between the study group and controls (p=0.32) but the median galectin-3 level was significantly elevated in the study group (p=0.003). Although there were marked differences in both serum apelin-13 and galectin-3 levels across different age subgroups, these differences were not statistically significant (Table II).

Table I. Comparison of demographics and baseline laboratory parameters between study patients and controls

Variable	Study group (n=44)	Control group (n=44)	p
Age (months)	42 (2-204)	48 (2-204)	0.68
Female gender, n (%)	18 (40.9)	18 (40.9)	0.99
Laboratory parameters			
Hemoglobin (g/dL)	9.8±1.5	12.2±1.5	**<0.001**
Hematocrit (%)	29.7±4.4	36.7±4.3	**<0.001**
RBC ($\times 10^6$ /μL)	3.6 (2.4-6.7)	4.7 (3.4-5.4)	**<0.001**
WBC ($\times 10^3$ /μL)	11.7 (8.4-16.4)	8.7 (4.6- 19.3)	0.01
Platelets ($\times 10^3$ /μL)	299 (18-902)	322 (146-802)	0.12
ANC ($\times 10^3$ /μL)	5.9 (1.1-25.8)	3.4 (0.8-13.3)	**<0.001**
ALC ($\times 10^3$ /μL)	2.5 (0.5-12.8)	3.8 (0.8-12.5)	0.02
CRP (mg/dL)	32.6 (0.9-345.7)	0.7 (0.1-16.8)	**<0.001**
ALT (U/L)	26.5 (6-245)	14.5 (7-41)	**0.005**
AST (U/L)	40.5 (18-527)	32 (16-58)	**0.005**
Urea (mg/dL)	20 (2-86)	22.5 (6-36)	0.37
Creatinine (mg/dL)	0.22 (0.6-2.8)	0.33 (0.21-0.79)	0.05
Sodium (mmol/L)	138.5 (124-161)	138 (131-144)	0.3
Potassium (mmol/L)	4.36±0.64	4.62±0.38	0.07
Chloride (mmol/L)	105 (92-130)	104 (99-111)	0.27
Calcium (mg/dL)	8.73±1.06	10.01±0.47	**<0.001**
Phosphorus (mg/dL)	3.9 (0.89-9.96)	4.7 (3.1-6.4)	**0.003**
Serum apelin-13 level (pg/mL)	649.6 (172.8-4000)	753.9 (223.4-4000)	0.32
Serum galectin-3 level (ng/mL)	6.65 (0.44-58.03)	2.53 (0.58-13.48)	0.003

Data presented as number (percentage), mean±SD, or median (interquartile range). ALC: absolute lymphocyte count, ALT: Alanine aminotransferase, ANC: absolute neutrophile count, AST: Aspartate aminotransferase, CRP: C-reactive protein, RBC: Red blood cell, SD: standard deviation, WBC: White blood cell.

Table II. Comparison of serum apelin-13 and galectin-3 levels across age-stratified groups

Variable	Serum apelin-13 level (pg/mL)			Serum galectin-3 level (ng/mL)		
	Study group	Control group	p	Study group	Control group	p
0 to 1 years (n=17)	487.43 (338.42-1936.00)	695.58 (358.74-951.10)	0.96	6.32 (1.84-24.87)	4.20 (1.43-7.53)	0.36
1 to 5 years (n=35)	1282.88 (522.09-2906.67)	911.67 (741.33-1712.00)	0.90	8.63 (1.43-21.83)	2.27 (1.36-2.82)	0.09
5 to 12 years (n=16)	497.97 (437.50-719.20)	651.42 (451.73-837.54)	0.57	8.56 (2.24-18.22)	2.52 (1.56-4.79)	0.10
12 to 18 years (n=20)	619.09 (423.78-911.67)	617.51 (575.71-3013.33)	0.57	5.19 (1.77-21.20)	5.03 (1.21-8.09)	0.39

Data presented as median (interquartile range).

Table III. Comparison of hemodynamic and respiratory parameters among three PARDS categories in study patients

Variable	Mild PARDS (n=11)	Moderate PARDS (n=22)	Severe PARDS (n=11)	p
OI	6.33±0.80	10.92±1.99	51.35±67.92	**<0.001**
Oxygen saturation (%)	99 (98-99)	98 (96-99)	96 (91-98)	0.04
Heart rate (/min)	125.54±22.88	119.72±23.68	134.36±22.47	0.24
Systolic BP (mmHg)	96.00±12.07	100.86±14.26	92.81±8.68	0.2
Diastolic BP (mmHg)	57.54±9.32	60.36±12.56	53.81±7.16	0.26
Respiratory parameters				
PEEP (cm H_2O)	5.27±0.47	5.32±0.78	7.45±2.77	**0.007**
PS above PEEP (cm H_2O)	14.00±4.05	18.55±8.34	23.09±8.06	**0.01**
FiO_2 (%)	60.00±0.00	60.00±0.00	60.00±0.00	1
MAP (cm H_2O)	10.36±3.59	13.02±3.40	17.36±4.13	**0.001**
Peak pressure (cm H_2O)	19.09±4.06	23.18±8.81	30.27±10.74	**0.01**
VTE (mL/kg)	136.91±86.25	126.14±79.14	150.27±111.67	0.83
Frequency (/min)	25.55±104.25	27.41±10.81	30.64±8.03	0.22
APRV (cm H_2O)	0 (0)	1 (4.5)	2 (18.2)	0.2
MV duration (days)	5.27±0.47	5.32±0.78	7.45±2.77	0.25
Arterial blood gas				
pH	7.37±0.06	7.37±0.11	7.24±0.16	**0.01**
pCO_2 (mm Hg)	49.5 (40.2-57.2)	50.2 (29-81)	49.9 (28.3-87.4)	0.92
HCO_3 (mmol/L)	28.36±4.27	28.14±5.10	23.95±6.56	0.08
BE (mmol/L)	3.14±5.00	2.73±5.38	-1.99±7.52	0.07
Lactate (mmol/L)	0.9 (0.3-25)	1.4 (0.3-6)	2.1 (0.5 – 13.9)	0.26
PaO_2/FiO_2	147.36±55.06	139.30±119.65	68.73±16.30	**0.001**
ICU stay (days)	3.64±1.36	8.36±18.50	7.18±5.19	0.3
Hospital stay (days)	5.55±1.75	11.14±19.48	13.18±9.02	0.06
Mortality (%)	0 (0)	5 (22.7)	4 (36.4)	0.1

Data presented as number (percentage) or median (interquartile range) Severity of PARDS was described based on OI: Oxygenation index value which was calculated based on MAP x FiO_2/PaO_2. Mild PARDS was defined as 4≤OI<8, moderate as 8≤OI<16 and severe as ≥16.

APRV: Airway pressure release ventilation, BP: Blood pressure, FiO_2: Fraction of inspired oxygen, MAP: Mean airway pressure, MV: Mechanical ventilation, OI: Oxygenation index, PARDS: Pediatric acute respiratory distress syndrome PaO_2: Partial arterial oxygen pressure, PEEP: Positive end-expiratory pressure, PS: Pressure support, VTE: Exhaled tidal volume.

Female gender was significantly more common in patients with severe PARDS compared to those with mild or moderate PARDS, but there were no significant differences in CBC, kidney and liver functional tests, or electrolyte values across the three severity categories. The median serum apelin-13 levels (p=0.002) and median galectin-3 levels (p<0.001) exhibited significant differences among the three groups. In pairwise group comparisons, the difference in median apelin-13 levels between patients with mild and moderate PARDS was not significant (p=0.10). However, median apelin-13 values in patients with severe PARDS were significantly lower than those in both mild PARDS (p<0.001) and moderate PARDS (p=0.006). Median galectin-3 levels were significantly elevated in both moderate PARDS compared to mild PARDS (p=0.04) and in severe PARDS compared to moderate PARDS (p=0.006) (Supplementary Table S1).

The only notable differences in hemodynamic and respiratory parameters between the three PARDS categories were that severe PARDS patients had significantly lower PaO_2/FiO_2 ratios (p<0.001), arterial blood gas pH (p=0.01), OI (p<0.001) and mechanical ventilator pressure values (p=0.007 for positive end-expiratory pressure [PEEP], p=0.01 for pressure support [PS] above PEEP, and p<0.001 for mean airway pressure [MAP]). Patients with mild PARDS exhibited shorter durations of intensive care and hospital stays; however, these differences did not achieve statistical significance (p<0.06). All patients with mild PARDS survived to discharge, but four (36.4%) of those with severe PARDS and five (22.7%) of those with moderate PARDS died of sepsis and multiorgan failure (Table III, Table IV). Serum galectin-3 level (odds ratio [OR]: 1.23, 95% confidence interval [CI]: 1.05-1.44, p=0.01) and PRISM III score (OR: 1.29, 95% CI: 1.039-1.602, p=0.02) were identified as univariate predictors of mortality. In multivariate analysis, serum galectin-3 level emerged as the sole independent predictor of mortality (OR: 1.20, 95% CI: 1.02-1.39, p=0.02). PRISM III score was found to be statistically signicifant for galectin-3, and OI was found to be significant for both galectin-3 and apelin-13 (p<0.001) (Table V). The ROC analysis demonstrated that galectin-3 had a statistically significant discriminatory ability (AUC = 0.68, 95% CI: 0.56–0.79, p = 0.03) (Supplementary Fig. S1). The optimal cut-off values (3.0, 3.07,

Table IV. Spearman correlation coefficients of apelin-13 and galectin-3 levels with clinical and laboratory parameters

Variable	Apelin-13		Galectin-3	
	r	p	r	p
Age	-0.02	0.89	-0.008	0.95
PRISM III Score	-0.26	0.08	0.57	**<0.001**
OI	-0.532	**<0.001**	0.67	**<0.001**
PS above PEEP	-0.316	0.03	0.247	0.10
Peak pressure	-0.395	**0.008**	0.276	0.07
MAP	-0.31	**0.04**	0.322	**0.03**
MV duration	-0.159	0.30	0.178	0.24
PaO_2/FiO_2	0.451	**0.002**	-0.277	0.069
PCO_2	0.041	0.79	-0.102	0.51
ICU stay	-0.003	0.98	0.187	0.22
Hospital stay	-0.115	0.45	0.176	0.25

FiO_2: Fraction of inspired oxygen, ICU: Intensive care unit, MAP: Mean airway pressure, MV: Mechanical ventilation, OI: Oxygenation index, PaO_2: Partial arterial oxygen pressure, PEEP: Positive end-expiratory pressure, PRISM: Pediatric risk of mortality, PS: Pressure support.

Table V. Univariate and multivariate predictors of mortality

Variable	p	OR	95% CI
Univariate predictors			
Age	0.29	1.00	0.995-1.017
PRISM III Score	**0.02**	1.29	1.039-1.602
OI	0.66	1.00	0.987-1.021
PS above PEEP	0.14	1.06	0.978-1.165
Peak pressure	0.06	1.07	0.996-1.161
MAP	0.12	1.14	0.964-1.370
MV duration	0.09	1.14	0.976-1.352
PaO_2/FiO_2	0.25	0.99	0.974-1.007
pCO_2	0.11	0.94	0.870-1.015
Apelin-13 level	0.11	0.99	0.994-1.001
Galectin-3 level	**0.01**	1.232	1.050-1.446
Multivariate predictors			
Galectin-3 level	**0.02**	1.20	1.02-1.39
PRISM III score	0.25	1.09	0.94-1.26

CI: confidence interval, MAP: mean airway pressure, MV: mechanical ventilation, OI: oxygenation index, OR: odds ratio, PEEP: positive end-expiratory pressure, PRISM: pediatric risk of mortality, PS: pressure support.

Table VI. ROC curve analysis of galectin-3 cut-off values for the diagnosis of pediatric acute respiratory distress syndrome (PARDS)

Cut-Off	Sensitivity (%)	Specifity (%)	PPV (%)	NPV (%)
3.0	65.9	59.1	61.7	63.4
3.07	65.9	61.4	63.0	64.3
3.37	61.4	63.6	62.8	62.2

NPV: Negative predictive value, PPV: Positive predictive value.

and 3.37 ng/mL) along with corresponding sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are presented in Table VI.

Discussion

Apelin-13 and particularly galectin-3 may serve as significant markers for the diagnosis, severity, and prognosis of PARDS. The study group had slightly higher median serum apelin-13 levels. However, mean galectin-3 levels were significantly higher—approximately threefold—than those in controls, with no notable changes observed in other laboratory parameters, including markers of multi-organ function, sepsis, or electrolyte values. Moreover, galectin-3 has the potential to function as a direct indicator of compromised respiratory function in PARDS, as it independently predicted mortality and exhibited a strong positive correlation with the PRISM III score, oxygenation index, and mean arterial pressure.

Many studies have investigated a wide range of biomarkers, including known inflammatory markers, such as C-reactive protein, granulocyte–macrophage colony-stimulating factor, human neutrophil elastase, and interleukins to predict the prognosis of PARDS in advance, and to guide treatment against clinical deterioration. It has been reported that coagulation and fibrinolysis parameters (e.g. antithrombin III and

plasminogen activator inhibitor-1), various epithelium-derived molecules (e.g. CC16/CC10, sICAM-1), endothelium-derived molecules (e.g. angiopoietin-2, endothelin-1, von Willebrand factor), surfactant proteins, and B-type natriuretic factor serve as significant markers in distinguishing non-survivors among children with PARDS.[13,14] However, efforts to revalidate biomarkers with prognostic value in adult ARDS for use in PARDS face challenges due to the fact that PARDS diagnostic criteria have only been standardized for about 10 years, and because the overall incidence of PARDS is low.[15]

The heterogeneity of PARDS arises not only from the complexity of the underlying pathology but also from factors such as age-related changes in lung capacity, the immune system, and other comorbid conditions in children. The general consensus in recent years has been to reduce the uncertainty caused by this heterogeneity in PARDS patients by identifying patient subgroups through biomarker-based enriched prognostic and predictive approaches. This strategy aims to support a targeted, individualized approach in both medical treatment and mechanical ventilation management to reduce mortality.[8] In fact, as in adults, it was recently demonstrated through latent class analysis that PARDS also has two phenotypes: hypoinflammatory and hyperinflammatory. This study highlighted the importance of phenotype-targeted therapy by reporting that phenotype-2 PARDS, characterized by markedly elevated levels of biomarkers such as angiopoietin-2, interleukin-1 receptor antagonist, interleukin-6, and interleukin-8, is associated with longer intensive care stays, prolonged mechanical ventilation, and higher mortality.[16]

The demonstration that the apelin/APJ system provides pleiotropic protection against acute lung injury and PARDS — by reducing mitochondrial reactive oxygen species (ROS)-triggered oxidative damage, mitochondrial apoptosis, and the inflammatory response induced via nuclear factor kappa B (NF-κB) and NOD like receptor containing pyrin domain (NLRP)3 inflammasome activation, as well as by triggering various other signaling pathways — has increasingly positioned it as a potential therapeutic target.[9,17] However, to date, no other studies in children have been reported apart from a single study by Zhang et al, which found that cord plasma apelin levels were significantly higher in preterm infants with respiratory distress compared to those without respiratory distress (158.9 ± 24.8 vs. 125.2 ± 18.2 pg/mL, respectively).[18] In our study, although apelin-13 levels in the PARDS group were higher than in the control group, this difference was not statistically significant; interestingly, apelin-13 levels were inversely correlated with increasing disease severity. Indeed, certain isoforms of apelin, which are indicators of the apelin/APJ system playing an essential role in vascular endothelial cell homeostasis, have been found to be low rather than elevated in pulmonary hypertension.[19] Furthermore, it has been reported that apelin levels acutely decrease and remain low for weeks in patients with vulnerable coronary artery plaques and acute myocardial injury.[20,21] Nevertheless, the literature still lacks data providing normal ranges of apelin levels in children across different age groups, and there is no evidence yet to determine which range of apelin levels in PARDS could reliably predict prognosis.

Although we did not find a statistically significant difference in apelin-13 levels between the overall patient and control groups ($p = 0.32$), the clear inverse relationship between disease severity and apelin-13 concentrations ($p = 0.002$) suggests that apelin-13 may function more as a dynamic marker of pulmonary injury progression than as a static indicator of disease presence. In support of this, multiple mechanistic and preclinical studies highlight plausible pathways by which apelin signaling may become depleted or suppressed as lung injury advances. For example, Lian et al.[22] demonstrated that in a ventilator-induced lung injury (VILI) animal model, exogenous apelin-13 reduced inflammation, oxidative stress, and apoptosis in lung tissue,

indicating that activation of the apelin/APJ axis may be a compensatory, protective response that is overwhelmed in severe injury states. Further, apelin has been shown to attenuate lipopolysaccharide (LPS)-induced acute lung injury via modulation of the Sirtuin 1 (SIRT1)/NLRP3 signaling pathway—thus suppressing endothelial cell pyroptosis and maintaining barrier integrity.[23] In another study apelin-13 was demonstrated to alleviate LPS-induced acute lung injury by inhibiting ROS generation, NF-κB activation, and NLRP3 inflammasome signaling.[24] Additionally, a recent study by Chen et al. showed that apelin-13 can preserve alveolar epithelial barrier function in LPS-induced injury, reducing edema and inflammatory cytokine leakage.[25] Taken together, these findings suggest that declining apelin-13 levels with increasing disease severity may reflect exhaustion of a local protective or reparative apelin/APJ response, impairment of endothelial–epithelial cross-talk, or enhanced peptide degradation.

The evidence supporting the role of galectin-3 levels in predicting worse outcomes in adult ARDS can be considered strong. In one study, galectin-3 levels in adult ARDS patients were significantly higher in survivors than in non-survivors (median [interquartile range]: 12.37 [7.94–18.79] vs. 5.01 [4.15–5.69] ng/mL, respectively, $p < 0.0001$), and a cut-off level of 10.59 ng/mL showed a sensitivity of 81.48% (95% CI: 0.62–0.94), although the specificity was not very high (55.56%; 95% CI: 0.38–0.72).[26] Another study reported that in 156 adult patients with ARDS due to COVID-19, elevated galectin-3 levels were a strong predictor of 30-day mortality, with risk significantly increased at levels above 35.3 ng/mL.[11] However, the most promising and convincing study on the diagnostic and prognostic role of galectin-3 in PARDS was a recent prospective case control study in 12 children with sepsis by Yehya et al.[27] The researchers showed, through plasma co-immunoprecipitation and downstream proteomics within 24 hours of ICU admission, that among the top 50 differentially expressed DNA-bound proteins, galectin-3 binding protein was the most informative discriminating protein for distinguishing children with PARDS from those without, thereby opening the door to the clinical translation of these findings. In our study, galectin-3 levels in patients were on average about four times higher than in controls, and showed a steady increase with increasing disease severity. Nevertheless, although galectin-3 emerged as an independent predictor of mortality in our multivariate model, its receiver operating characteristic - area under the curve (ROC AUC) of 0.68 suggests only moderate discriminative ability. Therefore, this finding must be treated cautiously rather than presented as definitive. Galectin-3 is unlikely to replace established clinical or laboratory prognostic tools, but may have additive value when integrated into a multimarker panel or risk score.

The main limitations of this study were its single-center and non-randomized design. The low incidence of PARDS also resulted in the constraint of a small sample size. Although both apelin-13 and galectin-3 levels differed by several fold across different severity levels, it should be considered that the heterogeneous age distribution of the children in the study group may have influenced the results regarding the predictive roles of apelin-13 and galectin-3 levels. Moreover, given the scarcity of pediatric-specific investigations on apelin and galectin levels, the generalizability and interpretation of our findings remain limited and should be considered with caution.

In conclusion, although the role of the apelin/APJ system in vascular endothelial homeostasis during acute lung injury has been demonstrated, more convincing studies are warranted to establish its diagnostic and predictive role in PARDS. Galectin-3 levels show a strong correlation with disease severity and outcome parameters, and further research is justified in larger studies involving age- and phenotype-homogenized pediatric subgroups to confirm galectin-3 as an independent predictor of mortality in PARDS.

Supplementary materials

Supplementary materials for this article are available online at https://doi.org/10.24953/turkjpediatr.2026.6648.

Ethical approval

The study was approved by University of Health Scienses Ankara Training and Research Hospital Ethics Committee (date: 06.12.2023, number: E-23-1434).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: ST, NA, AET, MAT; data collection: NA, İB, AET, GK, NK; analysis and interpretation of results: ST, GK, NK, RUS, MAT; draft manuscript preparation: ST, MAT. 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

Clinical and economic burden of preseptal cellulitis in children: a 6-year review

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ABSTRACT

Background. Children diagnosed with preseptal cellulitis frequently require hospitalization, leading to both clinical management challenges and substantial healthcare-related costs. The condition often necessitates intravenous antibiotic therapy, radiological imaging, laboratory tests, consultations, and inpatient care, which collectively contribute to the overall economic burden. However, data on the clinical characteristics and cost distribution among pediatric patients remain limited. This study aimed to evaluate both the clinical and economic burden of preseptal cellulitis in hospitalized children and to identify the clinical factors influencing healthcare costs.

Methods. This retrospective study included children aged 1 month to 18 years who were hospitalized with a diagnosis of preseptal cellulitis between January 2019 and December 2024. Patients were grouped according to age and presence of predisposing factors. Length of stay, total hospital costs, and cost components were analyzed based on clinical characteristics.

Results. A total of 166 patients were included (mean age: 70.1 ± 46.9 months; 62% male). The most common findings were periorbital swelling (96.4%) and erythema (75.3%). Median length of stay was 5 days, with no significant differences by age, sex, or predisposing factors ($p>0.05$). However, a strong positive correlation was found between length of stay and total cost (rho=0.775, $p<0.001$). The total hospital expenditure was 25,412.95 USD, with antibiotics accounting for the largest share (48.3%). Sinusitis and odontogenic infections were significantly associated with higher costs ($p=0.007$ and $p=0.030$). In multivariable analysis, length of stay, age, and odontogenic infection emerged as independent determinants of total cost, with costs increasing by approximately 15% per additional hospital day, 0.2% per month of age, and 25% in the presence of odontogenic infection.

Conclusion. Developing standardized treatment protocols and promoting rational antibiotic use are critical for optimizing healthcare resource utilization and preventing antibiotic resistance.

Key words: antibiotic, hospital cost, sinusitis.

Preseptal cellulitis is an infection confined to the eyelid and superficial periorbital tissues, without involvement of the globe or orbital contents.[1] In contrast, orbital cellulitis involves the tissues posterior to the orbital septum and is associated with more severe outcomes, including vision loss and life-threatening complications.[2] While preseptal cellulitis is

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more frequent and generally milder in children, distinguishing it from orbital cellulitis can be clinically challenging in certain cases.[3] When orbital involvement cannot be confidently excluded through physical examination, radiologic imaging, most often contrast-enhanced computed tomography (CT), is required.[4] Routine laboratory tests and blood cultures, though commonly used, contribute minimally to diagnosis.[5]

The cornerstone of treatment is prompt initiation of appropriate antibiotic therapy.[6] Factors that may adversely impact clinical outcomes include delayed intervention, immunodeficiency, resistant pathogens, incomplete vaccination, and concurrent sinusitis.[7] Management of hospitalized children with preseptal cellulitis, encompassing intravenous antibiotics, imaging, laboratory workup, consultations, and occasional surgical interventions, can result in substantial healthcare expenditures. Previous studies suggest that factors such as sinusitis, age over five years, and development of orbital complications are associated with increased hospital costs.[3,8]

The absence of standardized guidelines for the diagnosis and management of preseptal cellulitis has led to variability in antibiotic selection and healthcare resource utilization.[5] Thus, evaluating factors influencing healthcare costs is essential for optimizing care delivery and promoting cost-effective strategies. This study aims to analyze the clinical and economic burden of pediatric preseptal cellulitis by identifying cost-driving factors and quantifying the contribution of each resource category to overall hospital expenses.

Materials and Methods

This single-center retrospective study was conducted at Dr. Behçet Uz Children's Hospital, a tertiary care pediatric referral center in İzmir, Türkiye. The study included patients aged between 1 month and 18 years who were hospitalized with a diagnosis of preseptal cellulitis between January 2019 and December 2024. Eligible patients were identified through the hospital's electronic medical record system. Patients with incomplete medical records or concomitant orbital cellulitis were excluded from the analysis. The medical records of the patients were retrospectively reviewed.

Demographic and clinical data were collected, including age, sex, presenting signs and symptoms (e.g., periorbital swelling, erythema, fever), and predisposing factors (e.g., sinusitis, odontogenic infection, conjunctivitis, insect bite, local trauma). Details regarding the length of stay (LOS), laboratory test results (white blood cell [WBC] count, C-reactive protein [CRP] levels), radiologic imaging (magnetic resonance imaging [MRI] and CT), and administered antibiotic treatments were recorded.

Antibiotic therapy was determined collaboratively by pediatricians and pediatric infectious disease specialists, taking into account the etiologic factors, severity of clinical findings, and duration of response to treatment. There was no standardized institutional protocol for beta-lactam antibiotic selection.

The hospital costs of the patients were extracted from the hospital billing system for cost analysis. The costs were categorized as inpatient floor, radiology, laboratory, antibiotics, and other medications. Other medications included in the cost analysis consisted of non-antibiotic treatments such as isotonic fluids, analgesics, antipyretics, antihistamines, and ophthalmic drops. The hospital costs of the patients were converted to United States Dollars (USD) using the average annual exchange rate of the Turkish Lira to USD for the corresponding year between 2019 and 2024, based on data from the Central Bank of the Republic of Türkiye.

Statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as medians and interquartile ranges (IQR) due to non-parametric distribution, while categorical variables were presented as frequencies and percentages. The Mann–Whitney U test was used to compare non-parametric continuous

variables between two independent groups. Spearman's rank correlation coefficient was used to assess the relationship between the LOS and total hospital cost. A p-value of less than 0.05 was considered statistically significant. In addition, a multivariable generalized linear model with gamma distribution and log link function was used to identify independent factors associated with total hospital cost. The dependent variable was total hospital cost, and the model included age (months), sex, presence of sinusitis, presence of odontogenic infection, and LOS as covariates.

The study was approved by the local ethics committee of Dr. Behçet Uz Children's Hospital (date: 06.03.2025, decision no: 2025/05-09), in accordance with the Declaration of Helsinki.

Results

Patient characteristics

A total of 166 patients were included (mean age: 70.1 ± 46.9 months; 49.4% ≤5 years; 62.0% male). The most common clinical signs were periorbital swelling (96.4%) and erythema (75.3%). Fever (15.7%), pain (10.2%), and purulent discharge (8.4%) were less frequent. Predisposing factors were identified in 53.6%, with sinusitis (18.1%) and odontogenic infections (12.0%) being most common.

Median WBC count was 10,815/mm^3 (IQR: 8,700–13,762), and CRP was 2.4 mg/L (IQR: 0.7–29.8). MRI was performed in 62.7% and CT in 36.7% of cases. All patients received beta-lactam antibiotics, most frequently ceftriaxone (44.6%) and ampicillin-sulbactam (37.4%). Clindamycin was added in 72.3% of patients. Details are provided in Table I.

Length of stay

Median LOS was 5 days (IQR: 3–7). No significant differences in LOS were observed by age group, sex, or presence of predisposing factors such as sinusitis or dental infections (p>0.05) (Table II). A strong positive correlation was found between LOS and total hospital cost (Spearman's rho = 0.775, p<0.001).

Table I. Demographic and clinical features of the patients.

Characteristics	n (%)*
Age (months), mean ± SD	70.1 ± 46.9
≤5 years of age	82 (49.4%)
>5 years of age	84 (50.6%)
Sex	
Male	103 (62.0%)
Female	63 (38.0%)
Signs and symptoms	
Periorbital swelling	160 (96.4%)
Periorbital erythema	125 (75.3%)
Fever	26 (15.7%)
Periorbital pain	17 (10.2%)
Purulent discharge	14 (8.4%)
Predisposing factors	89 (53.6%)
Sinusitis	30 (18.1%)
Odontogenic infection	20 (12.0%)
Conjunctivitis	16 (9.6%)
Insect bite	13 (7.8%)
Local trauma	12 (7.2%)
Laboratory findings	
WBC (/mm^3), median (IQR)	10,815 (8,700–13,762)
CRP (mg/L), median (IQR)	2.4 (0.7–29.8)
Radiologic imaging	154 (92.8%)
MRI	104 (62.7%)
CT	61 (36.7%)
Antibiotic therapy	
Any beta-lactam antibiotic	166 (100.0%)
- Ampicillin-sulbactam	62 (37.4%)
- Amoxicillin-clavulanate	11 (6.6%)
- Ceftriaxone	74 (44.6%)
- Cefotaxime	19 (11.4%)
Clindamycin	120 (72.3%)
Vancomycin	7 (4.2%)
Metronidazole	2 (1.2%)
Ciprofloxacin	1 (0.6%)
Length of stay (days), median (IQR)	5 (3–7)

*Unless indicated otherwise. CRP, C-reactive protein; CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; SD, standard deviation; WBC, white blood cell.

Hospital costs

Total hospital expenditure was 25,412.95 USD. Antibiotics accounted for the highest share (48.3%), followed by inpatient floor costs (21.9%), other medications (12.2%), laboratory tests (8.8%), and radiology (8.8%). Median per-patient cost was 123.26 USD. Patients with sinusitis or odontogenic infections had significantly higher costs (p=0.007 and p=0.030, respectively). Antibiotic and medication costs were the primary contributors to this difference.

Among the antibiotics used, the average daily vial costs were as follows: ampicillin-sulbactam 4.65 USD, amoxicillin-clavulanate 9.00 USD, ceftriaxone 4.03 USD, cefotaxime 6.07 USD, clindamycin 4.41 USD, vancomycin 7.10 USD, metronidazole 3.61 USD, and ciprofloxacin 6.17 USD.

Full data on the overall cost distribution are presented in Table III, Table IV, and Table V.

Multivariable analysis of total hospital cost

In the multivariable generalized linear model with gamma distribution and log link function, LOS was identified as the strongest factor independently associated with total

Table II. Comparison of length of stay by demographic and clinical characteristics.

Characteristics	Group	Length of stay (days), median (IQR)	p value[a]
Sex	Male	5.0 (3.0-7.0)	>0.05
	Female	4.0 (3.0-7.0)	
Age	≤ 5 years	5.0 (3.0-7.0)	>0.05
	> 5 years	5.0 (3.0-7.0)	
Sinusitis	Present	5.5 (4.0-8.3)	>0.05
	Absent	5.0 (3.0-7.0)	
Odontogenic infection	Present	6.0 (3.3-8.0)	>0.05
	Absent	5.0 (3.0-7.0)	
Conjunctivitis	Present	6.0 (4.0-8.5)	>0.05
	Absent	5.0 (3.0-7.0)	
Insect bite	Present	4.0 (2.0-6.5)	>0.05
	Absent	5.0 (3.0-7.0)	
Local trauma	Present	5.5 (3.0-6.8)	>0.05
	Absent	5.0 (3.0-7.0)	
Fever	Present	5.0 (3.0-6.3)	>0.05
	Absent	5.0 (3.0-7.0)	

[a] Mann Whitney U test was used to compare two groups; IQR, interquartile range.

Table III. Hospital cost distribution and per-patient costs.

	Total cost (USD), n (%)	Per-patient cost, median (IQR) (USD)
Inpatient floor	5,575.03 (21.9%)	27.74 (18.49–44.00)
Radiology	2,229.84 (8.8%)	6.07 (3.02–11.74)
Laboratory	2,230.66 (8.8%)	10.20 (6.95–16.46)
Antibiotics	12,267.64 (48.3%)	53.71 (29.81–94.59)
Other medications	3,109.78 (12.2%)	12.32 (3.27–21.34)
Total hospital cost	25,412.95 (100.0%)	123.26 (75.45–188.43)

IQR, interquartile range; USD, United States dollars.

Table IV. Comparison of total hospital cost per patient by demographic and clinical characteristics.p valuea

Characteristics	Group	Per-Patient Cost, median (IQR) (USD)	p value[a]
Sex	Male	128.72 (78.65–197.54)	>0.05
	Female	115.51 (65.03–177.17)	
Age	≤ 5 years	112.85 (75.33–156.15)	>0.05
	> 5 years	138.16 (75.18–216.07)	
Sinusitis	Present	161.49 (115.19–204.06)	0.007
	Absent	113.06 (69.43–183.65)	
Odontogenic infection	Present	179.60 (96.67–209.73)	0.030
	Absent	116.87 (70.84–178.46)	
Conjunctivitis	Present	149.10 (114.13–257.70)	>0.05
	Absent	118.46 (69.71–185.62)	
Insect bite	Present	76.71 (54.34–195.16)	>0.05
	Absent	124.18 (80.20–189.88)	
Local trauma	Present	109.69 (63.00–149.27)	>0.05
	Absent	124.07 (76.43–194.49)	
Fever	Present	132.23 (73.17–171.45)	>0.05
	Absent	121.79 (75.86–201.16)	

[a] Mann Whitney U test was used to compare two groups; IQR, interquartile range; USD, United States dollars.

Table V. Comparison of per-patient hospital costs by presence of sinusitis.

	With sinusitis	Without sinusitis	p value[a]
Inpatient floor	34.92 (24.62–46.19)	25.13 (17.13–44.00)	>0.05
Radiology	10.03 (6.90–28.47)	10.20 (6.95–16.01)	>0.05
Laboratory	8.23 (3.16–14.45)	5.50 (3.01–10.55)	>0.05
Antibiotics	79.98 (46.61–106.82)	49.18 (28.36–85.71)	0.010
Other medications	17.37 (5.94–34.63)	11.25 (3.02–19.80)	0.030
Total hospital cost	161.49 (115.19–204.06)	113.06 (69.43–183.65)	0.007

[a] Mann Whitney U test was used to compare two groups; IQR, interquartile range; USD, United States dollars.

hospital cost. Each additional hospital day was associated with an approximately 15% increase in cost after adjustment for clinical and demographic variables. Age was also independently associated with higher total costs, with increasing age corresponding to a gradual rise in expenditure.

Odontogenic infection remained independently associated with higher total hospital costs, corresponding to an approximately 25% increase compared with patients without dental involvement. In contrast, sex and the presence of sinusitis were not independently associated with total hospital cost after multivariable adjustment. The results of the multivariable analysis are summarized in Table VI.

Discussion

This study evaluated 166 pediatric patients hospitalized with preseptal cellulitis. Sinusitis and odontogenic infections were identified as the leading predisposing factors in over half of

Table VI. Multivariable analysis of factors associated with total hospital cost.

Variable	B (SE)	95% CI	p value[a]	Interpretation
Sex (male vs female)	0.051 (0.064)	−0.076 to 0.177	>0.05	Not significant
Sinusitis (present vs absent)	0.100 (0.084)	−0.064 to 0.265	>0.05	Not significant
Odontogenic infection (present vs absent)	0.219 (0.097)	0.029 to 0.409	0.024	≈ 25% higher cost
Age (months)	0.002 (0.001)	0.001 to 0.003	0.002	≈ 0.2% increase per month
Length of stay (days)	0.140 (0.010)	0.120 to 0.160	<0.001	≈ 15% increase per day

[a] p values were obtained from a multivariable generalized linear model with gamma distribution and log link function; CI, confidence interval; SE, standard error.

the cases. While the median LOS was five days and not significantly affected by demographic or clinical factors, it strongly correlated with total hospital costs. Antibiotic treatment represented the largest portion of healthcare expenditure, particularly in patients with sinusitis or dental infections.

The clinical presentation in our cohort was consistent with previous studies, with swelling and erythema being the most prominent features.[1,3,9] Due to the diagnostic overlap with orbital cellulitis and the challenges of conducting a thorough physical examination in pediatric patients, imaging was commonly employed. MRI was preferred over CT, likely reflecting concerns about radiation exposure. Imaging-related costs accounted for 8.8% of total hospitalization expenses, aligning with earlier reports from the same institution.[3]

Sinusitis was again identified as the most common predisposing factor and was associated with increased overall treatment costs. However, in contrast to earlier findings,[3] we did not observe significant differences in imaging or laboratory expenditures between patients with and without sinusitis. This may reflect evolving clinical practices—such as more standardized imaging protocols—or changes in hospital cost structures over time. Similar findings have been reported in other studies, where sinusitis contributed to prolonged hospitalization and higher total costs, but did not specifically increase imaging or laboratory expenses.[3,8] Notably, sinusitis was not independently associated with total hospital cost after multivariable adjustment, suggesting that its impact on cost may be largely mediated through other factors.

In studies on periorbital cellulitis, the most commonly isolated pathogen is *Staphylococcus aureus*, followed by coagulase-negative staphylococci and various *Streptococcus* species.[7,10,11] Although the widespread use of *Haemophilus influenzae* type b (Hib) and pneumococcal vaccines has reduced the prevalence of these pathogens, they remain significant risk factors in incompletely vaccinated patients.[7] Ampicillin-sulbactam is commonly the preferred agent for treating preseptal cellulitis associated with sinusitis or odontogenic infections.[5,10] In our study, 44% of patients received either ampicillin-sulbactam or amoxicillin-clavulanate, while 56% were treated with third-generation cephalosporins. Clindamycin was added to beta-lactam antibiotic regimens in 72.3% of patients, and vancomycin was included in 4.2%. The high rate of clindamycin use (72.3%) likely reflects concerns about methicillin-resistant *S. aureus* (MRSA) and anaerobic coverage. Murphy et al.[12] reported that in pediatric periorbital cellulitis, a combination of another anti-anaerobic drug (metronidazole) and ceftriaxone was the drug of choice for preseptal cellulitis with a rate of 73.9%. However, this pattern warrants attention, as unnecessary use of broad-spectrum antibiotics may contribute to antimicrobial resistance. Development of evidence-based treatment protocols may help reduce variation and improve cost-efficiency. Among beta-lactam antibiotics, ampicillin-sulbactam was

found to be more cost-effective compared to amoxicillin-clavulanate, and ceftriaxone had a lower cost than cefotaxime.

In our study, a significant and strong correlation was found between LOS and total hospital cost. Importantly, this association remained robust after multivariable adjustment. The median LOS for our patients was found to be 5 days, which is consistent with the average LOS reported in the literature (4.5–7.7 days).[3,10,13] Okay et al.[1] reported that clinical improvement occurred more rapidly in children aged ≤5 years compared to those older than 5 years. Similarly, Çağlar et al.[3] noted prolonged hospitalization in patients over 5 years of age and those with sinusitis. However, in our study, no significant effect of age groups and predisposing factors such as sinusitis, odontogenic infection, conjunctivitis, insect bite, and local trauma on the LOS was observed.

This study is one of the few in the literature to provide a detailed cost analysis related to healthcare utilization in pediatric patients hospitalized with a diagnosis of preseptal cellulitis. Furthermore, it makes a significant contribution due to its larger sample size and reflection of current data compared to previous studies. However, the main limitation of our study is its single-center and retrospective design. Data collection through patient records may lead to information gaps such as incomplete documentation of some clinical findings. The lack of a standardized protocol in examination and treatment processes is another important factor that may affect cost analysis. Similarly, the relatively high utilization of radiologic imaging might have contributed to an increase in total hospital costs.

In conclusion, our findings reveal that antibiotic expenses constitute the largest component of costs in pediatric patients hospitalized with a diagnosis of preseptal cellulitis. Furthermore, the presence of sinusitis and odontogenic infections was identified as a contributing factor to increased overall costs. Radiologic imaging also represents a considerable component of total hospital costs; its rational limitation, when clinically appropriate, may help reduce both overall expenses and unnecessary radiation exposure. LOS and odontogenic infection were identified as independent drivers of increased total cost, highlighting potential targets for cost containment through optimized discharge planning and focused management of dental-source infections. The implementation of standardized treatment protocols and the promotion of rational antibiotic use may play a crucial role in optimizing healthcare resource utilization and preventing antibiotic resistance.

Ethical approval

The study was approved by ethics committee of Dr. Behçet Uz Children's Hospital (date: March 06, 2025, number: 2025/05-09).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: ÇÖ, DE, BKÇ; data curation: ÇÖ, PK, AÖ, GGÖ; formal analysis: HÖ, İD; investigation: ÇÖ, AÖ, GGÖ; validation: AAK, DO, NB; supervision: DO, NB, İD; draft manuscript preparation: ÇÖ, DE, PK, BKÇ, HÖ, AAK. 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

Comparative analysis of surgical costs vs. theoretical tiopronin therapy in pediatric cystinuria: a single-center experience from Türkiye

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ABSTRACT

Background. Cystinuria is a rare autosomal recessive disorder leading to recurrent cystine stone formation, often necessitating repeated surgical interventions. In Türkiye, tiopronin—a proven medical therapy—has become inaccessible since 2019, raising concerns about its economic and clinical consequences. This study aimed to compare the annual hospital costs of surgical management with the theoretical cost of tiopronin therapy in pediatric cystinuria patients.

Methods. This single-center, retrospective study included 10 consecutive pediatric patients (median age: 12 years; range: 3-17 years) with genetically or biochemically confirmed cystinuria who underwent surgery for cystine stones in 2023. The annual cost of surgical management was calculated by summing all direct medical costs (operating room, anesthesia, devices, hospitalization, and related diagnostics) obtained from the hospital billing database. The theoretical annual cost of tiopronin therapy was calculated based on the last accessible market price of the drug in Türkiye, converted to Turkish Lira at the 2023 average exchange rate, and adjusted per patient using a standard dosing regimen of 15 mg/kg/day. Costs were compared using the Mann-Whitney U test.

Results. The median annual surgical cost per patient was 49,936 TL (range: 14,791–84,576 TL), compared to a theoretical tiopronin cost of 27,923 TL (range: 9,307–27,925 TL). Surgical management was significantly more expensive than tiopronin therapy (p=0.001) in 9 of 10 cases. Six patients had a history of tiopronin use, and five of them experienced a surgery-free interval during medication (median duration: 3 years; range: 2-6 years). Preliminary follow-up data for 2024 revealed that 70% of patients required further surgical interventions (median: 2 surgeries per patient), demonstrating the persistent and recurrent nature of the disease when managed solely with surgery.

Conclusion. Surgical treatment of cystinuria poses a substantially higher economic burden compared to tiopronin therapy. Our findings support the reintroduction of tiopronin into the Turkish healthcare system, particularly for pediatric patients with frequent stone recurrence.

Key words: cystinuria, tiopronin, pediatric urolithiasis, healthcare costs, cost-effectiveness, Türkiye.

Cystinuria is a rare autosomal recessive disorder leading to impaired renal reabsorption of cystine, resulting in recurrent stone formation.[1,2] Cystinuria has a reported incidence of 1 in 2,155 to 1 in 7,000 in children, and constitutes 6–8% of pediatric and 1–2% of adult urolithiasis.[1-3]

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The disease often manifests in childhood and necessitates repeated surgical interventions, placing a significant burden on patients, families, and healthcare systems.[4,5]

The cornerstone of cystinuria management involves high fluid intake and urinary alkalization. For patients who continue to form stones despite these conservative measures, the 2025 European Association of Urology (EAU) Guidelines recommend the use of cystine-binding thiol agents, primarily tiopronin and D-penicillamine, and in selected cases captopril, to reduce cystine excretion and prevent recurrence.[4-6] Tiopronin has demonstrated efficacy in reducing urinary cystine levels and preventing new stone formation. In pediatric cystinuria, long-term treatment with cystine-binding thiols, including tiopronin, has been associated with longer stone-free intervals and a reduced need for repeated endoscopic or percutaneous stone surgery.[4-8]

In Türkiye, tiopronin was available and reimbursed until 2019, but was subsequently withdrawn from the market due to cost considerations. We noticed an increase in surgical frequency among our pediatric cystinuria patients following this withdrawal. This study aimed to objectively compare the annual hospital costs associated with surgical management with the theoretical cost of tiopronin therapy in pediatric patients treated at our center in 2023.

Materials and Methods

Study design and ethical approval

This single-center, retrospective cost-comparison study was conducted at a tertiary care university hospital. The study was approved by the local ethics committee (Approval number: 25-4T/110).

Patient characteristics

The study included the first ten consecutive pediatric patients (aged 0-18 years) with a confirmed diagnosis of cystinuria (based on stone analysis and/or genetic testing for *SLC3A1* or *SLC7A9* mutations) who underwent at least one surgical intervention for cystine stones at our institution during the 2023 calendar year. Patients with non-cystine stones, those with incomplete medical or financial records, and patients who were primarily managed at another center were excluded from the analysis.

A total of 10 patients who met the inclusion criteria were identified from the hospital's electronic database. The collected data included age, sex, body weight, the number and types of surgical procedures performed in 2023, surgical interventions in 2024 (where available), history of previous tiopronin use, and current medications.

Treatment protocols and cost calculation

The total annual cost for surgical management per patient were obtained directly from the hospital's billing database and are presented in Turkish Lira (TL) at 2023 prices. These billings include costs for the operating room, anesthesia, surgical devices and equipment, inpatient hospital stay, medications, and laboratory and radiological investigations related to the procedure. The total cost was calculated by summing all direct medical costs associated with each stone-related procedure in 2023.

The theoretical annual cost of tiopronin therapy was calculated individually for each patient using a standardized dosing and pricing approach. Tiopronin was assumed to be administered as 100-mg tablets, and pricing was based on the last accessible market price of the commercially available tiopronin formulation in Türkiye (€34.11 per 100-tablet package). This price was converted to Turkish Lira using the average exchange rate for 2023. The daily tiopronin dose was calculated as 15 mg/kg/day, divided into three equal doses. For each patient, the total daily dose (mg/day) was divided by the tablet strength to determine the number of tablets required per day. The annual cost was calculated by multiplying the daily

tablet requirement by 365 days and the unit cost per tablet.

Statistical analysis

Statistical analyses were performed using SPSS Statistics for Windows, Version 11.5 (SPSS Inc., Chicago, IL, USA). Normality of continuous data distribution was assessed using the Shapiro-Wilk test, histograms, and Q-Q plots. Since the cost data were not normally distributed, non-parametric tests were used. The Mann-Whitney U test was applied to compare the annual costs of surgical management versus theoretical tiopronin therapy. A p-value of < 0.05 was considered statistically significant. Continuous variables are presented as median and range.

Results

The median patient age was 12 years (range: 3-17 years). The median patient weight was 33 kg (range: 12-87 kg). Seven children were boys and three were girls. The diagnosis of cystinuria was genetically confirmed in three patients (*SLC3A1* mutations in two patients and an *SLC7A9* mutation in one patient). For the remaining seven patients, the diagnosis was established based on consistent biochemical parameters (urinary cystine excretion >400 mg/L) and stone analysis. All patients received standard conservative management consisting of potassium citrate at 1–3 mEq/kg/day in 2–3 divided doses, titrated to maintain a urinary pH target of 7.0–7.5. In addition, patients were instructed to maintain a high fluid intake (>2–3 L/m²/day) and dietary sodium restriction (<2 mEq/kg/day) to optimize urine dilution and cystine solubility.

These ten patients each underwent a median of 2 surgeries in 2023, with individual surgical counts ranging from one to ten. The surgeries performed included ureterolithotripsy, retrograde intrarenal surgery, cystolithotomy, and percutaneous nephrolithotomy (PNL) (Fig. 1). The median annual cost for surgical management per patient was 49,936 TL, with costs ranging between 14,791 TL and 84,576 TL.

Based on the dosing regimen and the price of tiopronin (€34.11 per 100 tablets), the median annual cost of tiopronin per patient was 27,923 TL (range: 9,307 TL–27,925 TL). Statistical analysis demonstrated that the cost of tiopronin therapy was significantly lower than the hospital costs associated with surgical management ($p = 0.001$). In all but one patient, the cost of surgical management exceeded the estimated cost of tiopronin therapy (Table I). A cost analysis demonstrated a statistically significant

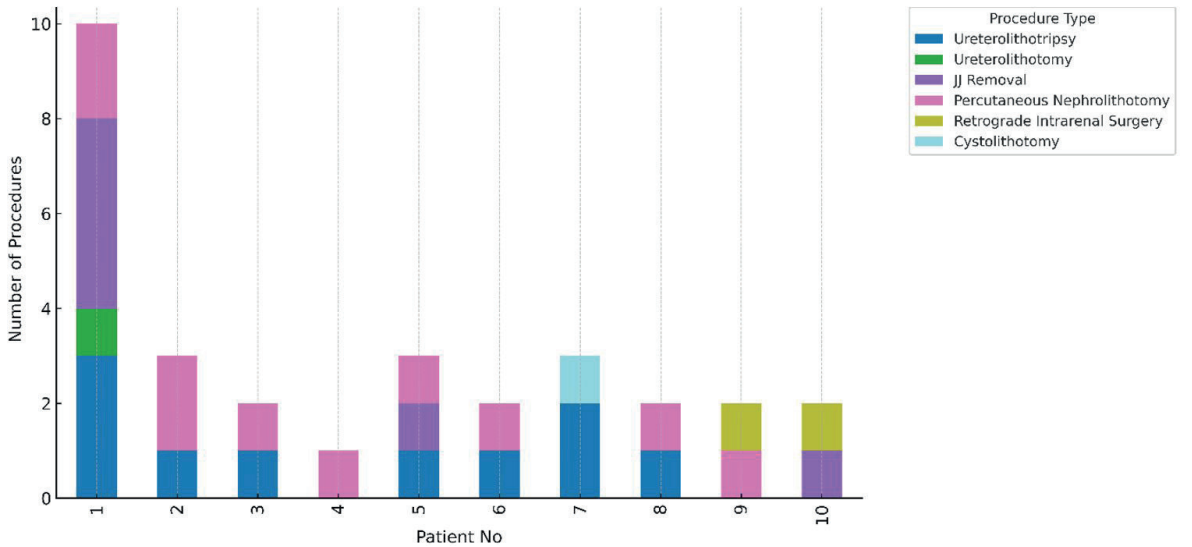

Fig. 1. Types of surgical procedures per patient.

Table I. Comparison of annual hospital costs for surgical management versus theoretical tiopronin therapy in 10 patients treated for cystinuria in 2023.

Patient no	No. of surgeries (2023)	Surgical cost (TL)	Tiopronin cost (TL)	Cost ratio
1	10	84,576	27,922.5	3.03
2	3	67,644	27,922.5	2.42
3	2	32,753	9,307.5	3.52
4	1	70,293	27,922.5	2.52
5	3	81,827	27,922.5	2.93
6	2	28,759	27,922.5	1.03
7	3	37,208	9,307.5	4.00
8	2	30,913	18,615.0	1.66
9	2	50,591	27,922.5	1.81
10	2	14,791	18,615.0	0.79

The table includes the number of surgeries per patient, total surgical costs, estimated annual tiopronin therapy costs (based on weight-adjusted dosing), and the cost ratio of surgical to medical management. In all but one case, surgical treatment was more expensive than tiopronin therapy.

difference favoring tiopronin over surgical treatment ($p = 0.001$) (Fig. 2).

We also evaluated whether prior use of tiopronin influenced the frequency of surgical interventions. Among these ten patients, six had a history of tiopronin use. All six patients with a history of tiopronin use initiated therapy with potassium citrate and tiopronin following their initial surgical diagnosis. Despite overall requiring multiple surgeries in a year, only one of these six patients underwent surgical intervention during the period in which tiopronin was actively administered. The remaining five patients experienced a surgery-free interval during tiopronin therapy, with a median duration of three years (range:2-6 years). One patient (16.6%) required a percutaneous nephrolithotomy and JJ stent removal during the second year of treatment. This same patient experienced disease recurrence and required a repeat PNL one year later, suggesting a partial or inadequate response to medical therapy in this specific case.

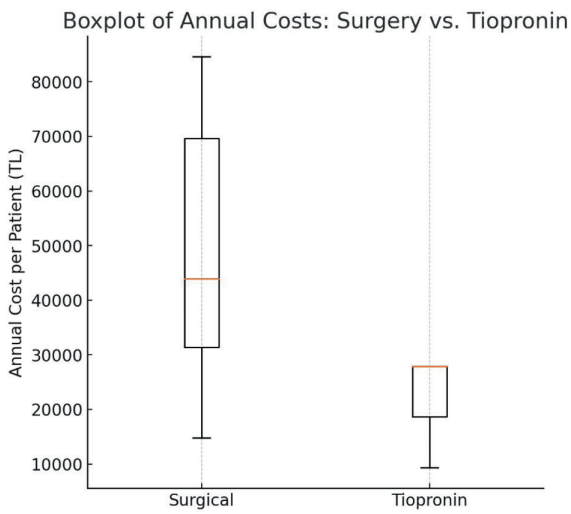

Fig. 2. Boxplot showing distribution of surgical and tiopronin therapy costs. Surgical management exhibited greater cost variability and a higher median value.

Despite undergoing surgical procedures in 2023, 70% of the cohort (7 out of 10 patients) required at least one additional surgical intervention in 2024. The median number of surgeries per patient in this period was 2 (range: 0-3).

Discussion

Cystinuria management entails a dual challenge encompassing both clinical complexity and economic burden. Our findings clearly show that the average annual cost of surgical intervention in cystinuric patients far exceeds the projected cost of tiopronin therapy. Importantly, tiopronin therapy not only reduces the frequency of stone

formation but may also prevent the need for surgical treatment altogether, as evidenced by the low surgical intervention rate during prior tiopronin availability in our patient cohort. This clinical benefit is supported by a detailed series from Türkiye by Asi et al., who evaluated 36 pediatric patients with cystine stone disease over a median follow-up of 6.4 years. The median age at diagnosis was 42 months, and most children presented with recurrent bilateral stones.[9] Pharmacological management, including potassium citrate and cystine-binding thiols, was associated with a reduction in stone recurrence from 100% to 60% over time. Predictors of successful stone clearance included early initiation of medical therapy and strict adherence to alkalization. During follow-up, patients required various surgical procedures such as ureterorenoscopy, percutaneous nephrolithotomy, and shock-wave lithotripsy, but the frequency of repeat interventions decreased substantially among those maintained on medical therapy.[9] This is in alignment with previous studies supporting long-term medical therapy for cystine stone prevention.[4,5,7,9]

Our follow-up data from 2024 clearly demonstrate that surgical intervention does not break the cycle of recurrence. In contrast, historical data from our cohort show that tiopronin therapy provided a median surgery-free interval of 3 years. This stark difference emphasizes the urgent need for accessible medical therapy to reduce the cumulative economic and clinical burden of repeated surgeries.

Complementary non-pharmacological strategies have also been shown to support long-term disease control in hereditary renal disorders, including structured hydration routines, improved patient–family education, and adherence-support measures.[10] The 2025 EAU Guidelines emphasize aggressive hydration, dietary sodium restriction, and urinary alkalization—with a target urine pH of 7.0–7.5—as the core of recurrence prevention.[6] Recent systematic reviews highlight emerging therapeutic avenues such as molecular pathway-targeted treatments, genotype-guided approaches, and novel cystine-solubilizing compounds, although these remain investigational.[1,7] Pediatric literature further underscores the importance of individualized metabolic evaluation, urine monitoring, and multidisciplinary follow-up to optimize outcomes in children with cystinuria.[11]

In addition to tiopronin, alternative pharmacological agents have been explored for the management of cystinuria; however, their overall clinical effectiveness remains limited. D-penicillamine is capable of forming soluble cystine complexes, but its long-term efficacy is compromised by poor tolerability and limited sustained use in pediatric populations.[4,5] Captopril, despite containing a sulfhydryl group, has demonstrated only modest and inconsistent reductions in urinary cystine levels and has not reliably prevented stone recurrence in clinical practice.[1,2] Alpha-lipoic acid has shown preliminary biochemical efficacy in experimental and early clinical studies; however, evidence supporting its clinical effectiveness, particularly in children, remains insufficient.[7] Consequently, current international guidelines do not recommend these agents as first-line therapy for pediatric cystinuria.[6]

However, in patients who continue to form stones despite adequate hydration, urinary alkalization, and dietary sodium restriction, cystine-binding thiol drugs remain the cornerstone of second-line therapy. According to contemporary recommendations, including the 2025 EAU Guidelines, agents such as tiopronin and D-penicillamine are the primary pharmacological options for reducing urinary cystine levels, while captopril may be considered in selected cases when other thiol drugs are unavailable or not tolerated.[6] By increasing cystine solubility, these agents help prevent recurrent stone formation and may reduce the need for repeated surgical interventions.[2,9]

Tiopronin is generally better tolerated than other thiol-binding agents; however, adverse

effects such as gastrointestinal intolerance, rash, arthralgia, and fatigue have been reported.[4,5] Clinically relevant proteinuria and rare cases of membranous nephropathy may occur, particularly with long-term use, necessitating regular monitoring of urine protein and renal function.[2] A recent systematic review on pharmacological metaphylaxis in cystinuria confirmed that, while thiol agents effectively reduce stone recurrence, tiopronin demonstrates a more favorable tolerability profile than D-penicillamine when appropriately monitored.[7,12]

Tiopronin was withdrawn from the Turkish market due to its low demand and high procurement cost. However, the findings of this study highlight that surgical management, although more readily accessible, is associated with significantly higher annual costs. Importantly, the present analysis only accounts for hospital-billed expenses and does not capture the full economic burden of care. Additional unaccounted costs include the use of specialized and costly surgical instruments for stone procedures, which are not always reimbursed. Furthermore, the economic impact extends beyond direct medical expenses; families may experience substantial productivity loss due to time away from work during their child's hospitalization and postoperative care. Recurrent stone formation and repeated surgeries also pose long-term risks to renal health, potentially resulting in chronic kidney damage and escalating healthcare costs over time.

These findings emphasize the need for a broader health-economic perspective in evaluating treatment strategies for cystinuria. The case for reintroducing tiopronin to the Turkish market is not only a clinical necessity but also an economic imperative. Future cost-effectiveness studies should include these broader direct and indirect costs to better estimate the long-term benefit of medical therapy in cystinuria.

Limitations

First, we included only direct hospital costs, as indirect costs (e.g., parental work absenteeism, travel expenses, and long-term renal complications) were not retrospectively accessible. Second, the small sample size may limit generalizability. However, the large effect size and consistent cost difference across patients strengthen our conclusions. Additionally, laboratory data regarding kidney function, including estimated glomerular filtration rate (eGFR), were not consistently available, and patient adherence to conservative measures such as dietary sodium restriction, high fluid intake, and potassium citrate use could not be objectively assessed, which may influence recurrence patterns and overall cost outcomes. Future multicenter studies incorporating detailed renal function monitoring and adherence metrics, as well as broader societal perspectives, may provide a more comprehensive economic assessment.

Conclusion

This retrospective study demonstrates that the cost of surgical management in cystinuric patients who require operative intervention is significantly higher than the potential cost of tiopronin therapy. While not all patients may benefit equally from medical management, enhancing access to tiopronin—particularly for those with recurrent stones—could reduce the frequency of invasive procedures and alleviate the economic burden on both families and the healthcare system. These findings support policy initiatives aimed at reintroducing tiopronin into the Turkish market for the benefit of selected cystinuric patients who are most likely to require repeated surgical treatment.

Ethical approval

The study was approved by Ege University Ethical Board of Medical Research (date: 17.04.2025 number: 25-4T/110).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: ST; data collection: SS; analysis and interpretation of results: SS, HU, AT, İU, ST; draft manuscript preparation: SS, ST. 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

Decoding joint complaints in children: a diagnostic approach to rheumatic and non-rheumatic disorders

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ABSTRACT

Introduction. Musculoskeletal (MSK) complaints are common in children, with many cases ranging from benign to serious conditions. While these patients are often referred to pediatric rheumatologists, only about half are diagnosed with rheumatic diseases. The objective of this study is to identify key clues that assist in the differential diagnosis of patients presenting with joint complaints at pediatric rheumatology outpatient clinic.

Material Methods. In this one-year study, patients with joint pain were assessed using a standardized form. Demographic, clinical, and examination data were collected and anonymized. Initial assessments were done by pediatric rheumatology fellows or residents, with final diagnoses confirmed by a pediatric rheumatologist.

Results. This study included 414 patients aged 0-18 years with joint pain, of whom 273 were diagnosed with rheumatologic conditions and 141 with non-rheumatologic conditions. Patients with rheumatologic conditions had significantly higher laboratory values, including leukocyte counts, neutrophils, platelets, C-reactive protein, and erythrocyte sedimentation rate, all with $p < 0.001$. Multivariable analysis revealed that arthritis (adjusted odds ratio [aOR] 2.63, 95% confidence interval [CI] 1.09-6.33) and rash (aOR 4.37, 95% CI 1.38-13.86) predicted rheumatic disease in acute presentations, while in chronic complaints arthritis (aOR 2.61, 95% CI 1.30-5.21), morning stiffness (aOR 3.47, 95% CI 1.69-7.11), migratory pain (aOR 3.45, 95% CI 1.01-11.80), and fever (aOR 12.89, 95% CI 4.41-37.68) were independent predictors, whereas myalgia was associated with non-rheumatic conditions (aOR 0.35, 95% CI 0.15-0.83).

Conclusion. In conclusion, this study emphasized the importance of clinical clues in diagnosing rheumatic diseases in children with joint pain. An accurate diagnosis depends on a thorough history and physical examination. Improving the differential diagnosis of joint pain is essential to reduce unnecessary referrals and enhance the efficiency of healthcare services.

Key words: arthralgia, arthritis, joint complaints, pediatric rheumatology, rheumatic disease.

Musculoskeletal (MSK) complaints constitute approximately 10-20% of pediatric presentations in primary care clinics.[1] Studies indicate that around 50% of children and adolescents experience MSK complaints at least once in their lifetime.[1] The underlying causes of these complaints are highly diverse, spanning from benign muscular issues to rheumatic diseases or even malignancies. Key clinical features, including constitutional symptoms such as fever and fatigue, the nature and anatomical location of pain, the duration of morning stiffness, and abnormal findings on physical examination, can aid in identifying the underlying etiology.

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Certain "red flags" also assist clinicians in the differential diagnosis. Many patients presenting with joint pain, fever of unknown origin, elevated acute phase reactants (APRs), or positive anti-nuclear antibody (ANA) are often referred to pediatric rheumatologists. However, the underlying causes frequently include infectious, orthopedic, or traumatic conditions, which can be managed by primary care pediatricians.[2] Studies have shown that only about half of patients referred to rheumatology clinics ultimately receive a rheumatic disease diagnosis.[3-5]

Previous studies have demonstrated that isolated musculoskeletal pain has poor predictive value for rheumatic disease, as most children with chronic arthritis present instead with joint swelling or gait abnormalities.[6] Additionally, multiple cohorts have reported that only 40%-55% of children referred to pediatric rheumatology ultimately receive a rheumatic diagnosis, contributing to significant over-referral and unnecessary specialist burden.[4,5] Although several studies have attempted to identify predictors of juvenile idiopathic arthritis (JIA) or chronic arthritis, these models were developed in selected populations and have not been validated in heterogeneous groups of children presenting with any type of MSK complaint.[7,8] Despite the large number of referrals, there is limited evidence identifying which specific clinical and laboratory features most reliably distinguish rheumatic from non-rheumatic causes of joint pain in children. Existing decision-support tools, such as SimulConsult, show potential but remain underutilized in daily clinical practice, emphasizing the need for real-life data to guide diagnostic frameworks.[2]

Therefore, the primary objective of this study was to identify clinical and laboratory predictors that distinguish rheumatic from non-rheumatic conditions in children presenting with joint complaints. We hypothesized that specific features—particularly arthritis, rash, morning stiffness, and fever—would strongly predict rheumatic disease in both acute and chronic presentations. This study aimed to analyze data from children with joint complaints presenting to a pediatric rheumatology outpatient clinic over a one-year period, in order to assist clinicians in evaluating these patients. This approach will provide a practical method for pediatricians working in emergency or outpatient settings to use in the differential diagnosis of patients presenting with joint pain.

Materials and Methods

Study population

In this one-year observational study, all patients presenting with joint pain to the pediatric rheumatology outpatient clinic were systematically evaluated using a standardized assessment form.

Demographic data, including age, gender, consanguinity, and family history of rheumatic diseases, were meticulously collected as part of the patient evaluation. Clinical features, such as the nature, duration, and severity of joint pain, the presence of systemic symptoms (e.g., fever, fatigue), and findings from the physical examination (e.g., joint swelling, range of motion), were also systematically documented. All data were anonymized to ensure confidentiality, with each patient assigned a unique identification code by the attending physician. This approach ensured that personal identifiers were not linked to clinical information during data analysis. In addition, the specialty of the referring physician, whether from pediatrics, general practice, or another medical field, was carefully recorded to assess potential patterns or referral biases in the patient cohort.

All patients aged 0-18 years who presented with joint complaints to the pediatric rheumatology outpatient clinic between May 2023 and May 2024 were included in the study. Patients were followed until a final diagnosis could be confirmed; the duration of follow-up ranged from a single visit to several months, depending on the clinical context. Patients

with incomplete records or lacking a confirmed diagnosis at the end of follow-up were excluded from the comparative analyses. Children were initially assessed by a fellow of pediatric rheumatology fellow or a pediatric resident and subsequently underwent a comprehensive evaluation by a pediatric rheumatologist prior to the establishment of the final diagnosis. Final diagnoses were independently verified and documented by a pediatric rheumatology specialist. The diagnosis of the patients was made based on the classification criteria for each rheumatologic condition. The classification criteria are described in the following sentences.

Acute joint complaints were defined as symptoms that lasted less than 6 weeks, while chronic joint pain is defined was symptoms persisting for more than 6 weeks.

International classification criteria were used for patient classification. The diagnosis of JIA was based on the International League of Associations for Rheumatology (ILAR) classification criteria[9]; autoinflammatory recurrent fevers were classified according to the Eurofever/Pediatric Rheumatology International Trials Organisation (PRINTO) clinical criteria.[10,11] Diagnoses of vasculitis followed the European League Against Rheumatism (EULAR)/PRINTO/Pediatric Rheumatology European Society (PRES) criteria[12]; Behçet's disease (BD) was classified according to the Pediatric BD Consensus criteria.[13] Systemic lupus erythematosus (SLE) diagnoses followed the Systemic Lupus International Collaborating Clinics (SLICC) criteria[14]; juvenile dermatomyositis was classified using the Bohan and Peter criteria.[15,16] Juvenile systemic sclerosis was diagnosed according to the PRES/American College of Rheumatology (ACR)/EULAR criteria[17]; juvenile localized scleroderma followed widely used recommended classification criteria[18], fibromyalgia diagnosis was based on the Budapest Pain Amplification Syndrome criteria[19], Raynaud's phenomenon diagnosis used the International Consensus Criteria [20], and acute rheumatic fever (ARF) was diagnosed based on the revised Jones Criteria.[21] Psoriasis, inflammatory bowel disease, and isolated uveitis were categorized under "rheumatologic disease" only because these patients were referred to pediatric rheumatology and assessed within the same clinical pathway.

Patients lacking clinical or laboratory indicators consistent with a rheumatic disease were classified under non-rheumatic conditions. For patients identified with non-rheumatologic conditions, diagnoses were corroborated and recorded by specialists from the relevant medical departments.

Statistical methods

All statistical analyses were performed using SPSS version 29.0 (IBM Corp., Armonk, NY, USA) and R 4.3.0 programs. The Kolmogorov-Smirnov test was applied to assess the assumption of normality. Continuous variables were reported as medians and interquartile ranges (IQRs) since the normality assumption did not hold. Categorical variables were reported as counts and percentages. Comparisons of continuous variables between rheumatic and non-rheumatic groups were performed using Mann-Whitney U test. Associations between categorical variables were examined using Chi-square test.

Multiple logistic regression analysis was performed to identify risk factors for rheumatic disease. Variables found to be statistically significant in the univariate analyses were first selected as candidate variables, then entered into the least absolute shrinkage and selection operator (LASSO) logistic regression analysis for feature selection. With the parameters selected by LASSO regression, a multiple logistic regression analysis was performed to calculate adjusted odds ratios (aORs) and 95% confidence intervals (CIs). A p-value <0.05 was considered statistically significant. The Sankey diagram was constructed to visualize how patients transition through these key clinical and laboratory features and how different

combinations of findings contribute to the final classification.

Results

A total of 463 patients aged 0-18 years were included in this prospective study. These patients presented to the pediatric rheumatology clinic for the first time with joint pain between May 2023 and May 2024. Of these patients, 59% (n=273) received a rheumatologic diagnosis, while 30.5% (n=141) were diagnosed with non-rheumatologic conditions. The final diagnoses of patients are depicted in Supplementary Table S1. The diagnoses for 5.2% (n=24) of patients were pending further evaluation, and 5.3% (n=25) were lost to follow-up before a final diagnosis was made (Fig. 1). Final analyses were conducted exclusively in the 414 patients with definitive diagnoses.

The initial presentation location differed significantly between the groups: 30% of patients (n=124) initially presented to the emergency department, while 70% (n=290) attended an outpatient clinic. Emergency department visits were more frequent among patients with rheumatologic conditions (n=98, 35.9%) compared to those with non-rheumatologic conditions (n=26, 18.4%; $p < 0.001$).

Detailed demographic, clinical, and laboratory data were analyzed for the 414 patients with a definitive diagnosis. These patients were classified as having either rheumatologic or non-rheumatologic conditions. Clinical and laboratory characteristics were compared between these groups (Table I). To further analyze acute and chronic joint pain, clinical features were compared between groups based on the duration of joint pain (Table II).

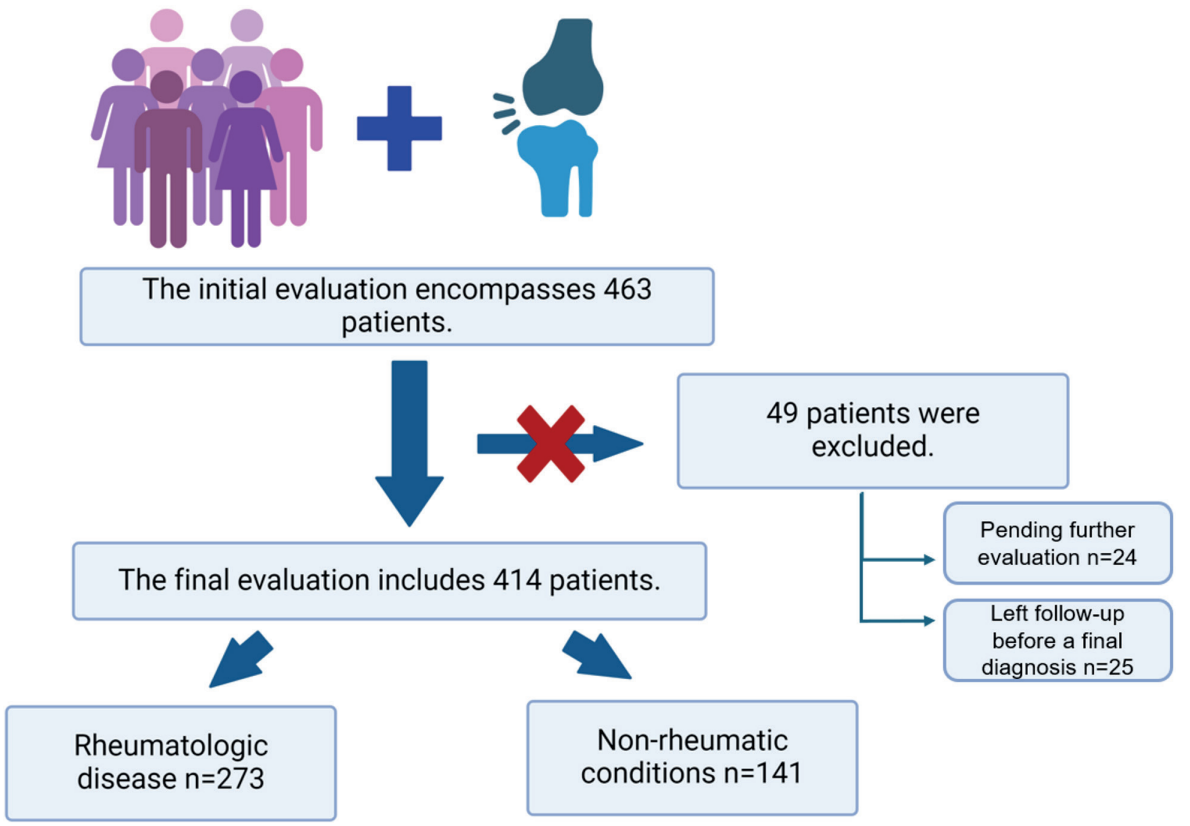

Fig. 1. Distribution of patients.

Table I. Comparison of demographic and clinical features between children diagnosed with rheumatic diseases and those with non-rheumatic musculoskeletal conditions

Demographic and clinical features	All patients (n=414)	Rheumatic disease (n=273)	Non-rheumatic conditions (n=141)	p value
Age, median (IQR), years	9.03 (5.95-12.34)	8.57 (5.88-11.83)	9.59 (6.13-12.94)	0.126
Sex (female/male)	202/212	140/133	62/79	0.178
Family history	108 (26.1)	73 (26.7)	35 (24.8)	0.724
Consanguinity	38 (9.2)	27 (9.9)	11 (7.8)	0.604
Arthralgia	287 (69.3)	173 (63.4)	114 (80.9)	**<0.001**
Monoarthralgia	39 (9.4)	22 (8.1)	17 (12.1)	**0.001**
Oligoarthralgia	201 (48.6)	118 (43.2)	83 (58.9)	
Polyarthralgia	47 (11.4)	33 (12.1)	14 (9.9)	
Arthritis	154 (37.2)	122 (44.7)	32 (22.7)	**<0.001**
Monoarthritis	69 (16.7)	41 (15)	28 (19.9)	**<0.001**
Oligoarthritis	75 (18.1)	71 (26)	4 (2.8)	
Polyarthritis	10 (2.4)	10 (3.7)	0 (0)	
Redness of the joint	38 (9.2)	27 (9.9)	11 (7.8)	0.604
Warmth	40 (9.7)	27 (9.9)	13 (9.2)	0.966
Morning stiffness	69 (16.7)	52 (19)	17 (12.1)	0.095
Duration of morning stiffness <30 min / >30 min	33 (7.9) / 36 (8.7)	22 (8) / 30 (11)	11 (7.8) / 6 (4.2)	0.109
Migratory pain	67 (16.2)	59 (21.6)	8 (5.7)	**<0.001**
Acute joint complaints	150 (36.2)	121 (80.7)	29 (19.3)	**<0.001**
Chronic joint complaints	264 (63.8)	152 (57.6)	112 (42.4)	**<0.001**
Large joint	383 (92.5)	263 (96.3)	120 (85.1)	**<0.001**
Shoulder	24 (5.8)	15 (5.5)	9 (6.4)	0.885
Elbow	33 (8)	20 (7.3)	13 (9.2)	0.629
Wrist	58 (14)	40 (14.7)	18 (12.8)	0.708
Hip	78 (18.8)	57 (20.9)	21 (14.9)	0.147
Knee	254 (61.4)	173 (63.4)	81 (57.4)	0.244
Ankle	217 (52.4)	153 (56)	64 (45.4)	**0.048**
Axial involvement	56 (13.5)	29 (10.6)	27 (19.1)	**0.024**
Neck	8 (1.9)	4 (1.5)	4 (2.8)	0.333
Lower back	39 (9.4)	17 (6.2)	22 (15.6)	**0.004**
Back	32 (7.7)	17 (6.2)	15 (10.6)	0.162
Small joint	21 (5.1)	15 (5.5)	6 (4.3)	0.758
Heel pain	24 (5.8)	8 (2.9)	16 (11.3)	**0.001**
Sacroiliitis	14 (3.4)	14 (5.1)	0	**0.003**
Fever	93 (22.5)	78 (28.6)	15 (10.6)	**<0.001**
Weight loss	2 (0.5)	0 (0)	2 (1.4)	0.116
Night sweats	11 (2.7)	8 (2.9)	3 (2.1)	0.756
Abdominal pain	93 (22.5)	81 (29.7)	12 (8.5)	**<0.001**
Myalgia	70 (16.9)	44 (16.1)	26 (18.4)	0.646
Rash	80 (19.3)	70 (25.6)	10 (7.1)	**<0.001**

All variables except for age were categorical and presented as n (%). Age was presented as median (IQR). For comparisons in rheumatic vs. non-rheumatic diseases, age was compared using the Mann-Whitney U test, and categorical variables using the chi-square test. The "All patients" column provides descriptive data and was not included in the statistical analysis. IQR, interquartile range.

Table II. Comparison of demographic and clinical features between patients with rheumatic and non-rheumatic joint complaints, stratified by symptom duration

	Acute joint complaints			Chronic joint complaints		
Demographic and clinical features	Rheumatic disease (n=121)	Non-rheumatic conditions (n=29)	p	Rheumatic disease (n=152)	Non-rhematic conditions (n=112)	p
Age (years), median (IQR)	8.47 (5.84-11.25)	8.69 (3.96-13.39)	0.973	8.74 (5.82-12.29)	9.69 (6.84-12.96)	0.116
Female sex	65 (53.7)	14 (48.3)	0.749	75 (49.3)	48 (42.9)	0.320
Family history	24 (19.8)	4 (13.8)	0.628	49 (32.2)	31 (27.7)	0.498
Consanguinity	11 (9.1)	2 (6.9)	1.0	16 (10.5)	9 (8)	0.638
Arthralgia	52 (43)	15 (51.7)	0.520	121 (79.6)	99 (88.4)	0.084
Monoarthralgia	8 (6.6)	4 (13.8)	0.494	14 (9.2)	13 (11.6)	0.092
Oligoarthralgia	33 (27.3)	7 (24.1)		85 (55.9)	76 (67.9)	
Polyarthralgia	11 (9.1)	4 (13.8)		22 (14.5)	10 (8.9)	
Arthritis	78 (64.5)	13 (44.8)	0.083	44 (28.9)	19 (17)	**0.028**
Monoarthritis	20 (16.5)	11 (37.9)	**0.001**	21 (13.8)	17 (15.2)	**0.002**
Oligoarthritis	51 (42.1)	2 (6.9)		20 (13.2)	2 (1.8)	
Polyarthritis	7 (5.8)	0		3 (2)	0	
Redness in the joint	21 (17.4)	7 (24.1)	0.564	6 (3.9)	4 (3.6)	1.0
Warmth	20 (16.5)	10 (34.5)	0.056	7 (4.6)	3 (2.7)	0.525
Morning stiffness	11 (9.2)	1 (3.4)	0.462	41 (27)	16 (14.3)	**0.020**
Duration of morning stiffness >30 min	5 (45.5)	0	NA	25 (61)	6 (37.5)	0.193
Migratory pain	36 (29.8)	4 (13.8)	0.131	23 (15.1)	4 (3.6)	**0.004**
Large joint	120 (99.2)	24 (82.8)	NA	143 (94.1)	96 (85.7)	**0.037**
Shoulder	6 (5)	1 (3.4)	1.0	9 (5.9)	8 (7.1)	0.884
Elbow	9 (7.4)	1 (3.4)	0.688	11 (7.2)	12 (10.7)	0.442
Wrist	20 (16.5)	2 (6.9)	0.250	20 (13.2)	16 (14.3)	0.934
Hip	26 (21.5)	7 (24.1)	0.952	31 (20.4)	14 (12.5)	0.128
Knee	71 (58.7)	13 (44.8)	0.254	102 (67.1)	68 (60.7)	0.300
Ankle	71 (58.7)	11 (37.9)	0.071	82 (53.9)	53 (47.3)	0.320
Axial involvement	5 (4.1)	3 (10.3)	0.184	24 (15.8)	24 (21.4)	0.311
Neck	2 (1.7)	0	NA	2 (1.3)	4 (3.6)	NA
Lower back	2 (1.7)	1 (3.4)	NA	15 (9.9)	21 (18.8)	0.058
Back	2 (1.7)	2 (6.9)	NA	15 (9.9)	13 (11.6)	0.802
Small joint	7 (5.8)	3 (10.3)	0.408	8 (5.3)	3 (2.7)	0.364
Heel pain	2 (1.7)	4 (13.8)	NA	6 (3.9)	12 (10.7)	0.056
Sacroiliitis	3 (2.5)	0	NA	11 (7.2)	0	**0.003**
Fever	22 (18.2)	10 (34.5)	0.094	56 (36.8)	5 (4.5)	**<0.001**
Weight loss	0	0	NA	0	2 (1.8)	NA
Night sweats	3 (2.5)	0	NA	5 (3.3)	3 (2.7)	NA
Abdominal pain	25 (20.7)	1 (3.4)	0.054	56 (36.8)	11 (9.8)	**<0.001**
Myalgia	29 (24)	1 (3.4)	**0.026**	15 (9.9)	25 (22.3)	**0.009**
Rash	60 (49.6)	4 (13.8)	**0.001**	10 (6.6)	6 (5.4)	0.881

All variables except for age were categorical and presented as n (%). Age was presented as median (IQR). For comparison in acute rheumatic vs. acute non-rheumatic and chronic rheumatic vs. chronic non-rheumatic diseases, age was compared using the Mann-Whitney U test, and categorical variables using the chi-square test . IQR, interquartile range.

Among all patients, 334 (80.7%) had no rash. Rash was present in 80 (19.3%) of all patients, with a significantly higher frequency in the rheumatic group (70/273, 25.6%) compared to the non-rheumatic group (10/141, 7.1%; p <0.001). Vasculitic rashes such as purpura (n=29, 7%) and palpable purpura (n=22, 5.3%) were observed predominantly in the rheumatic group (purpura: 9.5%, palpable purpura: 8.1%). Maculopapular rashes were seen in 18 patients (4.3%), and urticaria in 8 patients (1.9%). Erysipelas-like erythema (ELE) was observed in 3 patients (0.7%), all within the rheumatic group. Notably, palpable purpura and ELE were absent in the non-rheumatic group, whereas urticaria, purpura, and maculopapular rashes were present in only a few non-rheumatic patients (each n≤4).

Swollen joints were observed in 73.3% (n=113) of patients, with swelling, warmth (25.9%, n=40), and redness (24.6%, n=38) occurring more frequently in the rheumatologic group (p=0.001). Morning stiffness lasting over 30 minutes was reported by 30 patients with a diagnosis of rheumatic disease, which was higher compared to the non-rheumatologic cases, but did not reach statistical significance. Large joint involvement was significantly higher in the rheumatologic disease group (96.3% vs. 85.1%, p<0.001), and ankle involvement was also significantly more frequent in this group (56% vs. 45.4%, p=0.048). Axial joint pain was more common in the non-rheumatologic disease group (19.1% vs. 10.6%, p=0.024), as was lower back pain (15.6% vs. 6.2%, p=0.004). Heel pain was significantly more prevalent in patients with non-rheumatologic diseases (11.3% vs. 2.9%, p=0.001). Sacroiliitis was significantly more common in the rheumatologic disease group (5.1% vs. 0%, p=0.003). No significant association was found between disease groups and small joint involvement. Fever was significantly more common in patients with rheumatologic diseases compared to those with non-rheumatologic diseases (28.6% vs. 10.6%, p<0.001). Abdominal pain was also significantly more frequent in patients with rheumatologic diseases compared to those with non-rheumatologic diseases (29.7% vs. 8.5%, p<0.001).

Analysis of laboratory values revealed significant differences between groups. The median leukocyte count was higher in rheumatologic patients than in non-rheumatologic patients (8970/mm^3, IQR: 6850-28650 vs. 7740/mm^3, IQR: 6580-9860, p<0.001). Similarly, median neutrophil counts (4700/mm^3, IQR: 3540-5240 vs. 3780/mm^3, IQR: 1560-6430, p<0.001) and platelet counts (350,000/mm^3, IQR: 228,000-442,000 vs. 311,000/mm^3, IQR: 154,000-480,000, p<0.001) were significantly higher in the rheumatologic group. Inflammatory markers were also elevated, with higher median CRP levels (5 mg/dL, IQR: 3.5-7.5 vs. 1.15 mg/dL, IQR: 0.6-2, p<0.001) and ESR values (17 mm/h, IQR: 10-26 vs. 10 mm/h, IQR: 6-20, p<0.001) compared with non-rheumatologic patients.

When clinical features were compared based on the duration of joint complaints, oligoarthritis (42.1% vs. 6.9%, p=0.001), myalgia (24% vs. 3.4%, p=0.026), and rash (49.6% vs. 13.8%, p=0.001) were more common in patients with a diagnosis of rheumatic disease in the presence of acute joint pain. Arthritis (28.9% vs. 17%, p=0.028), morning stiffness (27% vs. 14.3%, p=0.02), migratory pain (15.1% vs. 3.6%, p=0.004), large joint involvement (94.1% vs. 85.7%, p=0.037), and sacroiliitis (36.8% vs. 9.8%, p<0.001) were more common in patients with a diagnosis of rheumatic disease in the presence of chronic joint pain.

Development of algorithms to facilitate diagnosis

To determine the key factors involved in diagnosing rheumatic diseases, all clinical and laboratory data were initially subjected to univariate analysis. Parameters found to be statistically significant in the univariate analysis were subsequently evaluated using multivariate analysis to identify independent predictors. In LASSO logistic regression analysis, the presence of arthritis (aOR 2.63,

95% CI 1.09-6.33, p=0.031) and rash (aOR 4.37, 95% CI 1.38-13.86, p=0.012) were independently associated with the diagnosis of rheumatic disease in patients with acute joint complaints. In patients with chronic joint complaints, the presence of arthritis (aOR 2.61, 95% CI 1.30-5.21, p=0.007), morning stiffness (aOR 3.47, 95% CI 1.69-7.11, p=0.001), migratory pain (aOR 3.45, 95% CI 1.01-11.80, p=0.049), and fever (aOR 12.89, 95% CI 4.41-37.68, p<0.001) were independently associated with the diagnosis of rheumatic disease. Furthermore, the presence of myalgia was independently associated with the diagnosis of non-rheumatic conditions (aOR 0.35, 95% CI 0.15-0.83, p=0.017; Table III). Fig. 2 presents a Sankey diagram illustrating how key clinical and laboratory features are distributed across the final diagnostic categories. Each vertical axis represents a diagnostic predictor (arthritis, migratory pain, heel pain, abdominal pain, neutrophils, and CRP), and the width of each connecting band indicates the proportion of patients exhibiting that feature in the rheumatic and non-rheumatic groups. This visualization highlights the strongest discriminative features—such as the presence of arthritis, migratory pain, elevated neutrophils, and elevated CRP—and provides a graphical overview of how these parameters jointly guide diagnostic classification. Based on the results of the Sankey analysis, a diagnostic decision chart (Fig. 3) was constructed to show the relative frequency of each feature in rheumatic versus non-rheumatic conditions.

Discussion

This study evaluated 414 children aged 0-18 years who were referred for an initial pediatric rheumatology assessment due to joint pain, aiming to identify clinical features predictive of rheumatic diseases through LASSO logistic regression analysis. The model demonstrated that distinct clinical indicators were associated with rheumatic diagnoses in acute versus chronic presentations. The analysis revealed that arthritis and rash were the most informative features in acute presentations, whereas in chronic cases, a combination of arthritis, morning stiffness, migratory joint pain, and fever showed strong associations with rheumatic diagnoses.

Table III. Univariable and multivariable logistic regression analysis results for predictors of rheumatic disease among children with musculoskeletal complaints, stratified by acute and chronic symptom duration

	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	p	aOR (95% CI)	p
Acute joint complaints				
Arthritis	2.23 (0.98-5.08)	0.055	2.63 (1.09-6.33)	**0.031**
Myalgia	8.83 (1.15-67.73)	**0.036**	6.11 (0.73-51.06)	0.095
Rash	6.15 (2.02-18.73)	**0.001**	4.37 (1.38-13.86)	**0.012**
Chronic joint complaints				
Arthritis	1.99 (1.09-3.65)	**0.025**	2.61 (1.30-5.21)	**0.007**
Morning stiffness	2.22 (1.17-4.19)	**0.015**	3.47 (1.69-7.11)	**0.001**
Migratory pain	4.81 (1.62-14.35)	**0.005**	3.45 (1.01-11.80)	**0.049**
Large joint	2.65 (1.12-6.24)	**0.026**	1.69 (0.65-4.41)	0.278
Fever	12.48 (4.80-32.45)	**<0.001**	12.89 (4.41-37.68)	**<0.001**
Abdominal pain	5.36 (2.65-10.83)	**<0.001**	2.33 (0.99-5.43)	0.051
Myalgia	0.38 (0.19-0.76)	**0.006**	0.35 (0.15-0.83)	**0.017**

Multivariable analysis was performed using the least absolute shrinkage and selection operator (LASSO) method. Odds ratios (OR) and adjusted odds ratios (aOR) are presented with 95% confidence intervals (CI).
Variables with statistically significant associations in univariable analysis were included in the LASSO model to identify the most predictive features for rheumatic diagnosis. Separate models were constructed for acute and chronic subgroups.

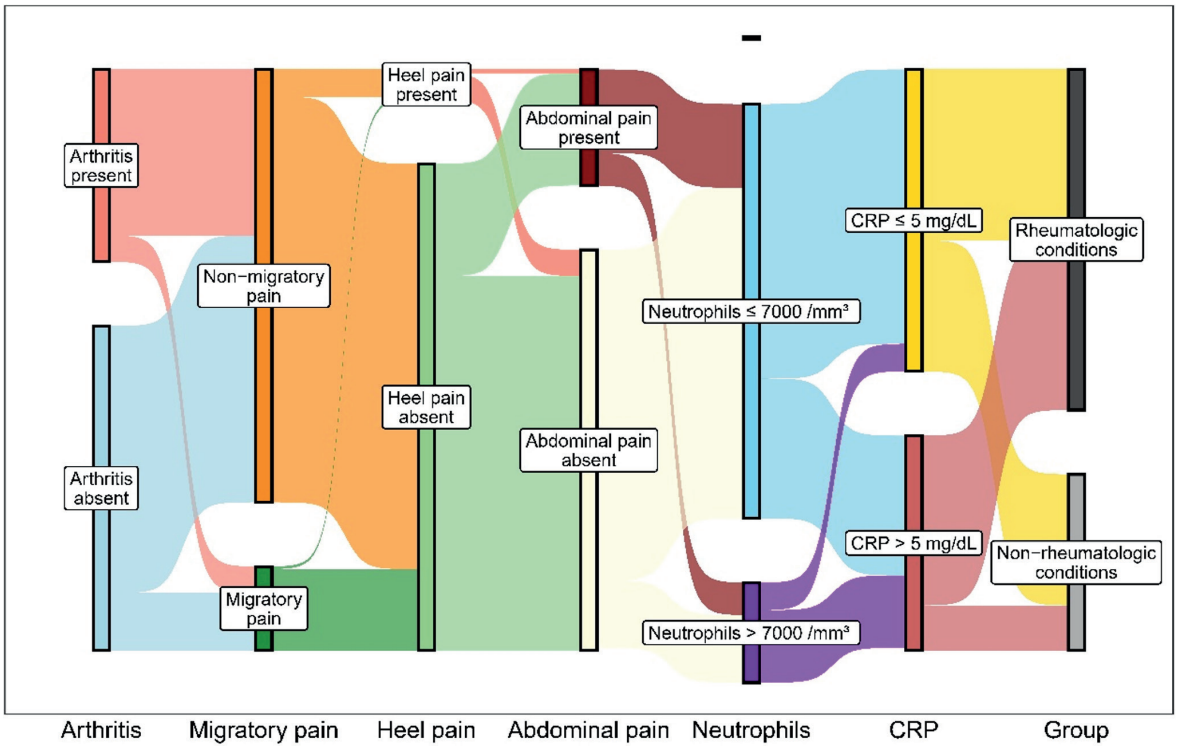

Fig. 2. Sankey diagram visualizing the relationship between key clinical features and the final diagnosis of rheumatic disease. Each vertical column indicates a diagnostic parameter, and the width of each connecting band reflects the proportion of patients moving between feature categories. The figure visually highlights the most discriminative factors used to construct the proposed clinical flowchart.

The Sankey diagram in our study provides a clinically meaningful visualization of how individual clinical features are distributed across rheumatic diseases and non-rheumatic conditions, highlighting the relative diagnostic weight of key predictors such as arthritis, migratory pain, neutrophilia, and elevated CRP. By mapping these feature patterns, the diagram helps clinicians focus on the most informative clinical findings during the initial assessment of joint complaints. Complementing this, Fig. 3 provides a simplified visual comparison of the presence or absence of these predictors, enabling rapid estimation of rheumatic disease likelihood in routine clinical practice. The prevalence of pediatric rheumatic diseases varies across geographical regions. For example, familial Mediterranean fever (FMF) is more prevalent in countries within the Mediterranean region, BD is commonly observed along the historical Silk Road, and SLE occurs more frequently in African-American populations.[5,22] A previous study from our country reported that 52% of all first referrals to the pediatric rheumatology department were diagnosed with a rheumatic disease, while 42% had non-rheumatic conditions. Among rheumatic diseases, FMF was the most common diagnosis, followed by JIA and vasculitis. In contrast, orthopedic or mechanical problems (24.7%) were the most frequent non-rheumatic conditions.[5] Although our study differed from previous ones by including only children with joint pain, the most common diagnoses among rheumatologic diseases were still FMF and JIA, while orthopedic and mechanical causes were the most frequent non-rheumatologic conditions. Fever and abdominal pain, prominent features of FMF, were also significantly more common in patients with rheumatologic diseases in our cohort.

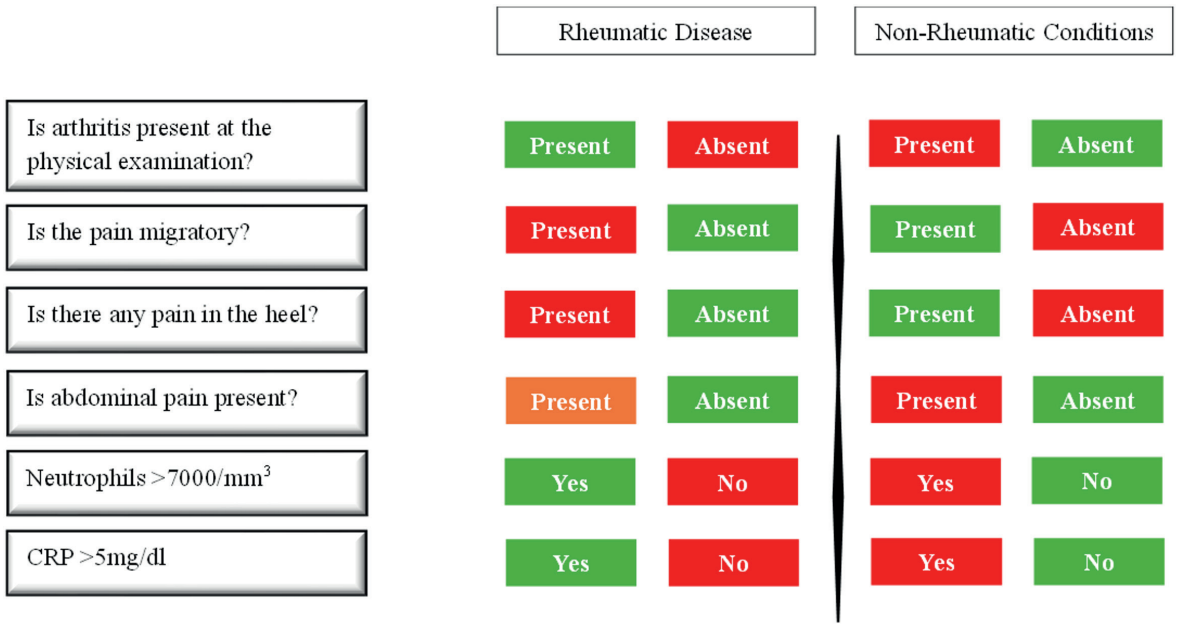

Fig. 3. Decision chart from Sankey analysis for children with musculoskeletal complaints. Each row represents a clinical variable included in the Sankey analysis. Columns show how the presence or absence of each feature relates to rheumatic versus non-rheumatic outcomes. Green boxes indicate features more common in a diagnostic group, suggesting a higher likelihood of that category. Red boxes represent less frequent features, indicating a lower likelihood. Orange boxes show features with a weaker association with the diagnostic group but limited discriminative strength.

CRP: C-reactive protein.

Pediatric rheumatology referrals are most often driven by joint pain or swelling, abnormal laboratory results such as elevated APRs and positive ANA, and unexplained fevers. However, these findings may suggest a wide range of underlying diseases, including infectious, genetic, hematologic, or orthopedic conditions.[6] Despite substantial advancements in laboratory diagnostics, the cornerstone of the diagnostic process continues to be a comprehensive medical history and a detailed physical examination. Given the frequent occurrence of joint pain in pediatric populations, it is crucial to carefully consider the duration and temporal pattern of symptom onset in the diagnostic assessment. For instance, pain that exacerbates with activity and progresses throughout the day, coupled with worsening swelling, should raise suspicion for a mechanical etiology. Algorithms that assist clinicians in making differential diagnoses can help reduce unnecessary referrals. Pilot studies have been conducted on this topic. For instance, Segal et al.[2] developed decision support software aimed at minimizing diagnostic errors in pediatric rheumatology practice (available at www.simulconsult.com). SimulConsult has expanded the diagnostic scope of complex cases, increased the success rate of early-stage diagnoses, and achieved results comparable to those of traditional assessments performed by experienced pediatricians.[2] Len et al.[23] proposed a questionnaire designed to facilitate the early identification of patients suitable for referral to pediatric rheumatology centers. Their 12-item score identified candidates for referral based on symptom patterns, with a cutoff score of 5. Structured tools such as SimulConsult or the 12-item referral questionnaire proposed by Len et al. offer algorithmic or score-based support for triage decisions.[2,23] However, our study complements these tools by identifying

diagnostic clues grounded in real-world observational data, such as the presence of morning stiffness or oligoarthritis in patients with chronic versus acute symptoms. Apart from such approaches, studies based on real-life patient data can assist clinicians in guiding the diagnostic process. There are a limited number of studies conducted with this objective. Cattalini et al.[8] developed a predictive score for chronic arthritis in a cohort of children presenting with MSK complaints, achieving a sensitivity of 90.9% and a specificity of 95.3%. It incorporated clinical variables such as prolonged morning stiffness, non-mechanical pain, and limping. According to the study, recurrent pain occurring more than once a month was strongly associated with noninflammatory disorders, with evening/night pain more common in these patients. Pain precipitating factors differed by category: rest in 68% of chronic arthritis patients, prior infection in 79% of infection-related arthritis cases, and activity in 46% of noninflammatory disorder patients. Jeamsripong and Charuvanij[7] investigated clinical findings that could predict the diagnosis of JIA in children presenting with MSK complaints. They found that morning stiffness lasting longer than 15 minutes, joint swelling on MSK examination, a duration of MSK complaints exceeding 6 weeks, and limping were significantly associated with the final diagnosis of JIA. In contrast, isolated joint pain—commonly reported—was not found to be predictive of JIA. Another study aimed at identifying specific complaints indicative of systemic inflammatory disease found that isolated pain without other symptoms rarely suggests chronic arthritis.[6] Children with arthritis typically presented with joint swelling or gait issues. ANA and rheumatoid factor (RF) tests were not useful for evaluating musculoskeletal complaints.[6] In our study, due to the heterogeneous nature of the referring group, patients were analyzed both as a whole and stratified by the duration of their symptoms. Although our primary objective was to differentiate rheumatic from non-rheumatic conditions, we additionally performed subgroup comparisons based on the chronicity of symptoms to explore whether certain diagnostic clues differ in acute versus chronic presentations. This approach may aid clinicians in early triage decisions. Specifically, in patients with acute joint complaints (<6 weeks), the presence of oligoarthritis and a rash were highly indicative of a rheumatic etiology. One of the most frequent diagnoses in this subgroup was IgA vasculitis, formerly known as Henoch-Schönlein purpura (HSP), which supports this hypothesis. Detailed analysis of rash subtypes showed that vasculitic rashes, particularly purpuric and palpable purpura, were almost exclusively observed in the rheumatic group. Conversely, non-specific rashes such as maculopapular exanthems or urticaria were uncommon and appeared in both groups. These results suggest that the predictive value of rash in our model mainly depends on vasculitic presentations, consistent with diagnoses like HSP. Conversely, in patients presenting with chronic joint complaints (>6 weeks), the presence of arthritis, morning stiffness, large joint involvement, migratory pain, and sacroiliitis were significant clinical features that supported the diagnosis of a rheumatic disease. JIA, the most common cause of chronic arthritis in children, is particularly associated with morning stiffness. Thus, morning stiffness in the context of chronic complaints may serve as a key diagnostic clue for JIA.

The main limitation of our study is its single-center design; however, its significant strength lies in the prospective evaluation of all patients using a standardized form and deriving clinical insights based on definitive diagnoses. Although all diagnoses were confirmed by an experienced pediatric rheumatologist based on the international classification criteria for each rheumatologic disease, we did not formally assess inter-rater variability, which represents a methodological limitation.

In conclusion, this study aimed to highlight clinical clues for diagnosing rheumatic diseases in children with joint pain. Accurate diagnosis relies heavily on a detailed history and physical examination. Enhancing the clues for the differential diagnosis of joint pain is crucial to reduce unnecessary referrals and help the healthcare system provide more effective services.

Supplementary materials

Supplementary materials for this article are available online at https://doi.org/10.24953/turkjpediatr.2026.6305.

Ethical approval

The study was approved by Kocaeli University Ethics Committee (date: 13.07.2023, number: 2023-170).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: Hİ, SB, YEB, AÖ, NŞ, HES; data collection: Hİ, SB, YEB, AÖ, NŞ, HES; analysis and interpretation of results: Hİ, SB, YEB, AÖ, NŞ, HES; draft manuscript preparation: Hİ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

The impact of hematocrit, punch location, and cellular interference on neonatal screening for biotinidase deficiency

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ABSTRACT

Background. Biotinidase deficiency is a core condition in newborn screening programs worldwide. While fluorometric enzyme activity assays from dried blood spots (DBS) are the standard first-tier test, their accuracy can be susceptible to pre-analytical variation. To date, the specific impact of hematocrit (HCT), punch location, and cellular interference on fluorometric biotinidase measurements have not been systematically examined.

Methods. We prepared blood pools to isolate specific variables: a reference pool at 50% HCT (HCT50), a low-HCT pool at 34% (HCT34), and a leukocyte-depleted pool (HCT50(-W)). Secondary pools were created with biotinidase activities of 0, 50, 100, and 200 U. DBS samples were prepared from all pools. Biotinidase activity was measured fluorometrically from central and peripheral punches (n=12 per condition). Statistical analysis included t-tests and Cohen's d effect sizes, with a >10% deviation set as the threshold for clinical significance.

Results. Our results demonstrated a significant systematic bias: Peripheral punches yielded higher biotinidase activity than central punches across all sample types (13.36%–16.61% difference, $p<0.05$). Lower hematocrit (HCT34) led to a significant overestimation of activity, yielding >20% higher values at the critical biotinidase activity-50 U level. Crucially, leukocyte depletion resulted in a statistically significant decrease in measured activity (~10.6%, $p<0.05$), indicating that approximately 10% of the quantified activity in DBS is leukocyte-derived and constitutes a previously unaccounted source of analytical bias.

Conclusion. This study is the first to definitively quantify the effects of key pre-analytical variables on fluorometric biotinidase testing. Punch location, hematocrit, and cellular content are not merely sources of noise but are significant confounders that can lead to both false-positive and false-negative results. We strongly recommend that DBS calibrators and patient samples be punched from the center of the spot and that second-tier testing interpretations consider individual infant hematological parameters to enhance the clinical sensitivity of newborn screening for biotinidase deficiency.

Key words: biotinidase deficiency, newborn screening, dried blood spot testing, punch location, hematocrit, filter paper.

Profound biotinidase deficiency (BD), which classically presents in infancy with a triad of neurological (seizures, hypotonia, ataxia, sensorineural hearing loss), dermatological (alopecia, eczematous rash), and metabolic manifestations, may progress to irreversible optic atrophy or cognitive impairment if left untreated. Late-onset cases in adolescence may present with motor weakness and visual disturbances.[1] While biotin supplementation prevents the development of symptoms and reverses most active manifestations

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when initiated early in neonatal life, certain neurological complications - particularly developmental delay, hearing loss and optic atrophy - may become permanent if treatment is delayed.[2] This dramatic treatment response, coupled with biotin's exceptional safety profile, underscores the importance of newborn screening for BD.

Following the identification of BD in 1983, researchers developed a rapid colorimetric method in 1984 for the semiquantitative assessment of biotinidase activity in dried blood spots (DBS).[3,4] This advancement enabled the first pilot newborn screening program for BD in Virginia that same year, with broader implementation by 1985.[5] The introduction of this screening method into universal newborn screening programs enabled detection of both profound and partial deficiencies, with an estimated global incidence of ~1:60,000, and allowed for early treatment, significantly improving clinical outcomes.[6]

The Turkish neonatal screening program for BD started in 2008, initially utilizing a colorimetric assay before transitioning to a fluorometric assay in 2015, which utilizes biotinyl-6-aminoquinoline as a substrate, and offers enhanced clinical sensitivity and specificity for DBS analysis.[2,7-9] The fluorometric assay, which outperforms the colorimetric method, offers the following critical improvements: 1) compatibility with 3 mm DBS disks instead of 6 mm, saving valuable DBS sample for additional neonatal screening tests; 2) enables single-plate processing (vs. 4 plates in the colorimetric assay), eliminating the need for specialized filter plates and inter-plate transfer steps, and reducing consumable costs by 75% (plate savings); 3) minimizes potential handling errors, enhancing methodological robustness, and improving inter-assay reproducibility; 4) uses DBS matrix-matched calibrators/controls (vs. solution-based calibrators in colorimetric assay); 5) reduces total assay time by 30 minutes; 6) offers lower detection limits and a wider detection range.[9]

The reliable detection of biotinidase deficiency hinges criticially on assay precision, especially near the decision threshold that distinguishes profound (<10% activity) from partial (10–30% activity) deficiency.[10] While both profound (<10% activity) and partial (10–30% activity) deficiencies are treated with biotin supplementation, management protocols differ significantly: profound deficiency requires lifelong, high-dose (5-10 mg/day) biotin and urgent intervention to prevent severe neurological damage, whereas partial deficiency may need lower doses (2.5-10 mg/day) and is monitored for later-onset, often subtler symptoms.[10] Misclassification near the 10% decision threshold—due to assay imprecision—can therefore lead to either overtreatment and unnecessary lifelong burden or, conversely, under-treatment and risk of preventable morbidity. Consequently, analytical precision at this cutoff is not a mere technical concern but a direct determinant of appropriate, personalized patient care.

DBS analysis has been a cornerstone of newborn screening programs since their inception, yet persistent analytical challenges —including several chromatographic and pre-analytical interference factors— can compromise assay accuracy. Most newborn screening assays utilize 3.2 mm punches from DBS. The diameter of a DBS is influenced by both the applied blood volume and hematocrit level (HCT), which collectively alter the blood, red blood cell (RBC), and serum volumes contained within each 3.2 mm punch. Variations in HCT levels (40–65%) alter blood viscosity, leading to non-uniform analyte distribution and punch-to-punch variability.[11] Higher HCT levels reduce the serum volume per punch by 27% while more than doubling the RBC volume per punch, disproportionately affecting the quantity of RBC-associated and serum-associated analytes recovered per punch.[11] Punch location introduces further bias, with peripheral punches yielding higher analyte concentrations than central punches for several key analytes quantitated in neonatal screening programs.[12] While standardization efforts by

the Clinical and Laboratory Standards Institute (CLSI) have reduced paper batch variability — minimizing matrix effects—, white blood cell (WBC) contaminants (e.g., clotting factors in native heel prick blood, which may be absent in reconstituted calibrators) can alter analyte recovery.[11] Additionally, WBC lysis during drying has been suggested to release proteases or phosphatases, potentially degrading labile biomarkers like immunoreactive trypsin (IRT).[12]

Although the effects of blood volume and punch location have been investigated for tandem mass spectrometry (MS/MS)-quantified amino acids and acylcarnitines and enzyme-linked immunosorbent assay (ELISA)-based IRT and thyroid-stimulating hormone (TSH) measurements, no study to date has examined the impact of these chromatographic factors on fluorometric enzymatic activity assays for BD. Given that Türkiye screens over 1.2 million newborns annually, with BD incidence reaching 1:481 in certain regions, we aimed to investigate how pre-analytical factors affect the accuracy of fluorometric biotinidase activity assays.[13,14] While biotinidase is primarily produced in the liver and circulates in serum, its presence in leukocytes and fibroblasts is well-documented.[1] Although neonatal blood typically has a hematocrit of 50-55%, significant inter-individual variation exists. Therefore, we additionally examined how hematocrit variability and leukocyte content influence biotinidase activity measurements.

Materials and Methods

Preparation of DBS samples

A banked donor whole blood unit was obtained from the Turkish Red Crescent (Türk Kızılayı). The anonymized blood unit used in this analysis was procured as residual material, which had been designated for disposal by the Turkish Red Crescent. Use of residual materials for the production of quality assurance and control (QC) material production is explicitly authorized by the Republic of Türkiye Ministry of Health Directive (Circular 2013/19, No: 95966346), which provides the legal framework that enables the utilization of such otherwise-waste biological materials from public institutions. This study, which utilizes such material for QC-related methodological validation, falls within the scope of this directive. All personal identifiers were permanently removed by the source institution prior to our receipt, ensuring irreversible anonymization. The blood unit, whose HCT level was determined to be 34% on a Radim Seac HeCo automated analyzer (Radim Seac S.r.l., Pomezia, Italy), was divided into three portions to prepare blood pools with native HCT (measured to be 34%), 50% HCT, and 50% HCT-W (see below). HCT levels of the latter two were adjusted to 50% as explained in the following sub-section. As there is currently no method to determine biotinidase activity directly from whole blood, and biotinidase activity is measured in arbitrary units in the absence of a certified reference material (CRM), the biotinidase level of the undiluted form of each blood pool was designated as 200 U to simplify subsequent calculations. A serial dilution series was prepared from each pool to generate samples with decreasing biotinidase levels. To perform the dilutions, each of the three pools was aliquoted into two initial portions: a) 200 U BTD: Blood pools with peak biotinidase activity (untreated whole blood), b) 0 U BTD: Blood pools with no biotinidase activity. Biotinidase-deficient pools were prepared by centrifuging the whole blood to remove the serum fraction containing the biotinidase enzyme. The packed RBCs were then washed with phosphate buffer and reconstituted to target HCT levels, effectively replacing all native serum with phosphate buffer (containing 3% albumin) to eliminate enzymatic activity. Blood pools with intermediate biotinidase activities of 100 U and 50 U were generated through the serial 1:1 dilution of the 200 U pools with the corresponding BTD-deficient (0 U) pools. All four levels were employed in the experiments. DBS samples were prepared by pipetting 50 µL aliquots from each blood pool onto pre-labeled filter paper cards (Grade 226,

PerkinElmer), followed by ambient drying (20-25 °C, overnight). The dried samples were then packaged with desiccant packs and stored at 2-8 °C until analysis. The BTD level of each DBS sample was determined using the Trimaris Neonatal Fluorometric Biotinidase Kit (Bome-Trivitron, Türkiye) and was presented in Table I.

Fluorometric biotinidase assay

Biotinidase activity measurements were performed from the DBS samples according to the method developed by Wastell et al., using the Trimaris Neonatal Fluorometric Biotinidase Kit (Bome-Trivitron, Türkiye) with a linear quantification range of 5-350 U.[7] The assay was conducted in microplate format following the manufacturer's protocol, with fluorescence measurements acquired using a microplate-compatible fluorometer (excitation: 360 nm; emission: 460 nm). In this study, the primary objective was to compare biotinidase measurements across different matrices in relative terms rather than to ascertain their true absolute values. Accordingly, the peak biotinidase level of the initial blood pool was not calibrated against the kit calibrator. Instead, it was arbitrarily assigned a value of 200 U. Since HCT levels in newborns are typically 50-55%, a blood pool with 50% HCT was designated as the reference. The starting blood pool with 50% HCT with peak biotinidase activity was assigned a value of 200 U. This pool was then serially diluted 1:1 with biotinidase-deficient (0 U) blood to create calibrators of 100 U and 50 U. Since the Trimaris Neonatal Fluorometric Biotinidase Kit (Bome-Trivitron, Türkiye) has a linear quantification range of 5–350 U, DBS materials prepared from these serially diluted blood pools (50% HCT), were used to establish a calibration curve. Subsequently, biotinidase activities of all DBS samples were determined against this reference.

Assessment of hematocrit effect

The HCT level of the donor whole blood unit obtained from the Turkish Red Crescent was measured as 34%. The unit was divided into two equal portions: a) the first blood pool was kept at 34% HCT, b) the HCT level of the second portion was adjusted to 50% as explained previously to simulate neonatal blood composition.[11] (Briefly, the blood pool was centrifuged to separate RBC and serum fractions, and the supernatant serum was transferred into a fresh tube. To achieve the target HCT level, a calculated volume of autologous serum was gradually added back onto the packed cells. The HCT was verified using a Radim Seac HeCo automated analyzer [Radim Seac S.r.l., Pomezia, Italy] after each serum addition to ensure the exact HCT level. Blood pools of 34% HCT (HCT34) and 50% HCT (HCT50) with peak biotinidase activity (BTD-200U) were further used to prepare respective blood pools with varying biotinidase activities (BTD-0U, BTD-50U, and BTD-100U) as explained above.

Assessment of cellular interference

To investigate potential cellular interference from leukocyte-derived biotinidase in DBS-based assays, we prepared paired blood pools (with and without WBCs) at 50% hematocrit: HCT50 and HCT50(-W).[11] The initial blood pool (HCT34) was centrifuged (3,000 rpm, 5 min, deceleration: 3) to separate cellular components and serum. After careful removal of the buffy coat via pipetting, the remaining constituents were gently resuspended to homogeneity, creating the "50% HCT (-WBC)" test group HCT50(-W).

Assessment of punch location effect

To evaluate chromatographic effects of punch location on biotinidase recovery, we performed fluorometric assays on DBS samples prepared from three blood pools: HCT34, HCT50, and HCT50(-W). We collected 3.2 mm punches from both central and peripheral locations of each DBS (n=12 per condition).

Statistical analysis

For each condition, biotinidase activity was measured in 12 distinct DBS samples (n=12)

Table I. Effect of punch location on fluorescence intensity and measured biotinidase (BTD) activity in DBS samples over different blood-pools.

Blood pool	Biotinidase activity, units			Florescence intensity				Clinical effect magnitude
	Expected	Measured (Recovery %)		Mean ± SD (CV%)		P value	Effect size (Cohen d)	
		Center	Peripheral	Center	Peripheral			
HCT34	0	0	0	368 ± 30 (8.3)	371 ± 24 (6.5)	0.8479	0.11	0.82%
HCT34	50	**55 (110%)**	**65 (130%)**	3359 ± 196 (5.8)	3917 ± 358 (9.1)	**<0.0001**	1.93	**16.61%**
HCT34	100	107 (107%)	**124 (124%)**	6209 ± 249 (4)	7109 ± 657 (9.2)	**<0.0001**	1.81	**14.50%**
HCT34	200	204 (102%)	**232 (116%)**	11444 ± 568 (5)	12973 ± 1187 (9.1)	**0.0001**	1.64	**13.36%**
HCT50	0	1	1	421 ± 77 (18.2)	423 ± 44 (10.3)	0.1744	0.03	0.48%
HCT50	50	47 (94%)	53 (106%)	2958 ± 189 (6.4)	3256 ± 176 (5.4)	**0.0016**	1.63	**10.07%**
HCT50	100	103 (103%)	**116 (116%)**	5959 ± 529 (8.9)	6676 ± 477 (7.1)	**0.0004**	1.42	**12.03%**
HCT50	200	199 (100%)	217 (109%)	11180 ± 867 (7.8)	12144 ± 1066 (8.8)	**0.0134**	0.99	8.62%
HCT50(-W)	0	-1	-1	355 ± 43 (12.2)	363 ± 36 (9.8)	0.6338	0.20	2.25%
HCT50(-W)	50	**43 (86%)**	52 (104%)	2734 ± 117 (4.3)	3182 ± 218 (6.9)	**<0.0001**	2.56	**16.39%**
HCT50(-W)	100	91 (91%)	103 (103%)	5332 ± 258 (4.8)	5968 ± 493 (8.3)	**0.0014**	1.62	**11.93%**
HCT50(-W)	200	**177 (89%)**	204 (102%)	9986 ± 618 (6.2)	11427 ± 1083 (9.5)	**0.0003**	1.63	**14.43%**

Dried blood spot (DBS) samples were prepared from different blood pools (HCT34, HCT50, HCT50(-W)) of increasing biotinidase activity levels. Biotinidase activity was measured fluorometrically (Trimaris Neonatal Fluorometric Biotinidase Kit; n=12 per condition). Data are presented as mean fluorescence intensity ± standard deviation (% coefficient of variation). Measured biotinidase activity for all punches was calculated using a standard curve derived from the fluorescence intensities of central punches from HCT50 DBS samples. Statistical comparisons were performed using a t-test (significance threshold $p < 0.05$), with Cohen's d values reported for effect size. Deviations exceeding 10% are highlighted.

using the Trimaris Neonatal Fluorometric Biotinidase Kit. Paired central and peripheral punches were collected from the same DBS cards for positional comparisons. All data are expressed as mean fluorescence ± standard deviation (SD). Mean fluorescence values were used to calculate biotinidase activity recovery rates across different punch positions and conditions. Peripheral vs. center deviation ratios are presented as percentage differences between mean fluorescence values. For DBS-based measurements, the total allowable error (TAE) is generally accepted as 30%.[15] Assuming this error budget is allocated equally between random (imprecision) and systematic (bias) errors, 15% is conventionally assigned to analytical processes related to assay precision, and 15% is reserved for systematic deviations inherent to the sample matrix. Sample-related deviations in DBS-based analysis can arise from various sources. Although numerous factors can cause pre-analytical variation, this study focused on three parameters: hematocrit variation, cellular interference, and punch location. Allocating a separate 15% budget for each potential source of pre-analytical variation would cause the cumulative error to far exceed the 30% TAE. Considering that these factors would have additive effects in real-world samples, a threshold of 10% was established for the clinical effect magnitude (i.e., the relative percentage difference in fluorescence signals required to be considered clinically significant). Statistical analysis was performed using Analyse-it software. For comparisons across all groups, a one-way ANOVA was applied, with significant outcomes further analyzed by Tukey's honestly significant difference (HSD) post-hoc test. Pairwise comparisons between two conditions were conducted using an unpaired t-test. A p-value of less than 0.05 was considered statistically significant. Effect sizes for pairwise comparisons are reported as Cohen's d. For DBS-based measurements, the TAE is set at 30%.[15] Based on established error budgets, deviations greater than 15% were considered to represent a clinically significant effect size, as this value exceeds the expected analytical imprecision and indicates a potential pre-analytical or biological effect. To quantify the impact of variations in BTD activity measurements on clinical decision-making, the percentage difference in mean fluorescence intensity between compared samples was calculated, and is presented as the "Clinical Effect Magnitude" in Table I, Table II, and Table III.

Results

In all samples containing serum biotinidase (regardless of the blood pool characteristics), the biotinidase activity measured from peripheral punches was statistically significantly higher than the activity measured from central punches (Fig. 1B-D; red dashes).

Furthermore, in peripheral punches, the biotinidase activity measured from DBS samples with a higher serum ratio (HCT34) was found to be statistically significantly higher than that from samples with a low serum ratio (HCT50) for all biotinidase containing levels (Fig. 1B-D; green dashes). Although a similar trend was observed in central punches, statistical significance was achieved only in BTD-50U samples, which are close to the clinical decision threshold (Fig. 1B; blue dashes).

In BTD-0U samples, an opposite effect was observed: the biotinidase activity signals obtained from both central and peripheral punches were statistically significantly higher in HCT50 samples compared to HCT34 samples. The biotinidase activities measured from leukocyte-depleted samples (HCT50(-W)) were lower than those from their whole blood counterparts at the same hematocrit level (HCT50) at all biotinidase levels (BTD-0U, BTD-50U, BTD-100U, and BTD-200U). This trend was visible across all punches; however, statistical significance was achieved for all biotinidase levels in central punches (Fig. 1A-D; blue dashes), but only at the BTD-0U and BTD-100U levels in peripheral punches (Fig. 1A, Fig. 1D; green dashes).

Table II. Effect of hematocrit level on fluorescence intensity and measured biotinidase activity in DBS samples.

Blood pool	Biotinidase activity, units			Florescence intensity				Clinical effect magnitude
	Expected	Measured (Recovery %)		Mean ± SD (CV%)		P value	Effect size (Cohen d)	
		HCT50	HCT34	HCT50	HCT34			
Center	0	1	0	421 ± 77 (18.2)	368 ± 30 (8.3)	**0.0322**	-0.91	**-12.59%**
Center	50	47 (94%)	**55 (110%)**	2958 ± 189 (6.4)	3359 ± 196 (5.8)	**<0.0001**	2.08	**13.56%**
Center	100	103 (103%)	107 (107%)	5959 ± 529 (8.9)	6209 ± 249 (4)	0.1951	0.60	4.20%
Center	200	199 (100%)	204 (102%)	11180 ± 867 (7.8)	11444 ± 568 (5)	0.4898	0.36	2.36%
Peripheral	0	1	0	423 ± 44 (10.3)	371 ± 24 (6.5)	**0.0010**	-1.47	**-12.29%**
Peripheral	50	53 (106%)	**65 (130%)**	3256 ± 176 (5.4)	3917 ± 358 (9.1)	**<0.0001**	2.34	**20.30%**
Peripheral	100	**116 (116%)**	**124 (124%)**	6676 ± 477 (7.1)	7109 ± 657 (9.2)	**0.0265**	0.75	6.49%
Peripheral	200	217 (109%)	**232 (116%)**	12144 ± 1066 (8.8)	12973 ± 1187 (9.1)	**0.0323**	0.73	6.83%

Dried blood spot (DBS) samples were prepared from blood pools with varying hematocrit (HCT34, HCT50) and increasing biotinidase activity levels. Biotinidase activity from central or peripheral punches was measured fluorometrically (Trimaris Neonatal Fluorometric Biotinidase Kit; n=12 per condition). Data are presented as mean fluorescence intensity ± standard deviation (% coefficient of variation). Measured biotinidase activity for all punches was calculated using a standard curve derived from the fluorescence intensities of central punches from HCT50 DBS samples. Statistical comparisons were performed using a t-test (significance threshold $p < 0.05$), with Cohen's d values reported for effect size. Deviations exceeding 10% are highlighted.

Table III. Effect of cellular interference of leukocytes on fluorescence intensity and measured biotinidase activity in dried blood spot samples.

Blood pool	Biotinidase activity, units			Florescence intensity				Clinical effect magnitude
	Expected	Measured (Recovery %)		Mean ± SD (CV%)		P value	Effect size (Cohen d)	
		HCT50	HCT50(-W)	HCT50	HCT50(-W)			
Center	0	1	-1	421 ± 77 (18.2)	355 ± 43 (12.2)	**0.0039**	-1.06	**-15.68%**
Center	50	47 (94%)	**43 (86%)**	2958 ± 189 (6.4)	2734 ± 117 (4.3)	**0.0159**	-1.43	-7.57%
Center	100	103 (103%)	91 (91%)	5959 ± 529 (8.9)	5332 ± 258 (4.8)	**0.0016**	-1.51	**-10.52%**
Center	200	199 (100%)	**177 (89%)**	11180 ± 867 (7.8)	9986 ± 618 (6.2)	**0.0024**	-1.59	**-10.68%**
Peripheral	0	1	-1	423 ± 44 (10.3)	363 ± 36 (9.8)	**0.0002**	-1.49	**-14.18%**
Peripheral	50	53 (106%)	52 (104%)	3256 ± 176 (5.4)	3182 ± 218 (6.9)	0.4190	-0.37	-2.27%
Peripheral	100	**116 (116%)**	103 (103%)	6676 ± 477 (7.1)	5968 ± 493 (8.3)	**0.0004**	-1.46	**-10.61%**
Peripheral	200	217 (109%)	204 (102%)	12144 ± 1066 (8.8)	11427 ± 1083 (9.5)	0.0628	-0.67	-5.90%

Dried blood spot (DBS) samples were prepared from blood pools at 50% hematocrit with (HCT50) or without (HCT50(-W)) leukocytes, with varying biotinidase activity levels. Biotinidase activity was measured fluorometrically in central and peripheral punches (Trimaris Neonatal Fluorometric Biotinidase Kit; n = 12 per condition). Data are presented as mean fluorescence intensity ± standard deviation (% coefficient of variation). Measured biotinidase activity for all punches was calculated using a standard curve derived from the fluorescence intensities of central punches from HCT50 DBS samples. Statistical comparisons were performed using a t-test (significance threshold $p < 0.05$), with Cohen's d values reported for effect size. Deviations exceeding 10% are highlighted.

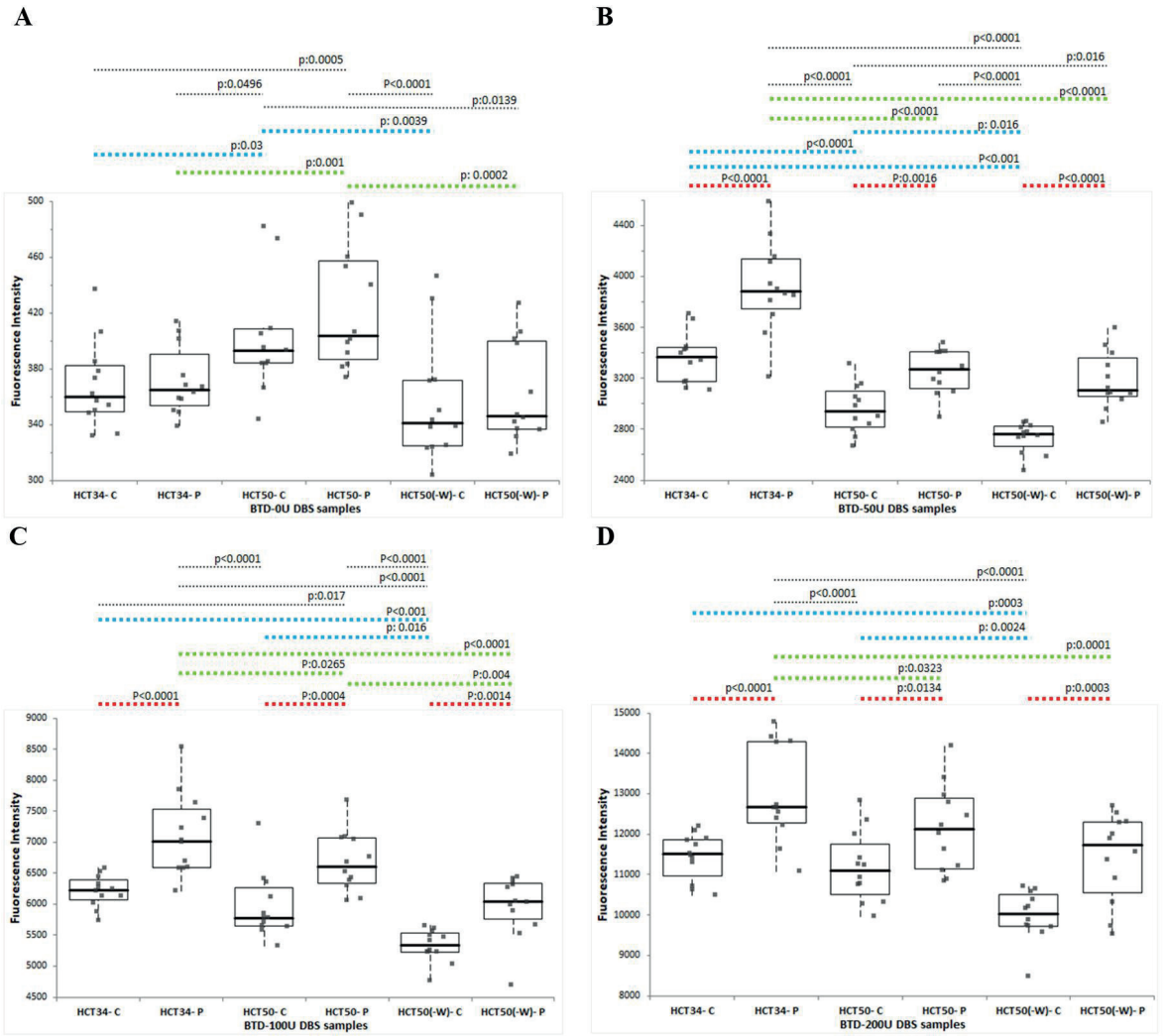

Fig. 1. Comparison of fluorescence intensities from central and peripheral punches of DBS samples.

DBS samples were prepared from HCT34, HCT50, or HCT50(-W) blood pools with varying biotinidase activity levels. **(A)** BTD-0U, **(B)** BTD-50U, **(C)** BTD-100U, **(D)** BTD-200U. For each condition, biotinidase activity from 12 punches was measured with Trimaris Neonatal Fluorometric Biotinidase Kit (n=12). Box plots show the median with interquartile ranges. Statistical significance ($p < 0.05$) is indicated by dashed lines: red for central vs. peripheral punches from the same DBS sample; blue for central punches from different blood pools; green for peripheral punches from different blood pools; black for other cross-group comparisons.

DBS: dried blood spot. HCT34: DBS samples prepared from blood pools having 34% hematocrit level. HCT50: DBS samples prepared from blood pools having 50% hematocrit level. HCT50(-W): DBS samples prepared from blood pools deficient of white blood cells (W) and having 50% hematocrit level. P: 3.2 mm punch taken from the peripheral location on the respective DBS. C: 3.2 mm punch taken from the central location on the respective DBS.

In both central and peripheral punches, biotinidase activity was significantly lower in leukocyte-depleted (HCT50(-W)) samples than in HCT34 samples (with a higher serum component) across all biotinidase -containing levels (Fig. 1A-D; blue and green dashes).

A standard curve derived from the fluorescence intensities of central punches from HCT50 DBS samples was used to calculate the biotinidase activity units for all samples. An assessment of analytical precision, based on repeated measurements of 12 samples, revealed that

all % coefficient of variation (%CV) values fell within the 15% imprecision budget, at below 9.5%; the BTD-0U value was disregarded from the precision assessment as it fell below the limit of detection (LOD).

The fluorescence intensities measured from central punches were systematically lower than those from peripheral punches. This difference was both statistically ($p<0.05$) and clinically significant. The close similarity between the %CV values of repeated measurements from central punches (n=12) and peripheral punches (n=12) indicates that punch location does not significantly affect the repeatability (precision) of the assay. When the clinical effect magnitude—defined as the relative difference in fluorescence signals between central and peripheral punches of DBS samples prepared from different blood pools—was analyzed, the difference was found to be substantial across all samples. The magnitude of this effect, ranked from largest to smallest, was as follows: HCT34 (13.36–16.61%), HCT50(-W) (11.93–16.39%), and HCT50 (8.62–12.02%) (Table I).

A decrease in hematocrit levels consistently resulted in higher fluorescence intensities for biotinidase activity assessments. This effect was most pronounced in peripheral punches, where the difference between the fluorescence intensities of HCT34 and HCT50 samples was statistically significant across all biotinidase levels. In central punches, the difference in fluorescence intensities reached statistical significance at the BTD-0U and BTD-50U levels. When these fluorescence values were converted to biotinidase activity units, around the clinical decision limit (BTD-50U), the measured biotinidase activity was significantly higher in HCT34 samples than in HCT50 samples. This difference exceeded the 10% clinical significance threshold for both punch locations, with a substantial 20.30% increase in peripheral punches and a 13.56% increase in central punches (Table II).

Leukocyte-depleted samples consistently yielded lower fluorescence intensities for biotinidase activity assessments. This effect was most pronounced in central punches, where the difference between HCT50(-W) and HCT50 samples was statistically significant across all biotinidase levels. In peripheral punches, the difference in fluorescence intensities reached statistical significance at the BTD-0U and BTD-100U levels. Consequently, the calculated biotinidase activity was significantly lower in HCT50(-W) samples than in HCT50 samples. The difference was clinically significant (exceeded the 10% threshold) for central punches at the BTD-100U and BTD-200U levels (10.52% and 10.68%, respectively) and for peripheral punches at the BTD-100U level (10.61%) (Table III).

Discussion

Given that assay precision is paramount for accurate and reliable neonatal screening, managing the constrained TAE budget, set at 30% and equally divided between imprecision and bias for DBS-based assays like the biotinidase deficiency screening, becomes a critical endeavor.

To understand, address, and pave the way for mitigating the imprecision stemming from pre-analytical parameters in DBS-based BD screening, this study investigated the impact of key pre-analytical factors, namely, hematocrit variation, cellular interference, and punch location, on biotinidase activity measurements. The findings reported in this study reveal that even without considering other potential pre-analytical variables, these three parameters alone are sufficient to consume an error magnitude equivalent to the entire systematic error budget, which constitutes half of the total allowable error. To elaborate, 1) peripheral punches yielded higher biotinidase activity than central punches across all sample types (13.36%–16.61% difference, $p<0.05$); 2) lower hematocrit (HCT34) led to a significant overestimation

of activity, yielding >20% higher values at the critical BTD-50U level; and 3) leukocyte depletion resulted in a statistically significant decrease in measured activity (~10.6%, $p<0.05$), indicating that approximately 10% of the quantified activity in DBS is leukocyte-derived.

The rapid colorimetric method employing biotin-4-amidobenzoic acid, which was developed in 1984 for the semiquantitative assessment of biotinidase activity in DBS, soon started to be used in high-throughput neonatal screening programs worldwide.[3-5] The later-developed fluorescent technique, which utilizes biotinyl-6-aminoquinoline as a substrate (and was subsequently optimized for an ultramicroassay format), offers enhanced clinical sensitivity and specificity for dried blood spot analysis, outperforming the colorimetric method.[7-9] Molecular genetic testing of the *BTD* gene, ranging from targeted variant analysis to complete sequencing, provides diagnostic confirmation.[1]

A 1998 pilot study demonstrated that the incidence of BD in Türkiye (1:11,614) was significantly higher than reported in other countries, with profound and partial BD occurring at rates of 1:14,866 and 1:53,093, respectively.[16] Marked regional variations were observed, particularly in consanguineous populations, where incidence reached 1:2,359 in Diyarbakır and 1:481 in Adıyaman.[13,17] Further analysis of a 2016–2023 Van cohort revealed parental consanguinity in 44.7% of cases and a positive family history of BD in 24.6% of patients.[2] BD screening was added as a parameter to the Turkish National Screening Program in 2008.[2] The program which initially employed a colorimetric assay for quantification of biotinidase activity, transitioned to a fluorometric assay in 2015.

It is well-established that sample-related variation is a significant challenge in neonatal screening assays utilizing DBS. When these systematic deviations occur near the clinical decision limit, they can lead to false-negative results and missed cases. To minimize this sample-induced bias and enhance clinical sensitivity, it is crucial to first decipher the sources of pre-analytical variation. Previous studies have unveiled the causes of sample-related pre-analytical variation for immunoassays (e.g., TSH, IRT) and MS-based quantifications (e.g., amino acids, acylcarnitines).[18] However, to date, a similar comprehensive study has not been conducted for biotinidase deficiency screening via enzymatic activity quantification. In Türkiye, approximately 1.2 million babies are born each year, and the incidence of BD is relatively high due to the high prevalence of consanguineous marriages.[2,13,14,17] To enhance the clinical sensitivity of neonatal screening programs for BD in Türkiye and beyond, this study aims to unveil the sources of pre-analytical variation by investigating the effects of key parameters—hematocrit level, punch location, and cellular interference—on the fluorometric biotinidase assay.

Our results demonstrated that, regardless of the blood pool characteristics (hematocrit, leukocyte content) investigated, biotinidase measurements from punches taken from the periphery of DBS were significantly higher than those from the center. The phenomenon of central punches yielding lower results than peripheral ones has been documented for other neonatal screening parameters.[11,19,20] This discrepancy can be explained by the faster diffusion rate of the serum component through the filter paper matrix compared to the cellular component. To prevent misinterpretations arising from punch location, we recommend that both calibrators and punches from infant heel-prick blood samples be taken from the center of the DBS.

Although reference values for neonatal blood hematocrit levels are accepted as 50-55%, significant variations can occur depending on the infant's overall health. Pioneering studies examining the effect of hematocrit on the diffusion rates of serum and cellular components on filter paper—and consequently on analyte measurements—have shown that as hematocrit increases, the serum ratio in central punches

decreases while the cellular ratio increases.[11,21] In this context, it has been reported that with increasing hematocrit, measured levels of TSH, octanoyl carnitine, and methionine from central punches decrease, while IRT measurements at HCT levels above 50% are higher.[19] In the fluorometric biotinidase measurements, it is observed that the biotinidase activity measured from low-hematocrit (HCT34) DBS samples was higher than that from high-hematocrit (HCT50) samples, in both central and peripheral punches. Although this elevation was observed at all biotinidase levels, the clinically relevant overestimation in HCT34 DBS became most apparent at the BTD-0U and BTD-50U levels. The fact that the magnitude of this bias is more pronounced near the clinical decision threshold than at higher biotinidase levels indicates that screening results, particularly those near the cutoff, may vary depending on hematocrit levels. To prevent false negatives in newborn screening, it may be beneficial to re-evaluate infants with biotinidase enzyme activity close to the clinical decision limit, taking their blood hematocrit percentage into account. Future studies should evaluate whether different clinical decision thresholds should be applied for different hematocrit levels.

The biotinidase enzyme, primarily synthesized in the liver, demonstrates its highest activity levels in serum.[1] While current diagnostic standards for BD employ serum-based activity assays (which serve as both primary diagnostic and second-tier confirmatory tests), documented expression in fibroblasts and leukocytes raises critical questions about potential cellular interference in DBS analyses, particularly given the known interindividual variability in leukocyte counts. In our cellular interference study, we observed that biotinidase measurements from leukocyte-depleted DBS were significantly lower, with a difference exceeding the 10% bias budget allocated for such variations. Considering that BTD-0U samples were serum-replaced, the higher signal obtained from HCT50 samples (with a higher packed-cell volume) compared to HCT34 samples strongly suggests that the biotinidase activity measured in BTD-0U samples is likely of cellular origin. This hypothesis is further supported by the results from leukocyte-depleted HCT50(-W) samples, in which calculated biotinidase activity was significantly lower in HCT50(-W) samples than in HCT50 samples. These results indicate that the biotinidase activity quantified from DBS is not solely serum-derived; approximately 10% originates from leukocytes. Given that screening kit calibrators are prepared with blood from healthy individuals with average cell counts, we recommend that second-tier BTD activity results be interpreted in conjunction with the infant's complete blood count (CBC) to avoid misinterpretation.

Due to the high volume of blood required, the DBS samples tested in this study were prepared from a donated adult blood unit. While it is not feasible to create an experimental setup for testing HCT and WBC differences with neonatal blood, future studies could directly assess the impact of peripheral versus central punching on BTD measurements in newborn screening by utilizing a larger number of DBS cards (e.g., >20) from infants with BTD levels close to the clinical cutoff, which would be highly valuable for understanding these effects at pathological levels.

In conclusion, our findings underscore the critical impact of pre-analytical variables—specifically hematocrit, punch location, and cellular interference—on the reliability of fluorometric biotinidase activity measurements. As biotinidase activity can vary even when samples are obtained from the same individual but tested in different laboratories, standardization of the testing procedures is required to improve precision. The integration of the above-mentioned factors into routine practice and data interpretation will enhance the accuracy and clinical sensitivity of newborn screening for biotinidase deficiency. Given the variability of enzyme activity, particularly in suspected biotinidase deficiency, molecular genetic analysis should always be performed for confirmation or exclusion of the diagnosis.

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Ethical approval

This study did not require ethical approval as it utilized anonymized residual blood samples originally collected for quality control material production. The study involved no direct contact with human subjects.

Author contribution

The author confirm contribution to the paper as follows: Study conception and design: CCS; data collection: CCS; analysis and interpretation of results: CCS; draft manuscript preparation: CCS. The author reviewed the results and approved the final version of the manuscript.

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Conflict of interest

CCS worked as the R&D manager for Bome Trivitron Sanayi Ürünleri Dış Ticaret AŞ between 2012-2017.

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Original Article

Neuroblastoma-associated opsoclonus-myoclonus-ataxia syndrome: an important yet overlooked diagnosis in pediatric ataxia

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ABSTRACT

Background. Opsoclonus-myoclonus-ataxia syndrome (OMAS) is a rare, immune-mediated neurological disorder, often associated with neuroblastoma (NB) in children. This study aimed to describe the clinical features, diagnostic challenges, treatment, and outcomes of pediatric patients with NB-associated OMAS.

Methods. We retrospectively reviewed medical records of seven children diagnosed with NB-associated OMAS between November 1, 2015 and January 31, 2025. Data on demographics, clinical presentation, tumor characteristics, treatment protocols, relapses, and outcomes were collected. The Mitchell-Pike OMS Rating Scale was used to assess severity.

Results. The cohort included four girls and three boys, aged 18–36 months (median 31). All had a history of infection and/or vaccination preceding symptom onset. Ataxia was the most common initial symptom (6/7, 85.7%), followed by behavioral disturbances and sleep disorders (5/7, 71.4% each). At presentation, opsoclonus was present in two patients, which was initially misdiagnosed as nystagmus. All but one patient had opsoclonus during the disease course. Neuroblastomas were located in abdominal (n=4), thoracic (n=1), and sacral (n=2) regions; all tumors measured <50 mm and were stage L1. First-line treatment included tumor resection, intravenous immunoglobulin, and corticosteroids. Three patients required second-line therapy (rituximab, cyclophosphamide, mycophenolate mofetil, or azathioprine). After a median follow-up of 40 months (range 26-64), four patients had no neurological sequelae; three had mild cognitive impairment.

Conclusion. NB-associated OMAS may present with non-specific symptoms, leading to diagnostic delays. Early recognition, thorough tumor screening, and prompt immunotherapy may improve neurological outcomes. Clinicians should suspect NB in children presenting with ataxia and behavioral/sleep disturbances, even in the absence of opsoclonus or abnormal findings on initial imaging.

Key words: Opsoclonus-myoclonus syndrome, ataxia, neuroblastoma, behavioral symptoms, sleep disorders, immunotherapy.

Opsoclonus-myoclonus-ataxia syndrome (OMAS), also called "Kinsbourne syndrome" or "dancing eye syndrome" is a rare, serious and often chronic neurological disorder. It consists of three main symptoms, including opsoclonus (conjugate, multidirectional, chaotic eye movements), myoclonus (nonepileptic limb jerking that may also involve the head and face), and truncal ataxia, causing gait imbalance. Sleep disturbances, cognitive dysfunction,

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and behavioral changes are often present.[1-3] Children with OMAS typically present with an acute or subacute onset of ataxia between 6 and 36 months of age, often accompanied by an inability to walk or sit independently.[4,5]

Due to its rarity, data on its epidemiology, clinical features, and outcomes are scarce.[6] Three out of the following four criteria should be met for the definitive diagnosis: (1) opsoclonus, (2) ataxia, (3) myoclonus, and (4) behavioral changes and/or sleep disturbances.[7] Up to one third of cases have an atypical presentation, causing delays in diagnosis by weeks or months.[8]

In the pediatric population, OMAS may be associated with neuroblastoma (NB), ganglioneuroblastoma, or ganglioneuroma. An underlying NB may be present in about half of OMAS cases. However, the development of OMAS as a paraneoplastic syndrome is very rare (2-3%) in children with NB. In a study performed in North America, at least 43% of OMAS cases were found to have NB.[8,9] The pathophysiology of NB-associated OMAS is thought to involve an immune-mediated encephalopathy triggered by cross-reactive autoimmune responses between tumor-associated antigens and central nervous system structures. Several antibodies have been described, including immunoglobulin (Ig) G and IgM targeting neural tissues and components such as Purkinje cells. In childhood OMAS, the presence of autoantibodies that react with neuronal surface antigens supports the hypothesis of an antibody-mediated pathogenesis. The observed neurological symptoms suggest that the immune response primarily targets the cerebellum and brainstem. However, the specificity of the identified antibodies remains limited, and the precise mechanisms and epidemiology of the disease have yet to be fully elucidated. Therefore, NB should be sought in every patient with OMAS. Occasionally, OMAS has been described in association with other entities such as ovarian teratoma or hepatoblastoma.[10-12]

In this paper, we aimed to evaluate the clinical characteristics, treatments, and outcomes of seven children who presented to the pediatric neurology clinic and were diagnosed with NB-associated OMAS.

Patients and Methods

Medical records of children who had been treated with a diagnosis of NB-associated OMAS between November 1, 2015 and January 31, 2025 were retrieved. Data included sociodemographic characteristics, clinical symptoms, patient histories, age at onset of symptoms, findings of the clinical examination, laboratory and radiological findings, time from onset of symptoms to diagnosis, treatment protocols, number and time of relapses, and treatment outcomes. The severity of ataxia, opsoclonus, myoclonus, and sleep or mood disturbances was also evaluated at the time of diagnosis and during treatment. The Mitchell-Pike OMS Rating Scale was utilized to assess clinical status, incorporating six categories (stance, gait, arm/hand function, opsoclonus, mood/behavior, and speech), with higher scores indicating more severe clinical presentations (Table I). Patients with OMAS not associated with NB were excluded.

The diagnosis of NB-associated OMAS was based on the presence of an NB or ganglioneuroblastoma accompanied by opsoclonus/ocular flutter and/or myoclonus and/or ataxia and/or behavioral changes/sleep disturbance, with or without irritability. Motor impairment was assessed depending on the degree of involvement, i.e., mild (the presence of abnormal neurological signs despite motor skills appropriate for age), moderate (mild or moderate decline in motor skills), and severe (severe decline in motor skills).

The patients were screened for a primary NB tumor by one or more of the following imaging or laboratory modalities: abdominal sonography, neck, chest, and abdominopelvic computed

Table I. Mitchell and Pike OMS Rating Scale

Stance	0	Standing and sitting balance normal for age
	1	Mildly unstable standing for age, slightly wide based
	2	Unable to stand without support but can sit without support
	3	Unable to sit without using hands to prop or other support
Gait	0	Walking normal for age
	1	Mildly wide-based gait for age, but able to walk indoors and outdoors independently
	2	Walks only or predominantly with support from person or equipment
	3	Unable to walk even with support from person or equipment
Arm/hand function	0	Normal for age
	1	Mild, infrequent tremor or jerkiness without functional impairment
	2	Fine motor function persistently impaired for age,
Opsoclonus	0	None
	1	Rare or only when elicited by change in fixation or
	2	Frequent, interferes intermittently with fixation or tracking
	3	Persistent, interfering continuously with function and tracking
Mood/behavior	0	Normal
	1	Mild increase in irritability but consolable and/or mild sleep disturbances
	2	Irritability and sleep disturbances interfering with
	3	Persistent severe distress
Speech	0	Normal for age, no loss
	1	Mildly unclear, plateaued in development
	2	Loss of some words or some grammatical constructs (i.e., from sentences to phrases) but still communicates verbally
	3	Severe loss of verbal communication and speech.

OMS: Opsoclonus-myoclonus syndrome.

tomography (CT), magnetic resonance imaging (MRI), I-metaiodo-benzyl-guanidine (MIBG) scintigraphy, serum neuron specific enolase (NSE), urinary catecholamine metabolites, and *MYCN*-amplification in the tumor sample.

Initial medical treatment included intravenous immunoglobulin (IVIG) at 1-2 g/kg over 2–5 days and intravenous methylprednisolone (MP) at 20–30 mg/kg/day (max 1 g/day) for 3–5 days. Treatment outcome was classified by clinical assessment as follows: 1) complete recovery (as defined by the restoration of normal developmental stages), 2) partial recovery with mild sequelae (persistence of main symptoms of OMAS or cognitive changes that do not affect daily activities or mobility), or 3) moderate or severe sequelae (persistence of main symptoms of OMAS or cognitive changes that require specific intervention).

The study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki.

Data were processed using the Statistical Package for Social Sciences (SPSS) version 18. Quantitative data were expressed as medians with ranges and qualitative data as frequencies and percentages.

Results

The study included seven pediatric patients (4 girls, 3 boys) who were diagnosed with and treated for NB-associated OMAS. The median age of the patients was 31 months (range 18–36). The time from symptom onset to the diagnosis of NB ranged from 3 weeks to 21 months (median 2 months). The median follow-up period was 40 months (range 26-64). Table II shows the clinical characteristics, treatments, and outcomes of the patients.

In all patients, a history of infection and/or vaccination was reported within 1–4 weeks prior to the onset of OMAS-related symptoms. Four patients (57%) had a history of infection, two patients (28.5%) had received vaccinations, and one patient (14%) had a history of both infection and vaccination.

Patients' OMAS scores ranged between 8 and 11 points at the time of admission. By history, ataxia was the most common initial symptom (6/7, 85.7%), and all patients exhibited ataxia at the time of admission. Three patients (43%) experienced severe ataxia that impaired their ability to stand. Behavioral disturbances (5/7, 71.4%) and sleep disorders (5/7, 71.4%) were the second most common initial symptoms. In patient 1, sleep disturbance preceded the onset of ataxia by two months. Of the five patients with behavioral symptoms, four (Patients 1, 2, 3, and 6) presented with significant behavioral abnormalities, including aggression and inconsolability. All patients but one (Patient 4) developed abnormal eye movements (opsoclonus/ocular flutter) during the clinical course; however, two patients (Patients 3 and 6) who initially presented with abnormal eye movements were misinterpreted as having horizontal nystagmus. Myoclonus developed later in two patients (28.5%).

Five patients (71%) received IVIG treatment before the diagnosis of NB-associated OMAS because they had initially been diagnosed with post-infectious cerebellar ataxia (Patients 1, 2, 3, 5, and 7). Patient 3 had received two diagnoses, first Guillain-Barre syndrome followed by post-infectious cerebellar ataxia.

In two patients (Patients 1 and 2), abdominal ultrasonography failed to detect intra-abdominal NB. These patients received IVIG with the diagnosis of post-infectious cerebellar ataxia, but symptoms recurred one month after IVIG, at which time MRI was performed, helping detect the tumors.

One patient (Patient 4) initially presented with ataxic gait, progressive limb weakness, inability to walk or sit, and loss of head control. Examination revealed paraparetic signs in the lower extremities. Spinal MRI showed spinal root compression at the T9–10 level. Another patient (Patient 6) presented at 8 months of age with abnormal eye movements interpreted as nystagmus. Cranial imaging at another center was normal, and IVIG and steroid therapy were administered. At 12 months of age, the patient developed ataxia and tremor, and spinal MRI performed at 29 months confirmed NB.

Routine biochemical tests were within normal limits in all patients. Serum NSE levels were measured in all patients, being normal in four and mildly elevated in three patients. None of the patients had elevated urinary catecholamine levels.

All brain MRIs were unremarkable. The localizations of NB were in the thoracic region (Patient 4), abdominal region (Patients 1, 2, 3, and 6), and sacral region (Patients 5 and 7). Among abdominal tumors, one was located behind the ovary, two in the adrenal region, and one at the lumbar vertebral level. The tumor size was less than 50 mm in all patients.

All patients had stage L1 tumors according to the International Neuroblastoma Risk Group Staging System (INRGSS). All were also in the very low-risk group according to the Turkish Pediatric Oncology Group-Neuroblastoma-2020 protocol. MIBG scans performed in four patients were negative.

Table II. Clinical features of 7 children with opsoclonus-myoclonus-ataxia syndrome and neuroblastoma.

Patient no/ Sex	Age (months)	Age at onset (months)	Previous history	Symptoms at presentation	Neurological symptoms	Mitchell and Pike OMS Rating Scale score	Time from symptom onset to diagnosis	Tumoral pathology	Location and size of tumor	NSE level	*MYCN* gene amplification	Treatment	Relapse	Recovery
1/Female	18	16	Infection	Ataxia, tremor	Ataxia, tremor, behavioral disturbances, ocular flutter, sleep disturbance, irritability	9	2 months	GNB	Left adnexal, posterior to the ovary 18x17x26 mm	Normal	Negative	Steroid + IVIG	No	Complete
2/Male	36	34	Infection	Ataxia, hand tremor	Ataxia, loss of head control, opsoclonus, tremor, behavioral disturbances, sleep disturbance	11	1.5 months	Ganglioneuroma	Right adrenal 12x10x10 mm	Mildly elevated	NA	Steroid + IVIG	No	Partial
3/Female	33	30	Infection	Ataxia, opsoclonus	Ataxia, opsoclonus, behavioral disturbances, myoclonus, sleep disturbance	8	3 months	GNB	Right adrenal 35x20x24 mm	Mildly elevated	Negative	None	Yes	Partial
4/Male	26 months	25	Infection and vaccination	Ataxia	Paraparesis, ataxia, myoclonus, behavioral disturbances	11	1 month	Neuroblastoma	Left posterior paravertebral area (T9-10) 32x18x40 mm	Mildly elevated	Negative	Steroid + IVIG + CTX + MMF	No	Complete
5/Female	34	31	Vaccination	Ataxia, tremor	Ataxia, tremor, opsoclonus	10	3 months	GNB	Sacral region 40x25x20 mm	Normal	NA	Steroid + IVIG	No	Complete
6/Male	29	8	Vaccination	Ocular flutter, tremor	Ataxia, opsoclonus, behavioral disturbances, sleep disturbance	10	21 months	GNB	Right posterior paravertebral area (L2-3) 31x14x7 mm	Mildly elevated	NA	Steroid + IVIG + Azathioprine	Yes	Partial
7/Female	31 months	30 months	Infection	Ataxia	Ataxia, opsoclonus, sleep disturbance,	9	3 weeks	Ganglioneuroma	Sacral region (S3-5), presacral 20x31 mm	Normal	Negative	Steroid + IVIG + Rituximab	Yes	Complete

CTX: Cyclophosphamide; GNB: Ganglioneuroblastoma; IVIG: Intravenous immunoglobulin; MMF: Mycophenolate mofetil; NA: Not available; NSE: Neuron specific enolase; OMS: Opsoclonus-myoclonus syndrome.

All patients underwent surgical excision, with complete removal of tumors except for one patient (Patient 6). In one patient (Patient 4), the diagnosis of NB was established via a tru-cut biopsy, and dexamethasone was initiated due to spinal root compression before total resection. Pathological evaluation after tumor excision revealed ganglioneuroblastoma in four patients (Patients 1, 3, 5, and 6), ganglioneuroma in two (Patients 2 and 7), and NB in one (Patient 4). N-Myc amplification performed in four patients was negative.

Following surgery, six patients (86%) were followed with monthly IVIG and steroid therapy for at least one year. Complete resolution was achieved with IVIG and steroids in patients 1, 2, and 5. One patient (Patient 3) who discontinued treatment after surgery developed recurrence of symptoms within the first year despite initial remission. Three patients (43%) received second-line therapy following inadequate response to first-line treatment, due to relapses in two (Patient 6 and 7) and due to partial improvement in one (Patient 4). Patient 7 experienced a relapse following an infection during the sixth month of IVIG and steroid treatment and was successfully treated with rituximab. Patient 6 received azathioprine and Patient 4 received cyclophosphamide and mycophenolate mofetil, both becoming symptom-free.

After a minimum follow-up of two years, four patients (57%) had complete recovery and three (43%) had partial recovery (Table II). No motor deficits were observed.

Discussion

NB-associated OMAS is a rare condition with many questions still unanswered. This study reports data on the presenting symptoms, diagnostic steps, clinical follow-up, and treatment of seven patients diagnosed with NB-associated OMAS. The female-to-male ratio was 4:3. Some studies reported a female predominance,[13-15] while others reported no sex difference.[16,17] OMAS has a lower incidence in infancy, with some studies reporting it as a rare diagnosis before age 1, which is thought to be related to the limited capacity of younger infants to produce specific antibodies to the nervous system in the first year of life.[18] The age range of the patients in our study was 18-36 months.

The symptoms of OMAS have been shown to coincide with the period during which routine pediatric vaccination schedules are carried out. Singhi et al. reported that all patients with NB-associated OMAS had a history of fever or vaccination 1–10 days previous to disease onset.[19] In an epidemiological study of OMAS patients, 85% of patients reportedly received vaccinations before the onset of neurological symptoms and NB-associated OMAS accounted for 41% of the patient population.[20] In a study conducted in Türkiye, prodromal infection was detected in 26% of all OMAS cases with or without NB.[16] All of our patients had a history of infection/vaccination before symptom onset, suggesting the role of infections or vaccines as triggering factors for OMAS.

Opsoclonus, the best-known symptom that gives its name to the syndrome, may appear as a late finding or may be absent in some atypical cases. Its intensity and frequency can vary within the same individual. In older individuals, it may also manifest as ocular flutter. It can be confused with nystagmus or epileptic seizures.[5,7,13,19,21] Myoclonus occurs less frequently. In a study by Galstyan et al., all patients developed ataxia and opsoclonus, with only one patient developing myoclonus.[13,17] In another study, opsoclonus, myoclonus, and ataxia were observed concomitantly in 67% of patients with OMAS at presentation, while a combination of two of these symptoms was observed in 33% of patients.[18] In the present series, two patients had myoclonus as a late symptom. One patient had no opsoclonus. Abnormal eye movements of two patients were misinterpreted as nystagmus at admission.

The occurrence of ataxia prior to opsoclonus or myoclonus in OMAS may lead to a misdiagnosis

of acute cerebellar ataxia.[13] Four of our patients were misdiagnosed as having postinfectious cerebellar ataxia, while one was misdiagnosed as Guillain-Barré syndrome and postinfectious cerebellar ataxia. Therefore, a diagnostic work-up for OMAS to differentiate it from acute cerebellar ataxia is critical to tumor diagnosis.[13] Diagnostic work-up should also include assessment of behavioral changes and sleep disturbances. Irritability and sleep disorders are reported in 60-83% of patients,[16,17,21] while some studies found behavioral changes in all patients.[3,19,22] Since acute cerebellar ataxia is almost universally the initial misdiagnosis in OMAS patients, a high index of suspicion is required in the presence of ataxia and irritability in toddlers, even if opsoclonus or myoclonus has not yet developed.[13]

Sleep disturbance or behavioral symptoms may be observed a few weeks before the onset of typical OMAS symptoms.[10] In one of our patients, sleep disturbance started two months before the onset of ataxia. Behavioral changes and sleep disturbances should be carefully questioned in pediatric patients presenting with ataxia, and an underlying tumor (namely NB) should be sought. Even if a tumor is not detected by ultrasonography, further imaging methods (CT/MRI) should be performed.

NB can occur anywhere in the sympathetic nervous system[23], making detection difficult and necessitating a comprehensive investigation. The first-line tests can be misleading, with high false-negative rates. Since dancing eye syndrome/OMAS-related tumors are usually low-grade, MIBG screening and tests dependent on metabolic activity such as urinary catecholamine metabolites may not be sensitive enough to detect the tumor.[21,22] In a study by Brunklaus et al., only 24% of NB-associated OMAS cases were positive for urinary catecholamines.[8] None of the patients in our study had elevated urinary catecholamine levels, while four patients showed a mild increase in NSE. Regarding tumor localization, retroperitoneal region (65%), adrenal glands (40%), mediastinum (15%), cervical region (11%), and pelvic region (3%) were most commonly reported.[24] In a study of 462 NB cases from Türkiye, the abdomen, thorax, pelvis, and neck were found at frequencies of 72.2%, 14.9%, 3.8%, and 3.2%, respectively.[25] In two studies on NB-associated OMAS, the abdominal region had significant predominance at 43% and 93%, each for the primary tumor localization.[9,29] One study reported a markedly higher rate for mediastinal tumor localization (49%) in patients with NB-associated OMAS, compared with NB patients without OMAS.[5] In our patients, mediastinal localization was seen in one patient (14.2%). Three patients had pelvic NB, one of which was located behind the left ovary and could not be visualized in two ultrasound examinations.

The diagnostic approach for pediatric patients with acute ataxia includes a thoracic X-ray, ultrasonography of the neck, abdomen, and pelvis, and urine tests for adrenal metabolites. If the results are normal, a detailed neck, chest, and abdominal MRI scan is performed.[7] Although primary tests such as thoracic X-ray and abdominal ultrasound may be useful,[8] thoracic/abdominal CT and MRI are the most sensitive imaging modalities to detect occult NB in OMAS.[26] In a study of OMAS patients conducted in the UK, MIBG could identify NB in none of four patients.[22] In another study, sensitivity rates of 86% and 99%, and specificity rates of 85% and 95% were found for full-body MRI and combined MRI and scintigraphy, respectively.[27] Therefore, MIBG should not replace MRI/CT in the diagnosis of NB-associated OMAS, but can be used to monitor disease recurrences.

Manifestations of symptoms depend on the tumor localization. In cases of spinal cord compression, symptoms are seen in 5-7% of patients.[24] One of our patients developed paraparesis due to spinal cord compression. Brain imaging is usually normal,[26] but abnormalities such as cerebellar or cerebral cortex atrophy may also be seen.[16,26,28] No cerebellar or cerebral cortex abnormalities were seen in our patients.

In recent years, NB has been increasingly diagnosed in patients with OMAS thanks to advances in imaging modalities,[6] though time to diagnosis of OMAS still remains highly variable.[13] In previous studies, the mean time from the onset of OMAS symptoms to diagnosis ranged from 2 days to 14 months.[16,20,29,30] The duration of symptoms before the detection of a tumor also varies from 6 weeks to as long as 17 months.[31] Early detection of the tumor may lead to early treatment of symptoms and improved quality of life.[13]

Compared to rates of 30–34% in the general NB population, the two-year survival rate is significantly higher (89.3%) in NB patients with OMAS, attributed to the autoimmune pathophysiology of OMAS and its limiting effect on tumor growth and spread.[5] Furthermore, NBs in OMAS patients are characterized by their smaller size possibly due to early diagnosis, with tumor diameters being <50 mm in 62–80% of cases.[26,32] In all our patients, tumor diameters were <50 mm.

Long-term neurological sequelae are seen in 70–80% of pediatric patients with OMAS.[18] Neurological sequelae developed in three of our cases (43%): one was diagnosed with a 29-month developmental delay, and another did not receive appropriate treatment despite relapse. A 5-year follow-up study from Turkey reported neuropsychiatric sequelae in 40% of patients.[33] Recent data suggest that use of multiple agents leading to increased immunosuppression improves developmental outcomes of OMAS.[13] On the other hand, reports have been discrepant regarding the relationship between delayed treatment of NB-associated OMAS and the development of neurological sequelae. In a case series from Japan in which the mean time to tumor diagnosis was 7 months after the onset of OMAS, neurological sequelae were more common in patients with a longer interval between tumor diagnosis and initial treatment.[34] In a long-term prognosis study, it was observed that the time between the onset of OMAS and the diagnosis of NB-associated OMAS was longer in the group with cognitive impairment.[9] Similar results were found in a study from Italy.[29] However, there have been studies that did not find this association.[21,35]

Bearing in mind the rarity of the condition, reported cases in the literature may provide new insights into pediatric cases with ataxia and OMAS that could be caused by an unrecognized tumor (i.e., NB).

The limitations of this study include its retrospective design, small sample size, differences in treatment protocols, and relatively short follow-up periods. Despite these limitations, with detailed clinical description, it addresses a significant diagnostic challenge in identifying NB-associated OMAS in pediatric patients presenting with acute ataxia.

Conclusion

NB-associated OMAS is a rare condition usually co-presenting with ataxia in the pediatric population. Delayed diagnosis is common in patients presenting with ataxia, which can lead to significant neurological sequelae. A detailed investigation for the underlying NB should be made in patients with ataxia, before establishing the diagnosis of acute cerebellar ataxia. Sleep dysregulation and behavioral changes usually suggest OMAS, and if present, the patient should undergo CT/MRI for NB, even if no tumor is detected on ultrasonography.

Ethical approval

The study was approved by Ethics Committee of the Koc University Faculty of Medicine (date: 25.07.2025, number: 2025.341.IRB2.163).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: AAA, RK; data collection: AAA, BOS, MFE, RK; analysis and interpretation of results: AAA, BOS, MFE, RK; draft manuscript preparation:

AAA, SU, RK. 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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Short Communication

Impact of a structured influenza seminar on pediatric residents' knowledge and attitudes: a pre-post single-group study

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ABSTRACT

Background. Influenza remains a primary global health concern associated with significant morbidity and mortality, especially among high-risk pediatric populations. Pediatric residents are involved in the diagnosis, treatment, and prevention of influenza during their training; however, gaps in influenza-related knowledge have been reported. The aim of this study was to evaluate the impact of a structured educational seminar on improving pediatric residents' knowledge of influenza symptoms, complications, treatment, and vaccination practices.

Methods. This prospective, single-center, pre-post study included pediatric residents at a tertiary hospital. Participants completed the same structured 25-item questionnaire immediately before and one month after a 60-minute educational seminar on influenza. The questionnaire assessed knowledge of clinical symptoms, transmission routes, antiviral treatment, chemoprophylaxis, and vaccination. Item-level correct response rates and the total knowledge score (range 0-25) were compared between pre- and post-seminar assessments.

Results. Sixty-two residents participated. After the seminar, correct response rates increased for several clinical features, including sudden onset of illness ($p = 0.006$), rapid progressive disease ($p = 0.003$), diarrhea ($p < 0.001$), abdominal pain ($p < 0.001$), febrile seizure ($p = 0.003$), and complex febrile seizure ($p < 0.001$). Knowledge regarding transmission routes and oseltamivir-related adverse effects improved significantly ($p < 0.05$), while chemoprophylaxis-related items showed mixed changes in correct response rates. The total knowledge score increased from 14 (interquartile range [IQR]: 12-16.25) to 18 (IQR: 15-21) after the seminar ($p < 0.001$).

Conclusion. A single, structured educational seminar was associated with improvements in several domains of influenza-related knowledge among pediatric residents. The observed declines in selected chemoprophylaxis items indicate that some topics may require repeated or reinforced educational approaches.

Key words: children, influenza, post-training, resident, survey.

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Influenza remains a significant cause of morbidity and mortality worldwide, particularly among children and other high-risk populations.[1,2] Early recognition of clinical manifestations, appropriate antiviral treatment, and timely vaccination are essential components of effective influenza management in pediatric practice.[1-3] Pediatric residents, who are actively involved in frontline patient care during their training, play an important role in the diagnosis, treatment, and prevention of influenza.

Previous studies have shown that physicians' knowledge and attitudes toward influenza may influence diagnostic accuracy, treatment decisions, and vaccine-related counseling.[4-6] Despite the availability of evidence-based guidelines, gaps in influenza-related knowledge have been reported among resident physicians, particularly regarding atypical clinical manifestations, indications for antiviral therapy, chemoprophylaxis, and vaccination recommendations.[7-9] Educational interventions have therefore been proposed to improve residents' understanding of influenza and support guideline-concordant practice.[10]

Short, structured educational programs are commonly used in residency training; however, data evaluating their effectiveness in improving pediatric residents' influenza-related knowledge are limited.[11,12] In addition, it remains unclear whether such interventions have a similar impact across different levels of training or reduce knowledge differences between junior and senior residents. The aim of this study was to evaluate changes in pediatric residents' influenza-related knowledge following a structured educational seminar.

Materials and Methods

This prospective study was carried out at the University Faculty of Medicine, Tepecik Training and Research Hospital in İzmir, Türkiye. Pediatric residents employed at the hospital during the study period constituted the study population. Residents with more than two years of clinical experience were categorized as *senior residents*, while those with less than two years of experience were categorized as *junior residents*. Residents on maternity, military, or research leave, and those who did not provide informed consent, were excluded.

Data were collected using a structured questionnaire administered face-to-face immediately before an influenza educational seminar. After completing the pre-training questionnaire, all participants attended a standardized, in-person educational seminar that addressed key aspects of influenza, including clinical features, transmission routes, complications, treatment options, and vaccination guidelines. The seminar lasted 60 minutes, was delivered by two pediatric infectious disease specialists, and combined didactic teaching with case-based discussions and interactive question-and-answer sessions. Educational materials were prepared in accordance with American Academy of Pediatrics (AAP) recommendations.[3]

The questionnaire consisted of 25 items assessing residents' knowledge of influenza-related clinical manifestations, transmission routes, antiviral treatment, chemoprophylaxis, and vaccination. It included single best-answer questions as well as statements intended to evaluate both correct and incorrect concepts, in accordance with current guideline recommendations. Items related to clinical recognition and transmission focused on typical symptoms, modes of spread, and contagiousness. Treatment-related questions addressed indications for antiviral therapy, treatment duration, and commonly reported adverse effects. Vaccination-related items examined recommended age groups, high-risk populations, and scenario-based immunization strategies.

Knowledge of chemoprophylaxis was assessed by presenting appropriate and inappropriate clinical and epidemiological statements, with responses recorded as correct or incorrect. Additional items gathered information

on demographic characteristics, influenza vaccination status, and reasons for non-vaccination.

The study was conducted between August 31, 2021, and December 1, 2021, just before the influenza season. One month after the seminar, the same questionnaire was re-administered to assess changes in knowledge. Written informed consent was obtained from all participants, and participation was voluntary, and anonymized numeric codes were used to match pre- and post-surveys. The study protocol was approved by the local ethical committee (decision no. 2019/12-22).

Statistical analysis

Statistical analysis was performed using SPSS 24.0 (IBM Corp, Armonk, NY). Categorical data were summarized as numbers and percentages, and continuous variables as mean ± standard deviation or median (interquartile range [IQR]), as appropriate. Pre-post comparisons of categorical variables were conducted using McNemar's test, while paired t-tests or Wilcoxon signed-rank tests were used for continuous variables, depending on data distribution. $P < 0.05$ was considered statistically significant. The total knowledge score was defined as the sum of correct responses across all 25 items (range 0-25).

Results

All 62 pediatric residents working at the same hospital participated in the study. The median age was 29 years (IQR 27-29), 75.8% (n = 47) were female, and 61.3% (n = 38) were senior residents. A total of 16.1% (n=10) reported having a chronic disease. Influenza vaccination rates did not differ between residents with and without chronic diseases ($p = 0.790$).

In the previous season, 71.0% (n = 44) of residents reported not being vaccinated. The most common reasons were lack of time (54.5%), perception that the vaccination was unnecessary (11.4%), vaccine unavailability (9.1%), and concerns about safety (4.5%). For the current season, 64.5% (n = 40) reported willingness to be vaccinated, 30% indicated that the COVID-19 pandemic influenced this decision.

Baseline knowledge of influenza symptoms was highest for fever, myalgia, and headache, and lowest for complex febrile seizures, diarrhea, and abdominal pain. As shown in Table I, post-seminar correct response rates increased for several symptoms, with statistically significant improvements in recognition of sudden onset of illness ($p = 0.006$), rapidly progressive disease ($p = 0.003$), abdominal pain ($p < 0.001$), diarrhea ($p < 0.001$), febrile seizures ($p = 0.003$), and complex febrile seizures ($p < 0.001$). Before the seminar,

Table I. Recognition of influenza symptoms by pediatric residents: before and after the seminar

Symptoms	Number of residents providing correct responses		p value
	Pre-survey, n (%)	Post-survey, n (%)	
Fever	62 (100)	62 (100)	-
Headache	60 (96.8)	61 (98.4)	1.000
Sudden onset of illness	44 (71)	54 (87.1)	0.006
Rapid progressive disease	33 (53.1)	47 (75.8)	0.003
Diarrhea	22 (35.5)	42 (67.7)	<0.001
Sore throat	49 (79)	54 (87.1)	0.302
Stomachache	22 (35.5)	47 (75.8)	<0.001
Myalgia	58 (93.5)	61 (98.4)	0.250
Cough	53 (85.5)	57 (91.9)	0.344
Fatigue	60 (96.8)	62 (100)	0.500
Febrile seizure	30 (48.3)	45 (72.6)	0.003
Complex febrile seizure	14 (22.6)	31 (50)	<0.001

senior residents demonstrated higher correct response rates for some symptoms; however, no significant junior-senior differences remained after the seminar (p > 0.05 for all).

Regarding transmission routes, droplet transmission was most frequently identified at baseline (95.2%, n = 59). Post-seminar rates were 95.2% (n = 59) for droplets (p = 1.000), 58.1% (n = 36) for aerosols (p = 0.020), 59.7% (n = 37) for contact (p < 0.001), and 35.5% (n = 22) for autoinoculation (p < 0.001). Awareness that influenza can be transmitted before symptom onset increased from 72.6% to 90.3% (p = 0.019). No significant differences were observed between senior and junior residents (p > 0.05 for all).

Knowledge of oseltamivir indications showed stable baseline performance, with no significant junior-senior differences before or after the seminar (p > 0.05 for all). Correct identification of nausea and vomiting as the most common adverse effects increased from 77.4% to 95.2% after the seminar (p<0.001).

Correct identification of pediatric risk factors for severe influenza was high at baseline and increased across all items following the seminar, without significant differences between training levels (Table II).

In vaccine-related scenarios, correct response rates improved for children aged 6 months to 8 years requiring two doses (67.7% to 82.3%, p=0.030), while correct response rates for universal vaccination recommendations showed a numerical increase that was not statistically significant (77.4% to 88.7%, p=0.143; Table III).

For chemoprophylaxis items, mixed changes were observed. Correct identification of the statement that household contacts should not routinely receive treatment showed a numerical decrease that did not reach statistical significance (87.1% to 75.8%, p=0.090), whereas correct identification of chemoprophylaxis indications in closed settings increased from 72.6% to 88.7% (p=0.021; Table III).

The total knowledge score increased significantly after the seminar (median [IQR]: pre-seminar 14 [12-16.25] vs post-seminar 18 [15-21]; Wilcoxon signed-rank test, Z = −5.918, p < 0.001).

Discussion

Influenza has long been a significant public health concern, causing acute respiratory infections, severe pneumonia, and, in some

Table II. Knowledge of pediatric residents regarding influenza vaccine recommendations for high-risk children: before and after the seminar

Risk groups	Number of residents showing the correct response		p value
	Pre-survey, n (%)	Post-survey, n (%)	
Children with chronic pulmonary disease	62 (100)	62 (100)	-
Children with chronic cardiac disease	57 (91.9)	58 (93.5)	1.000
Immunosuppressive children	61 (98.4)	62 (100)	1.000
Children with chronic kidney disease	57 (91.9)	59 (95.2)	0.720
Children with an increasing risk of aspiration	49 (79)	54 (87.1)	0.260
Children with metabolic diseases	57 (91.9)	58 (93.5)	1.000
Children with sickle-cell anemia	41 (66.1)	55 (88.7)	0.001
Children requiring constant salicylate treatment	48 (77.4)	55 (88.7)	0.110

Table III. Pediatric residents' knowledge of chemoprophylaxis indications in children: before and after the seminar

Propositions (if any transmission modes anticipated)	Number of residents showing the correct response		p value
	Pre-survey, n (%)	Post-survey, n (%)	
If a family member receives oseltamivir treatment, other household members should be considered for chemoprophylaxis (correct)	54 (87.1)	47 (75.8)	0.090
Children in high-risk groups who have not received the current season's influenza vaccine should be considered for chemoprophylaxis (correct)	52 (83.9)	42 (67.7)	0.020
Individuals living with or caring for immunocompromised children should receive chemoprophylaxis, especially if the current season's vaccine may not protect against the circulating virus (correct)	49 (79)	47 (75.8)	0.830
Chemoprophylaxis is not recommended for all school-aged children between 8 and 18 years unless they belong to a high-risk group or have had significant exposure (incorrect)	55 (88.7)	59 (95.2)	0.340
Children under six months of age are at high risk and cannot be vaccinated; therefore, chemoprophylaxis should be given to their close contacts (correct)	13 (21)	13 (21)	1.000
If a positive case is identified in a closed setting, such as a dormitory or military barracks, chemoprophylaxis should be administered to close contacts, including roommates, to prevent an outbreak (correct)	45 (72.6)	55 (88.7)	0.021

cases, death, and is associated with a substantial global disease burden in children.[13] While most cases resolve within a few days, the virus is still associated with substantial morbidity and mortality, particularly among high-risk groups.[2,3] Timely recognition of clinical manifestations, identification of individuals at risk for severe disease, and appropriate use of antiviral treatment or prophylaxis are essential components of effective influenza management. Vaccination remains the most effective preventive strategy, and healthcare workers play a key role not only in self-protection but also in reducing transmission to vulnerable patients and promoting vaccine uptake through informed recommendations.[2,3]

In the present study, influenza vaccination uptake among pediatric residents was low, with 71% reporting not being vaccinated during the previous influenza season. Commonly reported barriers included a lack of time, the perception that vaccination was unnecessary, limited access, and concerns about vaccine safety. These findings are consistent with previous studies demonstrating persistently low influenza vaccination rates among healthcare workers despite long-standing recommendations.[5,6,9,10] Notably, willingness to receive the influenza vaccine in the current season was higher than in the previous season. This observation may reflect increased awareness of viral transmission and disease severity during the COVID-19 pandemic; however, causal inferences cannot be drawn from the study design. Similar observations have been reported in prior studies, indicating that major public health events may temporarily improve vaccine acceptance among healthcare professionals.[11,12]

Chronic illness is a well-established risk factor for severe influenza, and vaccination is strongly recommended for individuals with underlying conditions.[2] However, in our cohort, no

significant association was observed between chronic disease and influenza vaccination status. This finding aligns with previous studies indicating that, even among high-risk groups, influenza vaccination coverage remains suboptimal.[14-16] Given the relatively young age and generally good health status of pediatric residents, traditional risk-based motivators such as age and comorbidity may be insufficient to drive vaccination behavior in this population. These results highlight the need for targeted educational and institutional strategies to improve vaccine uptake among young healthcare professionals.

Encouragingly, participants demonstrated strong baseline knowledge of certain high-risk conditions for severe influenza, such as chronic pulmonary disease and immunosuppression. Following the educational seminar, correct response rates showed an upward trend; however, these changes did not reach statistical significance, and differences between junior and senior residents diminished. Taken together, these findings do not demonstrate a statistically significant improvement but suggest that structured educational interventions may contribute to more uniform knowledge patterns across different levels of clinical experience.

Recognition of influenza symptoms is critical for timely diagnosis and appropriate management, particularly in severe cases where treatment should not be delayed while awaiting confirmatory testing.[2,17] In our study, common symptoms such as fever, myalgia, and headache were well recognized at baseline, whereas atypical or less common manifestations, including complex febrile seizures, diarrhea, and abdominal pain, were frequently underrecognized. Senior residents initially showed greater awareness of these atypical presentations, likely reflecting broader clinical experience. After the seminar, recognition of these symptoms improved, and the knowledge gap between junior and senior residents disappeared. This pattern suggests that targeted educational efforts may improve recognition of atypical influenza presentations, an important prerequisite for timely diagnosis and appropriate clinical decision-making.

Influenza transmission is most widely associated with droplet spread; however, aerosol transmission, direct contact, and autoinoculation also contribute to viral spread.[3] Inadequate recognition of these transmission routes may compromise infection control practices. In the current study, awareness of non-droplet transmission routes, particularly autoinoculation, was limited at baseline but improved following the seminar. These findings indicate that targeted educational content may help address specific gaps in understanding transmission mechanisms, which is relevant for infection prevention knowledge among trainees.

Oseltamivir remains the primary antiviral agent for influenza treatment, despite concerns regarding emerging resistance.[18,19] Correct use of oseltamivir, including appropriate indications, dosing, and duration, is emphasized in clinical guidelines and remains an important component of influenza management education. In our study, over half of the participants knew that high-risk and severe cases require prompt antiviral therapy. After the seminar, the correct identification of common adverse effects improved significantly, and knowledge gaps between experience levels narrowed. These findings may reflect confusion arising from complex clinical scenarios or overgeneralization of treatment principles during training. Importantly, these findings suggest that educational interventions should be balanced and should clearly distinguish between treatment and prophylaxis to reduce the risk of misunderstanding.

This study has several important limitations. First, it was conducted at a single center with a relatively homogeneous group of pediatric residents, which may limit generalizability. Second, although knowledge retention was demonstrated one month after the seminar, long-term retention and its translation into clinical practice were not evaluated. Future

multicenter studies with extended follow-up are warranted to determine whether such educational benefits can be maintained over time. Third, the questionnaire was developed in accordance with guideline recommendations but was not formally validated, which should be considered when interpreting the results. Moreover, the absence of randomization, a control group, and blinding fundamentally limits causal inference, and knowledge was assessed through self-reported responses rather than objective measures of clinical behavior or patient outcomes. Observed changes cannot be confidently attributed to the educational seminar alone and may reflect testing effects, recall bias, or short-term learning. Therefore, the findings should be interpreted as descriptive of short-term changes in knowledge rather than as evidence of educational effectiveness.

Although this study has limitations, our findings suggest that a structured educational seminar can improve multiple domains of influenza-related knowledge among pediatric residents and reduce disparities between junior and senior trainees. At the same time, declines observed in some items suggest that certain topics may require more careful, repeated educational attention. Incorporating regular, guideline-based training sessions into pediatric residency programs may support sustained knowledge acquisition and improve preparedness for seasonal and emerging viral infections.

Conclusion

Our findings indicate that pediatric residents had notable gaps in influenza-related knowledge, especially regarding transmission, atypical symptoms, and antiviral use. After the seminar, higher correct response rates were observed across multiple knowledge domains at all training levels, with a reduction in initial differences between junior and senior trainees. However, remaining inaccuracies suggest the need for repeated, targeted educational efforts. Incorporating guideline-based training into pediatric residency programs may improve consistency in pediatric residents' influenza-related knowledge and preparedness.

Ethical approval

The study was approved by Tepecik Training and Research Hospital's Ethics Committee (date: 22.12.2019, number: 2019/12-22).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: PGS, YEK, EKÖ, AKA; data collection: PGS, YEK, EBY; analysis and interpretation of results: PGS, YEK, EBY, DY; draft manuscript preparation: PGS, YEK, EKÖ, DY. 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

Response to modulator therapy in a cystic fibrosis patient with a single identified *CFTR* variant not eligible for modulator treatment

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ABSTRACT

Background. Cystic fibrosis (CF) is a multisystem disease caused by variants in the CF transmembrane conductance regulator *(CFTR)* gene affecting ion transport. CFTR modulator therapy has become a significant treatment option for many CF patients. However, access to modulator therapy remains a challenge for cases with rare variants.

Case Presentation. Our 9-year-old female patient, diagnosed with CF by elevated sweat chloride and history of steatorrhea from birth, carried the rare W1282X variant with no clear eligibility for modulator therapy. The family self-financed one month of elexacaftor / tezacaftor / ivacaftor (ETI) treatment. After one-month, clinical evaluation showed improvements in body mass index (BMI; 14.98 to 15.05 kg/m^2), an increase in forced expiratory volume in 1 second (FEV1%) by 12% (72% to 84%), decreased sweat chloride levels (from 83 mEq/L to 9 mEq/L), and enhanced exercise capacity. No pulmonary exacerbations occurred during therapy. Based on these findings, modulator therapy approval was obtained for continued treatment. Our patient is currently 10 years old and has been on modulator therapy for approximately 12 months.

Conclusions. Facilitating access to modulator therapies for patients with rare mutations is crucial, considering the potential long-term complications of CF. While organoid studies may not always predict clinical response, real-world cases demonstrate clinically meaningful benefit despite lack of organoid responsiveness. Short-term assessment of modulator response may not adequately reflect improvement in pulmonary function or exacerbation frequency, but decreases in sweat chloride, improvements in nutritional and functional parameters such as weight, BMI, and exercise capacity may be indicative of improvement in pulmonary function and exacerbation rates.

Key words: cystic fibrosis, CFTR modulatory therapy, W1282X.

Cystic fibrosis (CF) is a monogenic disease caused by variants in the CF transmembrane conductance regulator *(CFTR)* gene, affecting chloride and water transport across epithelial cells, leading to thick, sticky secretions in multiple organs.[1] The incidence of CF varies geographically, with 1 in 100,000–150,000 births in Asia and 1 in 3,500 in North America. *CFTR* mutations affect chloride channel function to varying degrees, resulting in a broad clinical spectrum. Respiratory manifestations include mucus plugging of small airways, air trapping,

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chronic productive cough, reduced spirometry volumes, recurrent lower respiratory infections, and bronchiectasis.[2] Severe CF cases may become lung transplant candidates due to chronic inflammation, hypoxia, and infection. Recent advances in CF treatment, particularly CFTR modulators, have markedly improved disease management and quality of life by targeting underlying molecular defects.[3] Ivacaftor monotherapy, through its potentiator effect, improves CFTR channel activity, resulting in better pulmonary function, reduced exacerbations, and weight gain in CF; however, its use is limited to ~5% of patients. The triple combination of elexacaftor / tezacaftor / ivacaftor (ETI) offering both corrector and potentiator actions, has demonstrated superior outcomes, particularly in those with one or two F508del alleles. Modulator eligibility is genotype-based, though for rare variants, responsiveness may be assessed *in vitro* using nasal epithelial samples or intestinal organoids in specialized centers.[4]

In Türkiye, the use of CFTR modulator therapy was officially authorized and included in the national reimbursement system as of July 2025. ETI combination therapy is reimbursed for patients aged ≥ 2 years with a confirmed diagnosis of CF (either by sweat chloride testing or genetic analysis) who carry at least one F508del mutation or another *CFTR* variant with proven responsiveness to the therapy. However, a subset of patients lacks identifiable mutations suitable for approved modulators, creating uncertainty regarding therapy benefits. In variants with premature termination codons, such as W1282X, modulator therapies are generally ineffective. Ongoing research for W1282X is exploring genetic approaches, including adenine base editing (ABE) and homology-independent targeted integration (HITI), as potential alternative treatment strategies.[5] We present our experience with a patient clinically diagnosed with CF and a single identified *CFTR* variant (W1282X), who was not clearly eligible for modulators, but nonetheless demonstrated a positive response to ETI therapy.

Case Presentation

A 9-year-old girl diagnosed with CF at 2 months of age due to elevated sweat chloride (92.8 and 95 mEq/L) and history of steatorrhea was followed for bilateral bronchiectasis and chronic *Pseudomonas aeruginosa* infection. After a 12-month course of inhaled tobramycin, sputum cultures remained negative for *P. aeruginosa*. Pancreatic insufficiency was managed with enzyme replacement and fat-soluble vitamin supplementation; and ursodeoxycholic acid was given for CF-associated liver disease. She continued to receive dornase alfa and hypertonic saline inhalation, and chest physiotherapy, although not regularly. Whole exome sequencing (WES) and multiplex ligation-dependent probe amplification (MLPA) revealed a single W1282X variant on one allele of the *CFTR* gene, with no variant detected on the other allele. Non-adherence to chest physiotherapy and supportive treatments was associated with reduced exercise capacity and more than three pulmonary exacerbations annually. We were unable to identify our patient's other variant with WES and MLPA. Ortiz et al. demonstrated ETI response in a case with W1282X and N1303K variant, which resulted in increased appetite, improved exercise capacity and body mass index (BMI), higher forced expiratory volume in 1 second (FEV1), and a reduced frequency of pulmonary exacerbations.[6] Mutyam et al. observed clinical improvement in a cystic fibrosis patient who was homozygous for the W1282X mutation following treatment with ivacaftor; they attributed this to an increase in the activity of the residual protein.[7] Given the existence of cases in the literature showing clinical benefit despite lack of clear genetic eligibility for CFTR modulatory treatment, a short-term trial of ETI therapy was planned. The patient's family preferred to start ETI therapy despite uncertain eligibility. Informed consent was obtained from the family before treatment. Along with ETI, our patient continued concomitant treatment with dornase alfa, hypertonic saline, chest physiotherapy, and supportive therapies

targeting other system involvements. At the initiation of treatment, she was able to maintain oxygen saturation on room air; however, sputum cultures revealed chronic methicillin-sensitive *Staphylococcus aureus* (MSSA) colonization. Computerized tomography (CT) of the chest demonstrated bronchial wall thickening and cylindrical bronchiectasis, as well as a mosaic attenuation pattern secondary to air trapping in the lungs. Baseline assessments included weight, spirometry, six-minute walk test and sweat chloride measurement.

Pre-treatment spirometry showed a forced vital capacity (FVC) of 76% and an FEV1 of 72%, which improved to 85% (+9%) and 84% (+12%), respectively, after one month of therapy, indicating marked improvement in lung volumes. The patient demonstrated improved exercise capacity, a substantial reduction in sweat chloride concentration (from 83 to 9 mEq/L) and a slight increase in BMI (from 14.98 to 15.05 kg/m^2) (Table I). Although these short-term gains appear modest, they are clinically meaningful in pediatric CF, as they may contribute to catch-up growth, improved pulmonary function and a reduced frequency of exacerbations. No treatment-related adverse effects were observed.

Following these results, the family successfully obtained official approval for ongoing modulator therapy from the Ministry of Health. After six months of treatment, the patient's growth parameters were 32 kg (SDS: -0,76), BMI 16.1 kg/m^2, sputum cultures remained sterile, FEV_1 was 85% and no pulmonary exacerbations requiring hospitalization occurred (Table I).

Informed consent was obtained from the legal guardian for the use of the patient's information in the publication.

Discussion

To our knowledge, this case represents the first reported patient in Türkiye with a single *CFTR* variant and no clear modulator eligibility, who responded well to ETI treatment. In our patient, the detection of only a single pathogenic variant, with the second variant not identified by MLPA or WES, precluded the initiation of modulator therapy. We presume that the treatment response may be attributable to the unidentified variant; however, as this could not be genetically confirmed, a formal eligibility assessment for the therapy could not be performed.

Table I. Clinical and laboratory findings at the beginning, the first month and the sixth months of therapy.

Parameter	Pre-treatment	First month of treatment	Sixth month of treatment
Weight	27.5 kg (SDS: -0.39)	30 kg (SDS: -0.07)	32 kg (SDS: -0,76)
BMI	14.98 kg/m^2 (SDS: -0,77)	15.05 kg/m^2 (SDS: -0,89)	16.1 kg/m^2 (SDS: -0,83)
FVC	76%	85%	81%
FEV1	72%	84%	82%
FEV1/FVC	96%	98%	99%
FEF25-75	72%	106%	87%
PEF	90%	91%	72%
Sweat chloride (mEq/L)	83.3	9	-
6MWT	330 m	498 m	-
Number of pulmonary exacerbations	> 3/yr	None	None

6MWT: six-minute walking test; BMI: body mass index; FEF 25-75: forced expiratory flow between 25% and 75% of forced vital capacity; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; FEV1/FVC: forced expiratory volume in 1 second to forced vital capacity ratio; PEF: peak expiratory flow.

Due to the premature termination codon, CF patients harboring the W1282X mutation typically exhibit severe disease, with early chronic infections, pancreatic insufficiency, poor growth, impaired lung function, and early bronchiectasis.[8]

CFTR modulator drugs are classified as potentiators or correctors; potentiators enhance channel opening, and correctors improve cellular processing and trafficking.[3] Clinical trials have demonstrated significant benefits of ETI in BMI, lung function, sweat chloride reduction, and decreased infections.[9,10] However, not all patients harbor mutations eligible for modulator therapy. A recent Turkish national registry study found that 57.2% of CF patients were eligible for modulators.[11]

For patients without clearly identified variants, organoid assays may help predict modulator responsiveness.[12] Unfortunately, such testing is not yet available in Türkiye. Experimental studies in mice suggest variable responses to modulators among rare mutations, with W1282X showing relatively better response than others.[13]

Premature termination codon mutations, such as W1282X, currently lack effective RNA-targeted therapies.[14] Nonsense-mediated mRNA decay (NMD) further limits the response to CFTR modulators by degrading the truncated protein. Experimental approaches have demonstrated that selective inhibition of NMD can partially restore protein function when combined with modulator therapy, offering a potential adjunctive strategy; however, due to the essential roles of NMD in normal cellular processes, precise targeting is required.[8,15]

In their experimental study, Haggie et al. demonstrated that treatment responsiveness could be achieved in W1282X variants using one corrector and two potentiators, and suggested that the currently available triple combination, containing two correctors and one potentiator, may be suboptimal in such cases.[16] In our patient, although the specific variant typically associated with responsiveness to the standard combination was not identified, a clear clinical benefit was achieved with the two-corrector/one-potentiator regimen. We believe that this response may be attributable to an unidentified second pathogenic variant. Clinical data also support modulator benefits in patients with rare or unidentified variants, even when organoid results are inconclusive.[17] Thus, clinical response remains the most reliable indicator for continuing treatment.

Conclusion

CF is a multisystem disease and genetic characterization is essential for modulator therapy eligibility, but some patients remain without identified variants. Early initiation of modulator therapy is vital for improving quality of life and preventing complications. New pathogenic variants are increasingly being recognized. In patients lacking genetic eligibility in whom organoid studies cannot be performed, assessment of short-term modulator response may provide guidance for treatment continuation based on clinical outcomes. Treatment options aimed at improving quality of life in chronic diseases should always be thoroughly evaluated, with individualized consideration given to each patient's unique circumstances.

Ethical approval

Informed consent was obtained from the legal guardian for the use of the patient's information in the publication.

Author contribution

The authors confirm contribution to the paper as follows: Case report conception anda design: MA; data collection: MA,EGO, ESKO; literature analyses: MNT, SB; draft manuscript preparation: NC. All authors reviewed the results and approved the final version of the manuscript.

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Case Report

Perianal and gluteal parasitic abscess of *Enterobius vermicularis*: case report and review of the literature

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ABSTRACT

Background. *Enterobius vermicularis* is a nematode that predominantly affects the pediatric population, particularly in families with school-aged children. While it typically causes intestinal symptoms, rare cases of extraintestinal involvement have been reported, including female genital tract involvement and complications such as appendicitis or enterocolitis. Perianal parasitic abscesses are also rare, with only a few cases reported in the literature.

Case Presentation. A 17-year-old female presented with abdominal pain during menstruation. Pelvic ultrasound revealed a septated cystic lesion located posterior to the uterus. Magnetic resonance imaging (MRI) demonstrated a perianal lesion with thick material, appearing iso- to hyperintense on both T1- and T2-weighted images. The lesion extended into the left gluteal muscles and showed peripheral contrast enhancement and diffusion restriction. Notably, there were no surrounding inflammatory changes, making an abscess diagnosis less likely. Surgical drainage revealed pus, and cytological analysis identified abundant parasitic oocytes consistent with *E. vermicularis*. The patient was treated with surgical drainage followed by pyrantel pamoate, resulting in near-complete resolution of the lesion at the one-month follow-up MRI. A literature review was also conducted to identify previously reported cases of parasitic abscesses and to explore the differential diagnoses of perianal cystic lesions.

Conclusions. Perianal abscesses due to parasitic infections are rare, particularly those caused solely by *E. vermicularis*. Given the high prevalence in childhood infestations, parasitic abscesses should be considered in the differential diagnosis of perianal collections in pediatric patients, especially in the absence of peripheral inflammatory signs.

Key words: *Enterobius vermicularis*, parasitic abscess, perianal abscess, enterobiasis, oxyuriasis, pinworm.

The perianal, retrorectal, and presacral spaces are potential sites for various lesions in pediatric patients.[1] While bacterial perianal abscesses are relatively common and often accompanied by signs of inflammation[2], parasitic abscesses are exceedingly rare.

Enterobius vermicularis is a highly host-specific nematode, primarily infecting humans, with rare exceptions. The parasite predominates in the pediatric population, particularly among members of families with school-age children.[3] While typically not associated with severe clinical manifestations, it can occasionally lead to complications such as abscess formation, ileocolitis, enterocutaneous fistula, pelvic inflammatory disease, appendicitis, tubo-ovarian abscess, and urinary tract infection.[4]

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This report describes the clinical and radiological findings of a rare case of a perianal parasitic abscess associated with *E. vermicularis* in a 17-year-old girl with no underlying risk factors.

Case Presentation

A 17-year-old girl presented to the emergency department with abdominal pain during menstruation. A cystic lesion was identified on pelvic ultrasound, prompting a referral to our hospital for further evaluation and treatment. Physical and digital rectal examinations were unremarkable, with no detectable mass. She had no fever, no significant past medical history, and her blood tests were within normal limits.

A suprapubic pelvic ultrasound revealed a septated cystic lesion measuring 7.5 x 6.5 cm, located posterior to the uterus and left ovary. The uterus and ovaries appeared normal in size and morphology. Magnetic resonance imaging (MRI) demonstrated a cystic lesion extending from the left perianal area to the left gluteal region. The lesion appeared iso- to hyperintense on T1-weighted images and hyperintense on T2-weighted images, with thick material and a lobulated contour. The gluteal extension measured approximately 8 cm in length. No edematous signal changes, effusion, or perianal fistula suggestive of inflammation were observed (Fig. 1). The lesion showed diffusion restriction and exhibited peripheral contrast enhancement (Fig. 2).

A bacterial abscess was deemed unlikely due to the absence of inflammatory features and rectal or gluteal pain. Imaging differential diagnoses included perianal developmental cysts, such as cystic teratomas and tailgut cysts, considering the patient's age. During surgery, the patient was positioned prone, and a midline posterior sagittal incision was made. Exploration revealed an abscess extending from the presacral region to the left gluteal area, approximately 8-10 cm in size, without a distinct cystic structure. Based on intraoperative findings, the lesion was considered a perianal abscess. It was drained via simple puncture, and a drain was placed to allow continuous drainage.

The abscess culture showed no bacterial growth, but cytological analysis of the drainage fluid revealed abundant parasitic oocytes consistent with *E. vermicularis*, along with inflammatory cells. The lesion was diagnosed as a parasitic abscess, and the patient received pyrantel pamoate at 11 mg/kg/day for three days. Esophagogastroscopy and colonoscopy revealed mild hyperemia and increased vascularisation of the rectosigmoid colon, with no evidence of inflammatory bowel disease. Pathologic evaluation of the endoscopic biopsies showed lymphoid hyperplasia and edema-congestion, but no eosinophilia was reported. On the one-month postoperative follow-up MRI, the gluteal component was completely drained, with a small residual perirectal component observed, which continues to be monitored following medical treatment. Written informed consent was obtained from the patient and her parents for this report and accompanying images.

Discussion

We presented a rare case of a perianal parasitic abscess extending into gluteal muscles, notable for the absence of edematous signal changes, effusion, or fistula. This perianal parasitic abscess necessitated consideration of congenital lesions in the differential diagnosis, particularly cystic teratomas and tailgut cysts. Unlike our case, most reports and reviews in the literature highlight perianal cysts misdiagnosed as abscesses, perianal fistulae, pilonidal sinuses, and ovarian tumors.[2,5,6] In our adolescent patient, cystic teratomas were prioritized in the differential as the most common presacral lesions in pediatric patients, alongside tailgut cysts, which predominantly affect young women. While these entities share overlapping clinical and radiological features, teratomas typically present earlier, during infancy or early childhood, compared to tailgut cysts.[6]

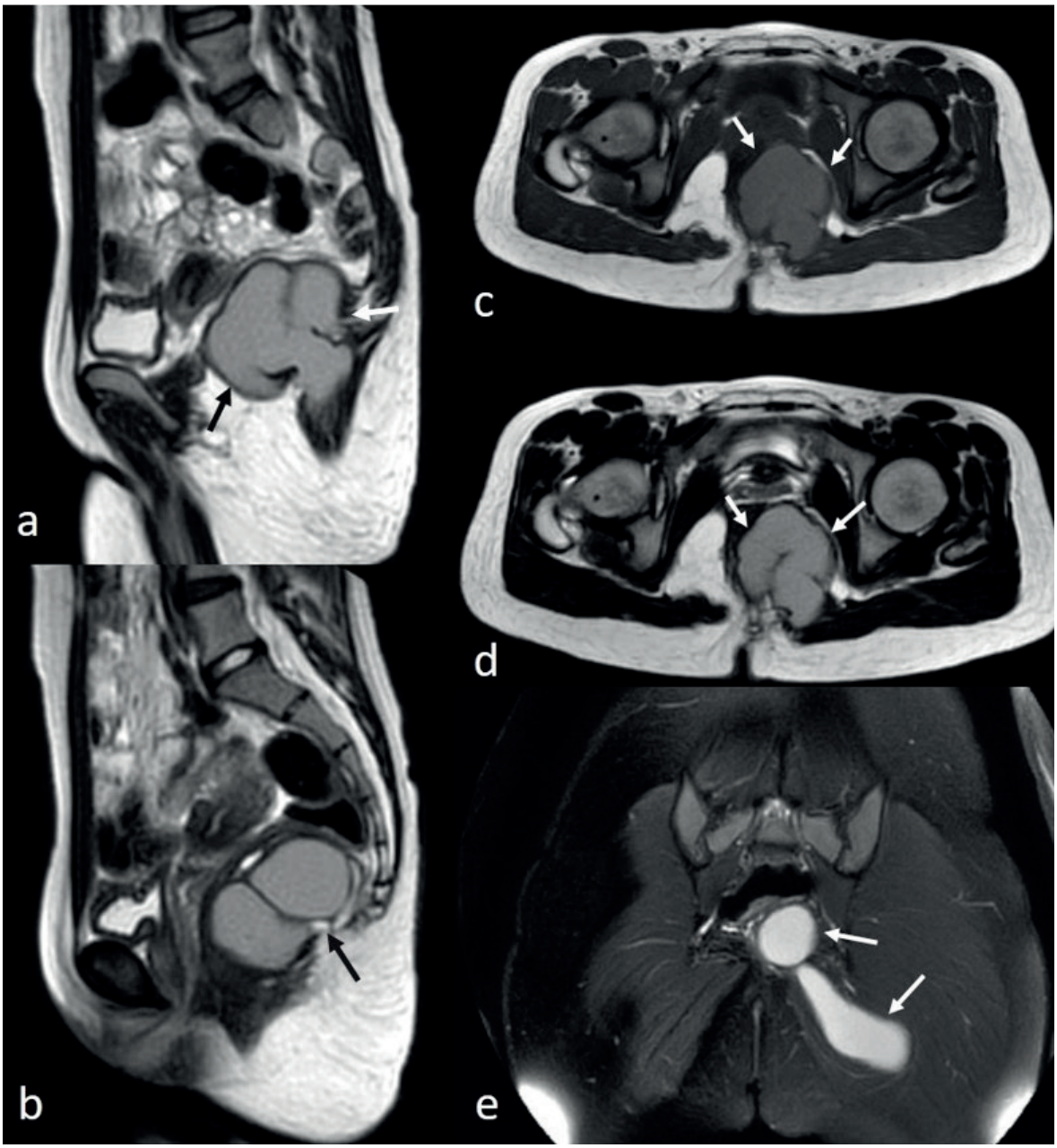

Fig. 1. T1-and T2-weighted magnetic resonance imaging of the lesion.

The sagittal T2-weighted images (a, b) reveal an iso- to hyperintense septated lesion located posterior to the rectum and anal canal, extending inferiorly to the pelvic floor. On the axial T1-weighted (c) and T2-weighted (d) images, the lesion appears iso-hyperintense with thick contents. The coronal fat-saturated T2-weighted image demonstrates extension of the lesion to the left gluteal region (e). There is no surrounding edematous signal or associated perianal fistula. Arrows indicate the lesion in all images.

Perianal cysts can become infected, often making it challenging to distinguish between a perianal abscess and an infected perianal cyst.[5,6] For example, Johnson et al. reported an adolescent female with a tailgut cyst misdiagnosed as a recurrent perianal fistula and pelvic abscess, underscoring the diagnostic difficulty. Features that should prompt consideration of a perianal cyst include a history of recurrent abscesses or multiple surgeries, the presence of a perianal

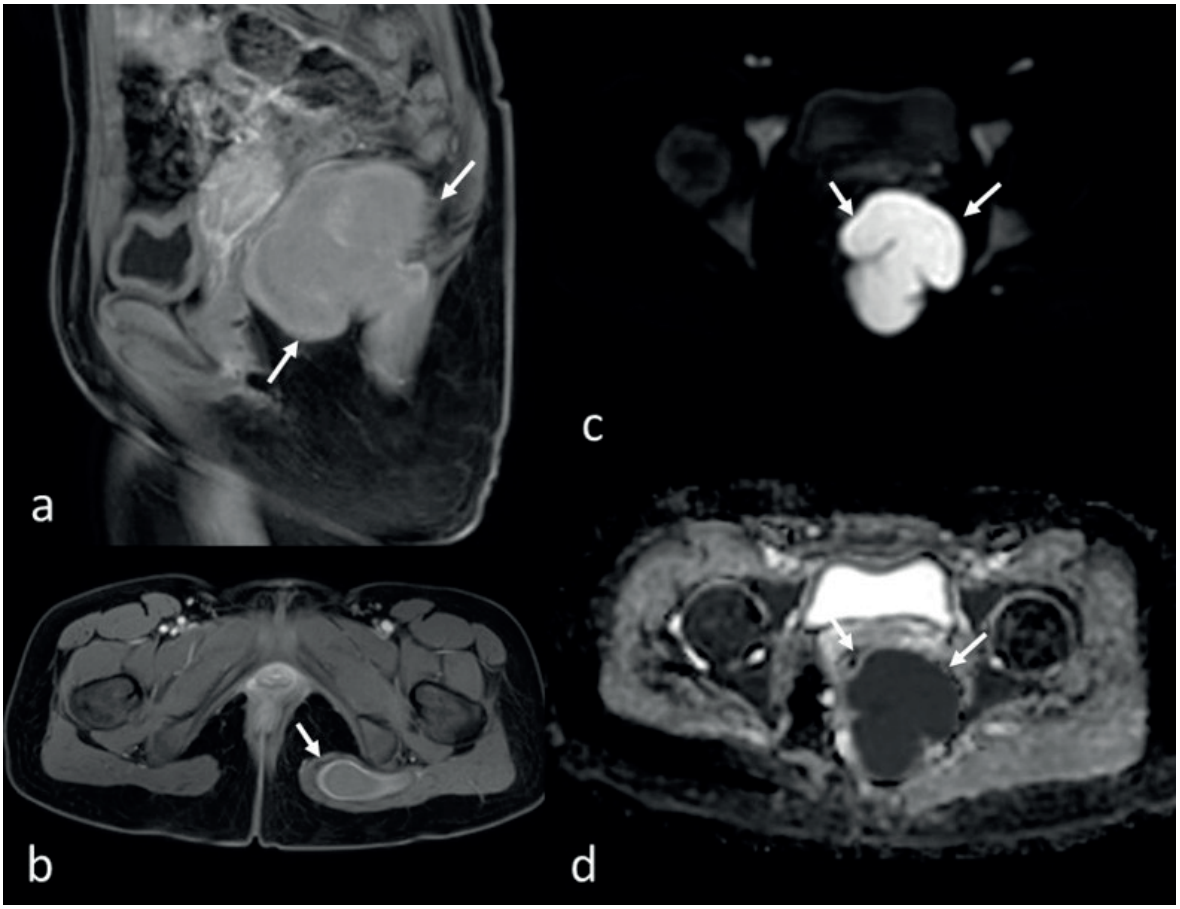

Fig. 2. Magnetic resonance imaging of the lesion (continued).

The sagittal (a) and axial (b) contrast-enhanced T1-weighted images reveal peripheral contrast enhancement in the lesion and its extended component (b) into the left gluteal area, without any solid components. The lesion shows diffusion restriction in the axial diffusion-weighted (c) and apparent diffusion coefficient (ADC) (d) images. Arrows indicate the lesion in all images.

or rectal sinus, failure to identify the infection's usual source, and the presence of a postanal dimple, which is characteristic of tailgut cysts.[6]

Uncomplicated perianal cysts typically appear on imaging as well-defined, thin-walled, uni- or multilocular lesions. In contrast, infected cysts or abscesses in the perianal space present as thick-walled lesions with irregular margins and surrounding inflammatory changes.[2,5]

Transabdominal ultrasonography is often limited in differentiating perirectal cystic masses and abscesses from ovarian cysts, especially when the lesion is large or in an atypical location. In our case, a septated cystic lesion located posterior to the uterus and left ovary was detected during a suprapubic pelvic ultrasound. However, these findings were not definitive, prompting the recommendation for further MRI evaluation.

Computed tomography (CT) and MRI are valuable in assessing the nature of perianal lesions, providing information on wall thickness, lesion contents, and their relationship to adjacent structures, such as the ureter, urinary bladder, rectum, uterus, blood vessels, and sacral bone. CT findings of uncomplicated perianal cystic lesions typically show no contrast enhancement and hypoattenuation.[2] In contrast, infected cysts or abscesses often present with thick, enhancing walls.[2,5]

MRI findings vary among perianal cysts and abscesses. Perirectal cysts are typically hypointense on T1-weighted images when purely cystic, but may show intermediate or high intensity depending on their content. Hyperintense T1 signals often result from mucoid or protein content in tailgut cysts or fatty content of teratomas/dermoid cysts, which disappear on T1-weighted fat-saturated images. The cysts are homogeneous and hyperintense on T2-weighted images.[2] Abscesses exhibit diffusion restriction on MRI, with bacterial abscesses accompanied by peri-focal inflammatory changes. Similar findings may appear in infected perianal cysts, and diffusion restriction can also occur in uncomplicated perianal cysts like epidermoid cysts.[5]

In our case, the lack of surrounding inflammatory changes made a bacterial abscess or infected perirectal mass less likely. Well-defined margins, as well as high intensity on T1-weighted images, suggested perianal cysts, such as teratomas and tailgut cysts, as potential differential diagnoses. However, diffusion restriction and thick enhancing walls, consistent with perianal abscess formation, led to diagnostic uncertainty. There was no evidence of perianal fistula. The final cytological diagnosis of parasitic abscess confirmed that the iso-hyperintense appearance on T1-weighted images was due to the thick pus content of the abscess.

Perianal bacterial abscess formation and sepsis are relatively common in pediatric patients, especially in cases of Crohn's disease, diabetes mellitus, immunodeficiency syndromes, trauma, and foreign bodies.[7] Theories on the pathophysiology of primary perianal abscess in children suggest infection of anal glands, related to the entrapment of migratory cells from the urogenital sinus or abnormally wide crypts of Morgagni.

In a perianal parasitic abscess, *E. vermicularis* may contribute through several mechanisms. Mahomed et al. emphasized that although the precise mechanism of involvement remains unclear, one possibility is that the direct migration of the threadworms through intact mucosa into the anal glands, where they cause irritation and tissue inflammation, leading to occlusion and abscess formation. Another proposed pathway is invasion through pre-existing fistulae or glandular crypts, leading to inflammation with ova in the abscess wall or parasites present in the lumen, thereby contributing to abscess formation. Abscesses may therefore arise either from occlusion of the gland or fistulae openings, or from a localized reaction to deposited ova or parasites.[7]

Perianal abscesses caused by *E. vermicularis* can be symptomatic, as described by Durgun et al., who reported a 16-year-old female patient with no medical history, presenting with a perianal abscess, swelling, chills, and anal pain.[8] Similarly, Shelat et al. described a 29-year-old male patient with a perianal abscess of *E. vermicularis* with swelling in the perianal region.[9] However, perianal nodules or granulomas associated with *E. vermicularis* are generally asymptomatic and are typically surrounded by intact perianal skin. Gupta et al. noted that eosinophilia or positive stool tests are uncommon in such cases, with ova usually found in the content of the lesion since adult worms degenerate and become undetectable.[10] In our case, the definitive diagnosis was made through cytological examination, which identified *E. vermicularis* oocytes.

Unlike the frequent occurrence of bacterial perianal abscesses, parasitic perirectal abscesses are exceedingly rare, with only a few cases reported in the literature. Sandhu et al. reported a recurrent perirectal abscess associated with *Schistosoma* in an HIV-infected adult male from an endemic area, presenting with sharp pain worsened during defecation, along with perirectal and lower sigmoid lymphadenopathies.[11] Van Horn et al. reported a recurrent perianal abscess associated with copepods (*Diacyclops thomasi*) in an adult male with Crohn disease, who presented with severe perianal pain and purulent discharge. In that case, bacterial cultures were also positive,

Table I. Summary of published case reports on perianal parasitic infections.

Authors	Age	Sex	Site	Parasite	Comorbidity
Mahomed et al.[7]	12	M	Perianal abscess	*Enterobius vermicularis*	None
	5	M	Perianal abscess	*Enterobius vermicularis*	None
Durgun et al.[8]	16	F	Perianal abscess	*Enterobius vermicularis*	None
Shelat et al.[9]	29	M	Perianal abscess	*Enterobius vermicularis*	None
Gupta et al.[10]	10	M	Perianal nodule	*Enterobius vermicularis*	None
Sandhu et al.[11]	47	M	Recurrent perianal abscess	*Schistosoma*	HIV
Van Horn et al.[12]	22	M	Perianal abscess and fistula	*Diacyclops thomasi*	Crohn
Abdalla et al.[13]	46	F	Perianal cyst	*Echinoccoccus granulosus*	None
Nasrallah et al.[14]	46	M	Perianal calcified cyst	*Echinococccus granulosus*	None

suggesting the parasitic involvement was secondary to bacterial abscess formation.[12] In contrast, our case involves a parasitic perianal abscess extending into the gluteal muscles, without any risk factors, bacterial involvement, underlying causes, or perirectal symptoms. *Echinoccoccus granulosus* can rarely present primarily in the perianal or pelvic region. Abdalla et al. reported a 46-year-old female with a painless perianal mass, diagnosed as an ischioanal fossa hydatid cyst.[13] Similarly, Nasrallah et al. described a 46-year-old male with refractory urticaria and bilateral pararectal partially calcified hydatid cysts (Table I).[14]

Perianal abscesses caused by parasitic infections, or presenting solely as parasitic abscesses, are rare. To the best of our knowledge, this is the first case report of a parasitic abscess extending into gluteal muscles associated with *E. vermicularis* in the pediatric population. As one of the most common parasitic agents causing an infestation in childhood, *E. vermicularis* should be considered as a potential cause of perirectal collections that occur without surrounding inflammatory changes. Accurate diagnosis relies on a combination of imaging and cytological examination. Optimal management requires surgical drainage complemented by targeted antiparasitic therapy, which is essential to achieve complete resolution, prevent recurrence, and avoid unnecessary interventions.

Ethical approval

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

Author contribution

The authors confirm contribution to the paper as follows: Case report conception and design: NGA, TB; literature review: TB, BAG; draft manuscript preparation: TB, NGA. All authors reviewed the results and approved the final version of the manuscript.

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Case Report

Exploring the link between adenovirus infection and Guillain-Barré syndrome in children: a case-based analysis

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ABSTRACT

Background. Adenovirus infections are commonly associated with respiratory tract infections, conjunctivitis, gastrointestinal disturbances, and in some cases, more severe illnesses such as pneumonia. Guillain-Barré syndrome (GBS), a rare autoimmune disorder that causes progressive peripheral nerve inflammation and paralysis, has been linked to various infections, including viral ones.

Case Presentation. We describe two newly diagnosed pediatric cases of GBS following adenovirus infection. Both patients were previously healthy boys, aged 3 and 6 years. Adenovirus was detected by nasopharyngeal PCR shortly preceding the neurological manifestations. Both were treated with intravenous immunoglobulin (IVIG); one also required plasma exchange and respiratory support. Both recovered fully during follow-up. Additionally, a relevant case from the literature was reviewed for comparison. Treatment included respiratory support, IVIG and plasma exchange therapy. During the 12-month follow-up no severe complications were observed in our patients.

Conclusions. In conclusion, while GBS is a well-established complication of several viral infections, including adenovirus, the association between adenovirus and GBS remains relatively underexplored. Our case reports, along with a review of the literature, highlight the rare but plausible link between adenovirus infection and the development of GBS. Although adenovirus infections are common, the occurrence of GBS following these infections appears to be uncommon, suggesting that additional factors may be at play. However, given the potential severity of GBS and the growing body of evidence, it is important for clinicians to remain vigilant for this rare complication in patients with a history of adenovirus infection.

Key words: Guillain-Barré syndrome, adenovirus, respiratory tract infection.

Adenovirus infections are commonly associated with respiratory tract infections, conjunctivitis, gastrointestinal disturbances, and in some cases, more severe illnesses such as pneumonia. Guillain-Barré syndrome (GBS), a rare autoimmune disorder that causes progressive peripheral nerve inflammation and paralysis, has been linked to various infections, including viral ones. Although the precise mechanisms are not entirely understood, there is evidence suggesting a possible association between adenovirus infection and the development of GBS. The relationship between adenovirus and GBS has been explored in a limited number of case reports and cohort studies. GBS is often triggered by viral infections, and adenovirus, as a known cause of respiratory and gastrointestinal illnesses, has been

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suggested as one of the possible viral triggers. The pathophysiology behind this connection may involve molecular mimicry, in which the immune system's response to the adenovirus infection inadvertently targets peripheral nerves, leading to autoimmune damage.[1,2] A few case studies have reported the development of GBS shortly after adenovirus infection, supporting the hypothesis that adenovirus can act as a potential trigger. For instance, a study by Loni et al.[3] described a case where a patient presented with a bulbar predominant atypical GBS variant following an adenovirus infection, although such reports remain relatively rare. Additionally, a review by Jacobs et al.[4] highlighted viral infections, including adenovirus, as potential antecedents for GBS, although they also emphasized that the exact mechanisms remain unclear.

In this study, we compiled data from our own patients diagnosed with GBS potentially associated with adenovirus infection, as well as cases reported in the literature. Our aim was to highlight the possible association between adenovirus and GBS emphasizing the need for further consideration of this relationship.

Case Presentation

Case 1

A 3-year-9-month-old male patient with no prior chronic conditions presented to our hospital on May 5, 2023, with increasing difficulty walking, weakness, and reluctance to stand. Symptoms began on April 20 with eye discharge, cough, and fever. By April 30, he exhibited back and leg pain, altered gait and difficulty walking independently. On admission, his vital signs were within normal limits. Neurological examination revealed no cranial nerve involvement. Mild weakness was present in the lower extremities with a Medical Research Council (MRC) scale of 4/5, and deep tendon reflexes were absent. No pathological reflexes were elicited. His gait was wide-based, and he exhibited difficulty maintaining balance. Cerebellar tests were normal. Superficial reflexes, including abdominal and cremasteric reflexes, were intact. No sensory level was detected. The spinal tap was traumatic, and cerebrospinal fluid (CSF) analysis revealed increased erythrocyte counts concurrent with the presence of blood and elevated levels of protein (354 mg/dL). Brain and spinal magnetic resonance imaging (MRI) were conducted, revealing no brain pathology. The spinal MRI was suboptimal due to wiggling and limited cooperation of the child. Electromyography (EMG) revealed demyelinating involvement in motor and sensory nerves, affecting both upper and lower extremities and was compatible with acute inflammatory demyelinating polyneuropathy (AIDP). GBS was considered based on the clinical and EMG findings. Adenovirus was detected in nasopharyngeal swab samples on admission. Respiratory support was not necessary during treatment. The patient received intravenous immunoglobulin (IVIG) therapy, and subsequent monitoring revealed improvement with ongoing rehabilitation.

Case 2

A 6-year-5-month-old male patient with no history of chronic illness presented with difficulty speaking, dyspnea, dysphagia, gait disturbance, and lower limb weakness in January 2022. He was referred to our center with those symptoms on the same day. Five days earlier, he had visited a local hospital for severe abdominal pain, nausea, and vomiting, diagnosed as acute gastroenteritis. On admission to our hospital, his vital signs were within normal limits. Neurological examination revealed no cranial nerve involvement, reduced muscle strength on both upper and lower extremities with a MRC scale of 3/5, and absent reflexes. No pathological reflexes were found. Abdominal and cremasteric superficial reflexes were intact and no sensory level was detected. Cerebellar

Fig. 1. Sagittal T2-weighted (A) and unenhanced T1-weighted (B) magnetic resonance images of Case 2 show no prominent abnormalities. Sagittal fat-suppressed and contrast-enhanced T1-weighted image (C) reveals thickening and enhancement in the region of the cauda (arrows).

function was assessed to be normal within the limits of the examination. CSF analysis showed an elevated level of protein (117 mg/dL). Spinal MRI showed significant contrast enhancement and thickening of the nerve roots of the cauda equina (Fig. 1 and Fig. 2).

EMG revealed a severe demyelinating involvement in motor and sensory nerves. The clinical and laboratory findings were consistent with a diagnosis of GBS. The patient received IVIG and plasma exchange therapy, further improvement noted in his neurological status. Adenovirus was detected in nasopharyngeal swab samples on admission. The patient received respiratory support for 10 days during hospitalization. After intensive treatment, including 7 days of IVIG and plasma exchange, the patient's condition improved sufficiently for discharge.

We have obtained informed consent from the patients of these patients for the publication of this case report. The summary of these two cases, along with the case of atypical GBS reported by Loni et al.[3] is presented in Table I.

Discussion

The exact mechanism by which adenovirus could trigger GBS is not well understood, but it is thought to involve a dysregulated immune response. During viral infections, the body's immune system may produce antibodies that cross-react with neuronal gangliosides, components of nerve cell membranes, resulting in demyelination and nerve damage.[2] This phenomenon, known as molecular mimicry, is a proposed mechanism for the development of GBS following infections.

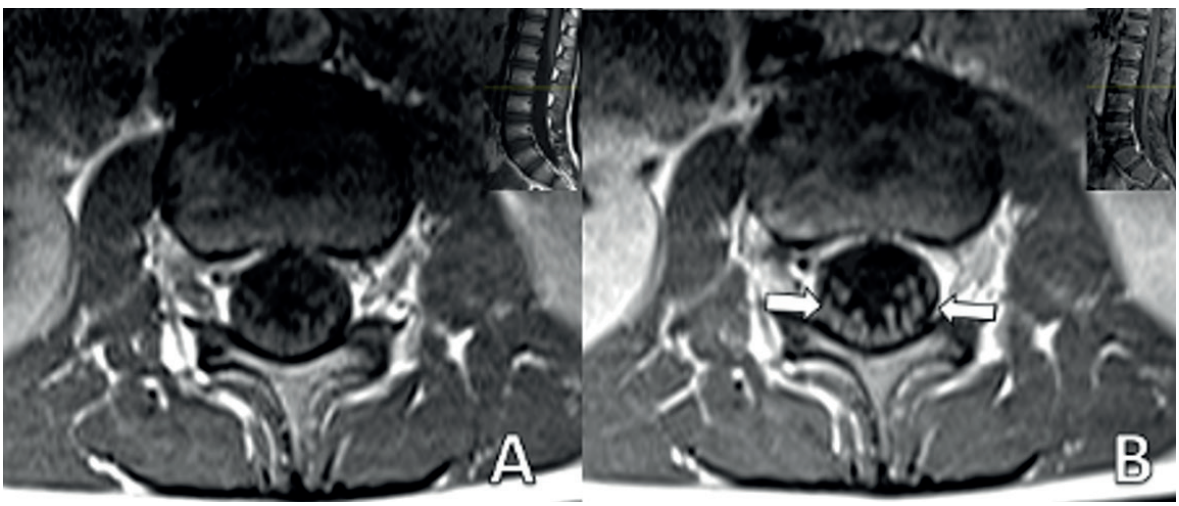

Fig. 2. Axial magnetic resonance imaging of the same patient (Case 2). There are no abnormalities observed in the unenhanced axial T1-weighted image (A). The contrast-enhanced axial T1-weighted image (B) reveals significant contrast enhancement and thickening of the nerve roots of the cauda equina (B, arrows).

Table I. The demographic and clinical data of patients with Guillain-Barré syndrome and adenovirus infection

Patient, year, age, sex	History and examination	CSF	MRI	EMG	Treatment	Outcome
Case 1 in present report, 2023, 3 yr, M	Lower limb weakness, walking difficulty, absent DTR	Glucose: 68 mg/dL, Protein: 354.5 mg/dL, Albumin: 87.6 mg/dL, Many RBC (traumatic puncture), No WBC	Brain MRI normal. Spinal MRI: Normal*	AIDP in the lower and upper extremities	IVIG at a dose of 0.4 gr/kg/d for 5 days	Recovery
Case 2 in present report, 2022, 6 yr, M	Speaking, swallowing, walking difficulties, urinary incontinence weakness, absent DTR	Glucose: 72 mg/dL, Protein: 117 mg/dL, Albumin: 60.9 mg/dL, No cells	Contrast enhancement and thickening of the nerve roots of the cauda equinaf	Severe AIDP of sensory and motor fibers	2 doses of IVIG 1 g/kg/dose, and 3 doses at of 0.4 g/kg/dose. Plasmapheresis x5.	Recovery
Report by Loni et al, 2024.[3], 6 yr, M	Swallowing and speaking difficulties, drooling, weak gag and cough reflexes, hyperreflexia without clonus, upgoing Babinski reflexes, and axial hypotonia with preserved limb tone.	Glucose: 77 mg/dL, Protein total: 14.54 mg/dL, Albumin: 95.6 mg/L, No cells	Brain MRI: Millimeter-sized nonspecific white matter lesions. Spinal MRI: Axial T1 weighted fat-saturated image with contrast shows thickened enhancing roots of cauda equina	Not performed.	MP for 3 days, followed by IVIG 2 g/kg over 48 hr in 2 divided doses.	Residual sequelae

None of the three patients had an underlying disease; *Spinal MRI evaluation was limited, as post-contrast sequences covered only the upper spinal levels (C1–T9); AIDP: Acute inflammatory demyelinating polyneuropathy, CSF: Cerebrospinal fluid, DTR: deep tendon reflexes, EMG: Electromyography, IVIG: intravenous immunoglobulin, MP: methylprednisolone, MRI: Magnetic Resonance Imaging, RBC: red blood cells, WBC: white blood cell.

Molecular mimicry refers to a phenomenon in which prior infection with microorganisms leads to the incidental sharing of identical epitopes between microbial and neural structures, thereby triggering a cellular immune response. Several microorganisms have been notably linked to GBS, including *Campylobacter jejuni*, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, Epstein-Barr virus, cytomegalovirus (CMV), varicella-zoster virus, and influenza virus. Among these, *C. jejuni* is the most frequently associated pathogen.[4] Other infections that have been associated with GBS include the Zika virus, influenza A virus, hepatitis E, hepatitis B, and human immunodeficiency virus (HIV). Despite the absence of a clear consensus, GBS has been strongly linked to severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) infection (coronavirus disease 2019, COVID-19). The precise pathophysiological mechanisms underlying COVID-19 as a potential cause of GBS remain unclear. Furthermore, adenovirus-based vaccines have been implicated in an increased risk of developing GBS.[5]

A recent systematic review reported that the incidence of GBS following COVID-19 vaccination was 8.1 cases per 1,000,000 vaccinations. The review further revealed that this increased risk was more strongly associated with adenovirus vector vaccines than with mRNA vaccines.[6] It is possible that the higher incidence of GBS in adenovirus vector-based vaccines may be related to the direct GBS-triggering properties of the adenovirus itself. However, with the current available data, this remains speculative. Nevertheless, in the current study, the possibility of an association between adenovirus and GBS in patients who had no underlying conditions and for whom no other causal factors could be identified during their illness cannot be disregarded. Adenovirus detection by nasopharyngeal PCR should be interpreted with caution, as positivity may occasionally reflect asymptomatic carriage or prolonged shedding.[7] However, in our patient, alternative causes were excluded through negative blood and CSF cultures and a comprehensive respiratory viral panel. In this context, adenovirus remains a clinically relevant finding and a plausible trigger for GBS, although causality cannot be proven solely by PCR positivity. While adenovirus infections are common, the occurrence of GBS following adenoviral infection is rare. However, the role of adenovirus as an occasional but plausible trigger for GBS warrants further investigation, particularly in specific patient populations or during outbreaks.

All patients in this case series underwent brain and spinal MRIs. Radiological studies are essential to rule out other potential causes when nerve conduction studies and CSF examinations yield inconclusive results. An MRI of the spine is particularly helpful, as it can help exclude other conditions, such as transverse myelitis and compressive causes of polyradiculopathy. If a non-contrast MRI is performed, it is important to administer contrast media if a specific diagnosis is suspected, as the non-contrast sequences are usually normal.[8] The most common site of enhancement in GBS is the anterior nerve roots, though enhancement of the posterior nerve roots can also occur.

In conclusion, while GBS is a well-established complication of several viral infections, including adenovirus, the association between adenovirus and GBS remains relatively underexplored. Our case reports, along with a review of the literature, highlight the rare but plausible link between adenovirus infection and the development of GBS. Although adenovirus infections are common, the occurrence of GBS following these infections appears to be uncommon, suggesting that additional factors may be at play. However, given the potential severity of GBS and the growing body of evidence, it is important for clinicians to remain vigilant for this rare complication in patients with a history of adenovirus infection.

The main limitation of this report is the small number of cases, which limits the generalizability of our observations. Larger case series are needed to better clarify the relationship between adenovirus infection and GBS.

Ethical approval

We have obtained informed consent from the patients for publication of the data.

Author contribution

The authors confirm contribution to the paper as follows: Data collection and clinical assessments: GT, KA, İÖ, GÇÇ; literature review: GT; analysis and interpretation of results: GT, KA, ABC; draft manuscript preparation: GT; table preparation: GT, KA; critical revisions: ABC. 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

Pediatric cervicofacial actinomycosis presenting with mandibular osteomyelitis: a diagnostic and therapeutic challenge and literature review

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ABSTRACT

Background. Actinomycotic osteomyelitis is a rare, chronic infection caused by *Actinomyces* species, anaerobic bacteria normally found in the oral flora. Mandibular involvement is uncommon and may mimic malignancies, complicating diagnosis.

Case Presentation. A 15-year-old previously healthy male presented with painful neck swelling and trismus. Examination revealed a firm mass at the angle of the mandible. Imaging suggested osteomyelitis but raised concern for malignancy. Surgical drainage was performed, and histopathology confirmed actinomycotic infection. The patient initially received empirical intravenous vancomycin, cefotaxime, and metronidazole. Due to persistent fever and elevated inflammatory markers, the regimen was switched to teicoplanin plus piperacillin/tazobactam. Therapy was subsequently escalated to meropenem due to recurrent fever and based on magnetic resonance imaging findings suggestive of osteomyelitis, then vancomycin was replaced with teicoplanin because of vancomycin-associated nephrotoxicity. Following clinical improvement, the patient was discharged on oral amoxicillin/clavulanate to complete a total of six weeks of therapy.

Discussion. Pediatric mandibular actinomycotic osteomyelitis is extremely rare. Its indolent course often mimics tumors or granulomatous disease. In this case, delayed diagnosis and nonspecific imaging findings led to initial misinterpretation. Surgical intervention played a key role in diagnosis and treatment. Early recognition and combined medical-surgical management are crucial to avoid complications. This case highlights the importance of considering infectious causes in mandibular masses and underscores the diagnostic challenges associated with them.

Key words: actinomycosis, *Actinomyces*, mandibular osteomyelitis, pediatric.

Actinomycosis is a chronic infection caused by anaerobic, Gram-positive filamentous bacteria of the genus *Actinomyces*. *Actinomyces* are normally found in the oropharynx, gastrointestinal tract, and genitourinary tract. Under certain conditions, these bacteria can become pathogenic.[1,2] Pediatric actinomycosis is rare and often presents with nonspecific symptoms that mimic other infections or tumors, complicating diagnosis. Actinomycotic infections typically involve primary soft tissues in chronic inflammatory conditions, rarely

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affecting the bones.[3] Bacterial cultures and histopathological examination are fundamental to establishing an accurate diagnosis.[4]

This case report presents a rare pediatric cervicofacial actinomycosis involving the mandible, highlighting the importance of imaging, biopsy, and multidisciplinary treatment for successful outcomes.

Case Presentation

A 15-year-old male patient with no known comorbidities presented to the clinic with progressively enlarging, painful neck swelling, difficulty opening his mouth and restricted neck movement over the past 10 days. On physical examination, hypertrophic tonsils and dental caries in the right mandibular region were noted. A firm-to-hard, diffuse erythematous swelling was observed in the paratracheal region, with restricted mobility in all directions.

Laboratory tests revealed an elevated C-reactive protein (CRP) level of 99 mg/L, erythrocyte sedimentation rate (ESR) of 38 mm/h, white blood cell (WBC) count of 8.13 $\times 10^3/\mu L$, hemoglobin level of 12.7 g/dL, absolute neutrophil count (ANC) of 5.18 $\times 10^3/\mu L$, and platelet count of 210000/μL

Ultrasound (US) examination showed thickened, inflamed subcutaneous tissue in the midline of the neck, with a 19x11 mm hypoechoic collection suggestive of phlegmon or abscess. A computed tomography (CT) scan revealed increased density and inflammatory changes extending from the anterior neck to the left mandibular region, consistent with deep neck infection. Mild density changes in the bone marrow of the left mandibular ramus raised concerns for osteomyelitis.

Empirical intravenous therapy with vancomycin, cefotaxime, and metronidazole was initiated (Fig. 1). An otolaryngology consultation resulted in the percutaneous drainage of approximately 3 mL of purulent material. On the third day of hospitalization, as the swelling and restricted mobility persisted, interventional radiology performed ultrasound-guided percutaneous drainage of the abscess.

On the fourth day, due to an inadequate clinical response, cefotaxime was discontinued and replaced with piperacillin/tazobactam, while vancomycin therapy was continued. On the seventh day, the patient developed vomiting following vancomycin administration, and an elevation in serum creatinine to 0.94 mg/dL raised concerns for vancomycin-associated nephrotoxicity. Vancomycin was replaced with teicoplanin.

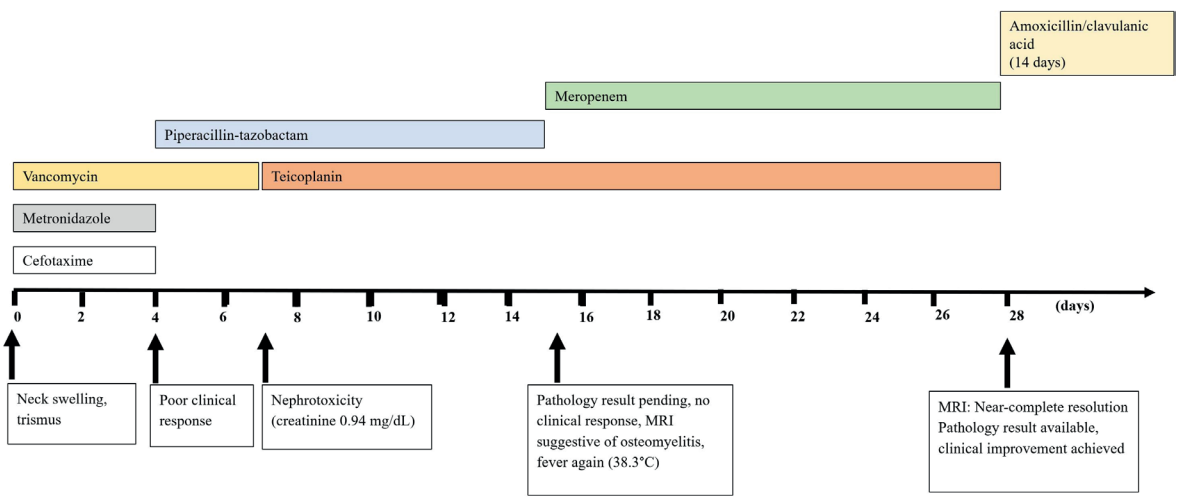

Fig. 1. Chronological summary of the clinical course and treatment.

Magnetic resonance imaging (MRI) revealed extensive anterior cervical soft tissue inflammation extending from the submental region to the thyroid level. A deep-seated lesion measuring 13×9 mm adjacent to the hyoid bone was identified, consistent with a phlegmon. Multiple enlarged cervical lymph nodes were observed. Additionally, signal alterations around the roots of the fourth and fifth mandibular molars raised suspicion for mandibular osteomyelitis (Fig. 2).

On the seventh day, cervical mobility had returned to normal. US demonstrated residual cellulitis and a 10×4 mm hypoechoic area consistent with a resolving phlegmon. On day 15, the patient developed a fever of 38.3 °C, although no new infectious focus was identified. Laboratory results were as follows: creatinine 0.76 mg/dL, CRP 7.5 mg/L, ESR 38 mm/h, procalcitonin 0.21 ng/mL, WBC $13\times10^3/\mu L$. Then, inflammatory markers worsened, with CRP increasing to 47 mg/L and WBC count rising to

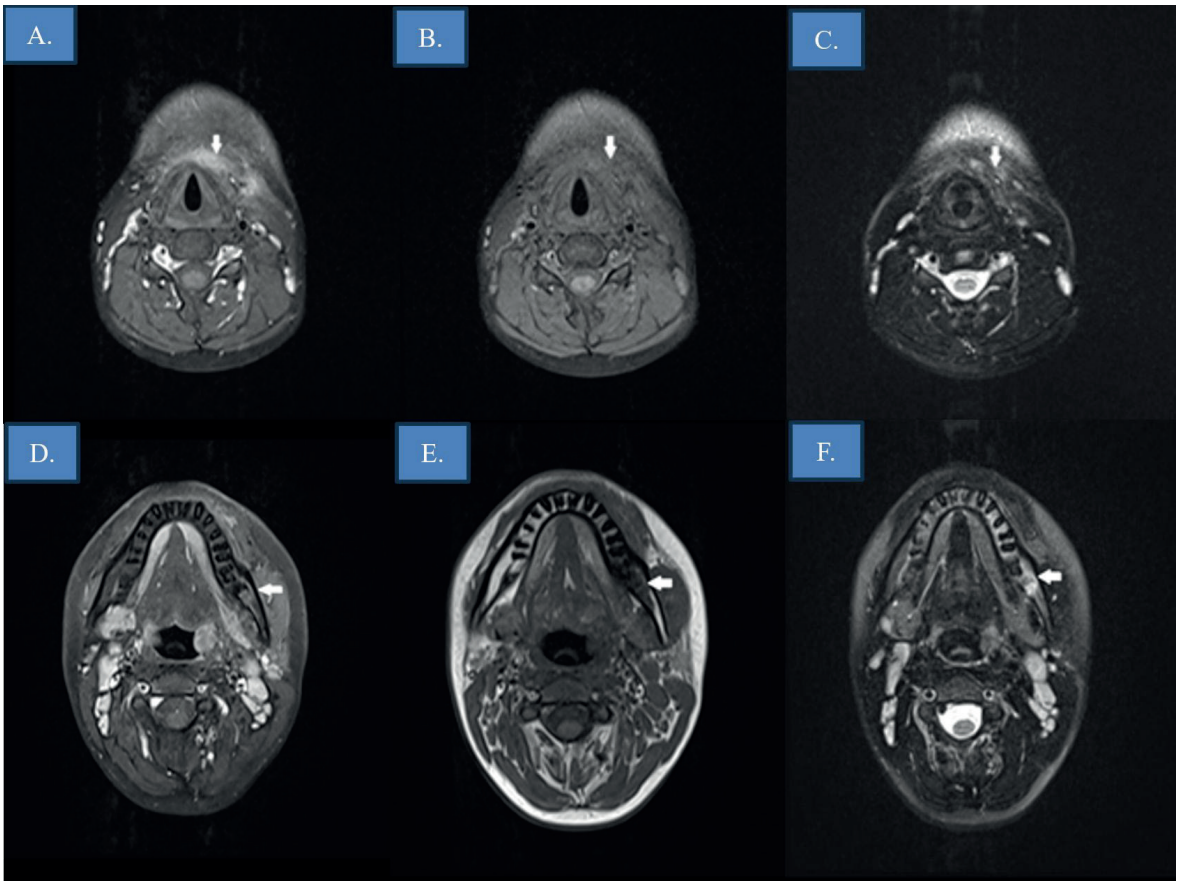

Fig. 2. Magnetic resonance imaging (MRI) showing altered signal intensity in the left mandibular ramus consistent with osteomyelitis and a 13 × 9 mm phlegmon in the anterior neck adjacent to the hyoid bone **A and B.** Axial T1-weighted fat-suppressed post-contrast images demonstrates diffuse inflammatory soft-tissue changes, consistent with phlegmon (arrows). **C.** Axial T2-weighted fat-suppressed MRI demonstrates a diffuse area of high signal intensity in the subcutaneous and deep cervical soft tissues (arrow), consistent with a phlegmon. **D.** Axial T1-weighted fat-suppressed post-contrast image demonstrates intense enhancement and marrow signal abnormality along the mandibular body (arrow), consistent with osteomyelitis. **E.** Axial T1-weighted MRI shows low signal intensity in the cortical and medullary portions of the mandibular bone (arrow), consistent with osteomyelitis. Adjacent soft-tissue inflammatory changes are also present. **F.** Axial T2-weighted fat-suppressed image shows hyperintense marrow signal and surrounding soft-tissue edema along the mandibular body (arrow), consistent with osteomyelitis.

15×10³/μL. Due to ongoing intermittent fever and the presence of suspected osteomyelitis, piperacillin/tazobactam was discontinued, and meropenem therapy was initiated.

Wound cultures showed no bacterial growth. Direct Gram staining of the drained fluid did not demonstrate identifiable organisms. Histopathological examination of the abscess material revealed abundant polymorphonuclear leukocytes and histiocytes, along with nonspecific inflammatory infiltrates and vascular proliferation. A cluster of filamentous microorganisms morphologically suggestive of *Actinomyces* species was identified, further supported by positive periodic acid–Schiff (PAS) staining (Fig. 3). Modified acid-fast staining was negative. This finding argues against *Nocardia* spp., which typically demonstrate partial acid-fast positivity due to the presence of mycolic acids in their cell walls. Therefore, the absence of acid-fast staining favored *Actinomyces* over *Nocardia* in the differential diagnosis. Blood cultures remained negative. Upon consultation with the microbiology department, it was noted that anaerobic cultures had not been performed. On day 21, follow-up ultrasonography demonstrated marked regression of the inflammatory process, with only a 9×3 mm residual hypoechoic lesion in the anterior cervical region. In light of the confirmed *Actinomyces* infection and mandibular osteomyelitis, the patient completed a total of four weeks of intravenous antibiotic therapy. Although *Actinomyces* species are highly susceptible to penicillin, de-escalation was not pursued in our patient due to the severity of infection, suspected mandibular osteomyelitis, and ongoing clinical instability at the time of histopathologic confirmation. Broad-spectrum therapy was therefore maintained to ensure adequate coverage until clinical resolution was achieved.

Follow-up MRI on day 28 demonstrated near-complete resolution of cellulitis, with no evidence of abscess formation. The patient was discharged on oral antibiotic therapy to

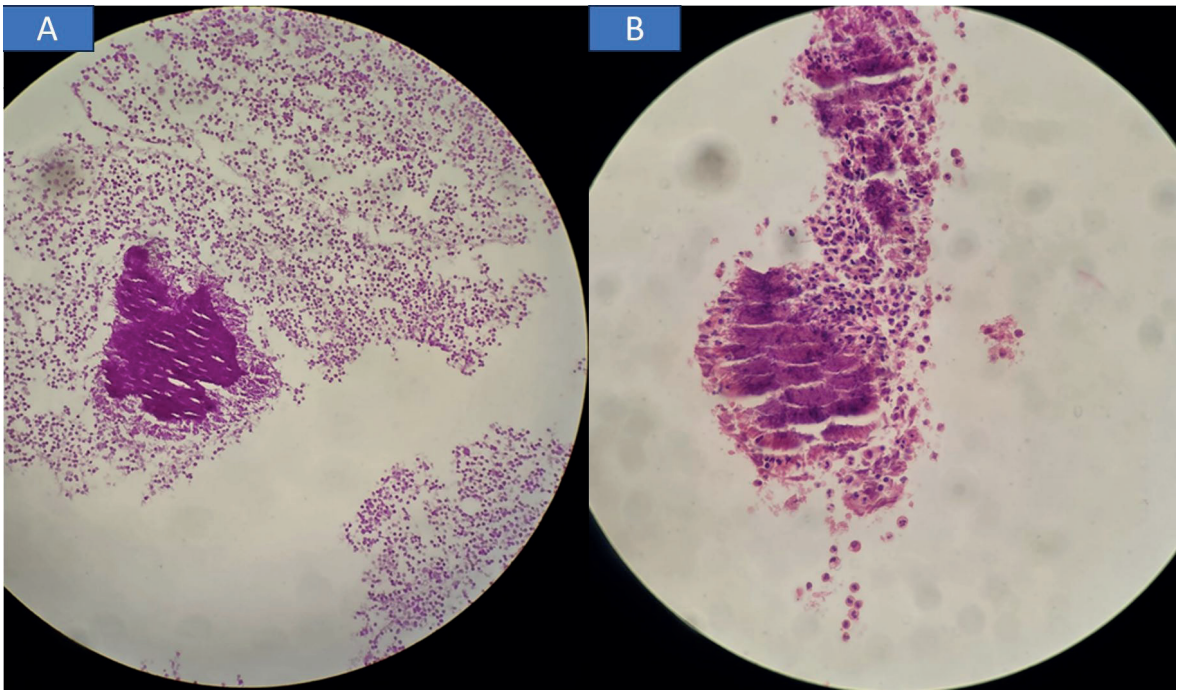

Fig. 3. Histopathological findings of the abscess material. **A.** Compact basophilic colony of filamentous microorganisms with radiating architecture, morphologically suggestive of *Actinomyces* species (H&E, original magnification x40) **B.** Filamentous bacterial colony highlighted by positive periodic acid–Schiff (PAS) staining.

complete a total of six weeks of treatment (Fig. 1). A written informed consent was obtained from the parents of the patient for this publication.

Discussion

Pediatric actinomycosis is a rare but challenging infection, often presenting as deep neck infections caused by *Actinomyces* species, Gram-positive, filamentous, anaerobic bacteria found in the oral cavity, gastrointestinal, and genitourinary tracts.[4] While these infections typically involve soft tissues with a chronic course, bone involvement is uncommon.[5] Poor oral hygiene and antecedent oropharyngeal disease increase susceptibility; in our patient, the presence of untreated dental caries likely contributed to the disruption of mucosal barriers, facilitating the invasion of *Actinomyces* and subsequent mandibular involvement.[6] A 16-year retrospective study by Chew et al. identified 14 pediatric cases, mostly cervicofacial, followed by thoracic and abdominopelvic forms.[6] The mandible's poor vascularity may contribute to its susceptibility.[7,8] A broader review of the literature reveals that pediatric cases of actinomycotic osteomyelitis are extremely rare, with only a limited number published to date.[9-20] These cases, summarized in Table I, highlight the variability in age, infection site, microbiologic findings, and management strategies and emphasize the diagnostic challenges associated with this unusual clinical entity.

This case is notable for its acute presentation, with trismus and a rapidly enlarging mass—features that mimicked malignancy. This aligns with prior studies showing that pediatric actinomycosis may resemble tumors or granulomatous diseases, leading to misdiagnosis or delayed treatment.[6] Although *Actinomyces* infections are typically chronic, they may present acutely in children, complicating diagnosis. Clinical and radiological findings are often nonspecific and may mimic malignancy or chronic infections. Chew et al.[6] similarly reported that pediatric actinomycosis can resemble neoplastic or granulomatous diseases, leading to delayed diagnosis and treatment.

Despite negative wound cultures, the diagnosis was ultimately confirmed via histopathologic analysis. This reflects existing challenges in isolating *Actinomyces* due to their slow growth and anaerobic nature.[4,7,8] Consequently, histopathology—particularly the detection of sulfur granules and filamentous Gram-positive organisms—remains a cornerstone in diagnosis. Although histopathology confirmed the presence of *Actinomyces,* anaerobic cultures were not performed in this case. This major limitation resulted in delays in both definitive diagnosis and initiation of targeted therapy, underscoring the critical role of anaerobic cultures when actinomycosis is suspected.

Surgical management of actinomycotic osteomyelitis, including curettage, sequestrectomy, and peripheral osteotomy, plays a critical role in both diagnosis and treatment.[21] Although penicillin is generally effective against *Actinomyces*, broad-spectrum antibiotics were initially preferred in our patient due to the infection's severity and poor early response. Chew et al.[6] recommend tailoring antibiotic regimens to the infection's extent, location, and course, supporting this approach.

Actinomyces species are slow-growing, with low metabolic activity, and form dense tissue abscesses and sinus tracts, which limit antibiotic penetration and delay clinical response.[2] Consequently, prolonged antibiotic therapy is required to achieve adequate tissue concentrations and prevent relapse. The standard regimen consists of high-dose intravenous penicillin G for 2–6 weeks.[1,4] This extended treatment is particularly important in cases with deep tissue or bone involvement, such as mandibular osteomyelitis. Shorter courses have been associated with higher relapse rates and suboptimal outcomes.

Although high-dose intravenous penicillin remains the standard of care, our patient received broad-spectrum antibiotics. This

Table I. Overview of pediatric osteomyelitis cases attributed to *Actinomyces*: clinical presentation, diagnosis, and management.

Author (year)	Age (yr) / sex	Location	Histopathologic diagnostic method	Culture result	Antibiotic treatment
Chew et al.[6] (2023)	9 / F	Cervical spine	Histopathologic diagnosis	Anaerobic culture negative	Ampicillin → AMC
Chew et al.[6] (2023)	9/ F	Mandible	Excision debridement	Anaerobic culture negative	AMC
Chew et al.[6] (2023)	9/ F	Mandible	Incision and drainage of the abscess	*Actinomyces israelii*	AMC and ceftriaxone
Chew et al.[6] (2023)	12/ F	Mastoid	Incision and drainage, mastoidectomy	Anaerobic culture negative	AMC
Conley et al.[14] (2022)	17 / M	Anterior skull base	Medial orbitotomy for drainage	*Actinomyces*	Clindamycin, ceftriaxone
Iwai et al.[11] (2021)	14 / F	Parotid-masseter	Histopathologic diagnosis	Anaerobic culture not reported	Ampicillin, later amoxicillin
Mou et al.[12] (2021)	5 / F	Right lower extremity	Debridement and drainage	*Actinomycetes europaeus*	Ampicillin-sulbactam
Boorman et al.[9] (2020)	7 / M	Nasofrontal region	Sequestrum, debridement	*Actinomyces funkei*	Chloramphenicol
Saarinen et al.[16] (2011)	13 / M	Mandible	Debridement	*Actinomyces*	Penicillin
Saarinen et al.[16] (2011)	11 / F	Mandible	No	*Actinomyces turicencis*	Penicillin
Saarinen et al.[16] (2011)	5 / F	Mandible	No	*Actinomyces*	Penicillin
Saarinen et al.[16] (2011)	17 / F	Mandible	No	*Actinomyces*	Amoxicillin
Catalano-pons et al.[17] (2007)	6/ F	Iliac bone	Histopathologic diagnosis	*Actinomyces israelii*	Amoxicillin
Catalano-pons et al.[17] (2007)	7/ M	Elbow and the mandible	Histopathologic diagnosis	*Actinomyces*	Metronidazole and amphotericin B, followed by amoxicillin alone
Robinson et al.[15] (2005)	4/ F	Ramus and angle of the jaw	Debridement, sequestrectomy,	*Actinomyces israelii*	Amoxicillin-clavulanate
Robinson et al.[15] (2005)	3/ M	Mandible	Sequestrectomy	*Actinomyces naeslundii*	Penicillin → clindamycin, then amoxicillin
Sobol et al.[13] (2004)	14/ F	Temporal bone	Tympanomastoidectomy	Anaerobic culture not reported	Oral penicillin
Thisted et al.[19] (1987)	3/ M	Mandible	Puncture	*Actinomyces* spp.	Ampicillin, metronidazole
Vannier et al.[20] (1986)	13/ F	Skull and atlas	Puncture, drainage	*Actinomyces israelii*	Erythromycin and metronidazole

AMC: amoxicillin / clavulanic acid, F: female, M: male.

Table I. Continued.

Author (year)	Age (yr) / sex	Location	Histopathologic diagnostic method	Culture result	Antibiotic treatment
Walker, et al.[18] (1981)	7/ M	Mandible	Curettage	*Actinomyces israelii*	Penicillin
Present case	15/ M	Mandible	Drainage	Anaerobic culture not performed, aerobic culture negative	Vancomycin, metronidazole, cefotaxime → teicoplanin, piperacillin/tazobactam → meropenem, teicoplanin → at discharge: oral AMC

AMC: amoxicillin / clavulanic acid, F: female, M: male.

decision was based on the severity of the infection, the presence of mandibular osteomyelitis, and clinical instability at the time of histopathologic confirmation. Given these factors, de-escalation to penicillin was not pursued, and therapy was maintained with broad-spectrum coverage until clinical resolution. The literature consistently supports prolonged penicillin therapy as first-line treatment; however, tailored regimens may be necessary in severe, refractory, or complicated cases.

Imaging techniques, including CT and MRI, were essential for both diagnosis and monitoring.[22] These modalities help distinguish infection from neoplasm and track disease progression. On day 28, follow-up imaging demonstrated near-complete resolution. This aligns with literature emphasizing the value of serial imaging to guide treatment duration and detect complications.[22,23]

In conclusion, this case highlights the need for a multidisciplinary approach including infectious disease specialists, radiologists, otolaryngologists, microbiologists, and pathologists. Pediatric cervicofacial actinomycosis, though rare, should be considered in persistent infections with negative cultures and osteomyelitis. Multidisciplinary care improves diagnostic accuracy and treatment outcomes.

Ethical approval

A written informed consent was obtained from the parents of the patient for this publication.

Author contribution

The authors confirm contribution to the paper as follows: Case report conception and design: SYA, ST, MD, EY, OE; literature review: SYA; draft manuscript preparation: SYA, ST, MD, EY, OE. 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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Beyond contamination rates: a broader lens on diagnosing neonatal sepsis

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To the Editor,

I read the recent interesting study published in The Turkish Journal of Pediatrics by Çalkavur et al.,[1] which addressed an important issue of blood contamination reduction in neonatal intensive care units (NICUs) using a structured interventional bundle. The study is timely and must be appreciated. As contamination directly affects the reliability of sepsis diagnosis, their efforts are highly relevant to improving overall diagnostic accuracy in practice. The observed decrease in the contamination rates demonstrates the efficacy of standardized protocols in enhancing clinical outcomes.

While the study's main focus was on reducing contamination, some additional factors may be considered in future work to further enhance the overall reliability of neonatal sepsis evaluation. Notably, risk determinants that were not within the scope of this study, such as premature rupture of membranes, maternal infection, low Apgar score, meconium-stained amniotic fluid, birth asphyxia, mechanical ventilation, and parenteral nutrition are all recognized risk determinants of neonatal sepsis and could be included in future analyses.[2]

Moreover, future studies can include multiple blood culture sites to enhance diagnostic sensitivity. As pointed out by Coggins et al.,[3] the collection of both peripheral and catheter-based blood cultures is important since the majority of infections can be missed while relying on a single location. Similarly, future studies focusing on diagnostic optimization could mention the sampling site which can greatly affect the results of cultures. For instance, umbilical cord blood cultures are more sensitive and more specific for the early detection of neonatal sepsis than are cultures using peripheral venous samples.[4,5]

Another consideration lies in the interpretation of results across different patient groups. Since pre- and post-intervention cultures were obtained from discrete cohorts of patients, so baseline differences such as bacterial colonization could have naturally varied. While this does not detract from the study's primary objective of contamination reduction, accounting for such variations in future analyses may help further clarify distinctions between true sepsis and contamination.

In conclusion, the current study provides a valuable contribution to the literature by highlighting in detail the framework of the interventional bundle used to effectively reduce contamination rates, for which the authors are to be appreciated. Building on such quality improvement initiatives, the development and implementation of standardized diagnostic frameworks will be essential for future studies related to sepsis diagnosis. This also entails the demand for a uniform definition of neonatal sepsis, consistent diagnostic parameters, and the incorporation of modern diagnostic

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instruments.[6] Moreover, the use of artificial intelligence (AI) to diagnose neonatal sepsis is also a promising way forward. Models based on AI have shown more sensitivity and specificity than conventional ones in terms of clinical assessment and thereby enable detection and treatment earlier and more accurately.[7]

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design of the LTE: MS; literature review: MS; draft manuscript preparation: MS, MB, FZ, NA. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

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Authors' reply to the letter "Beyond contamination rates: a broader lens on diagnosing neonatal sepsis"

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Dear Editor,

We are grateful for the insightful comments[1] and interest in our recently published article, "Effectiveness of a blood culture bundle in reducing contamination rates in a neonatal intensive care unit".[2] We appreciate the recognition of our study's contribution in highlighting the significance of structured interventional bundles in improving diagnostic reliability in the neonatal intensive care unit (NICU).

Sepsis risk determinants such as premature rupture of membranes, low Apgar score, and mechanical ventilation were not included in our analysis. We agree that these factors are crucial in neonatal sepsis development.[3] However, the primary objective of our study was not a comprehensive risk analysis of neonatal sepsis. Our specific focus was on improving the reliability of blood culture results through the implementation of a structured interventional bundle. We aimed to demonstrate that standardizing collection practices, rather than analyzing predisposing patient factors, is effective in reducing contamination. Also, in our NICU, the standard protocol dictates single blood culture sampling. This approach is primarily driven by local resource norms and the critical need to adhere to strict blood volume constraints in neonates, for whom even small sample volumes can be clinically significant. The decision to employ single blood culture sampling in our NICU is informed by the delicate balance between diagnostic need and patient safety, particularly concerning blood volume conservation in extremely low birth weight infants. By effectively reducing the rate of contamination, we indirectly but significantly improved the diagnostic accuracy of our cultures.

Second, a single blood culture limiting diagnostic sensitivity and the need to specify the sampling site are well taken. Our study protocol strictly followed NICU standards, which involved single-site peripheral blood sampling. While multiple-site sampling may enhance diagnostic sensitivity, our main goal was to specifically assess contamination reduction through bundle implementation related to peripheral blood cultures.[4] We confirm that blood cultures in this study were obtained exclusively from peripheral venous sites; no cord or central catheter samples were taken.

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Thirdly, we appreciate the concern that interpreting results across pre- and post-intervention groups might be affected by baseline differences. We confirm that pre- and post-intervention cultures were obtained from discrete cohorts. To robustly address potential baseline differences, we compared patient demographics and clinical characteristics between groups and found no significant differences.

Finally, we fully concur that incorporating standardized diagnostic frameworks, advanced laboratory methods, and artificial intelligence models are important future directions for improving early detection of neonatal sepsis. Our study's main objective was to demonstrate that structured bundle interventions successfully improve the reliability of blood culture collection, which remains the current gold standard for sepsis diagnosis. Our findings underscore the importance of standardization and bundle approaches for even seemingly simple routine procedures.[5] By improving the collection of blood cultures—the gold standard—our work enhances diagnostic reliability, patient safety, and positively impacts treatment costs.

We are grateful for the constructive feedback, which has been helpful in clarifying the specific focus and limitations of our work. We hope our article will continue to stimulate discussions among clinicians and researchers dedicated to improving NICU practices.

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Conflict of interest

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Perspectives on "Assessment of hormone measurement methods in girls with premature adrenarche, polycystic ovary syndrome, and non-classical congenital adrenal hyperplasia"

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We read with interest the article by Uçar et al. entitled "Assessment of hormone measurement methods in girls with premature adrenarche, polycystic ovary syndrome, and non-classical congenital adrenal hyperplasia.".[1] Their comparison of traditional immunoassays with liquid chromatography – tandem mass spectrometry (LC-MS/MS) for measuring steroid hormones in hyperandrogenic conditions highlights an important diagnostic issue. Variability in outcomes of assay measurement can not only lead to unnecessary testing but may also delay diagnosis and affect outcomes. After carefully reviewing the methodology and results of the article, we would like to emphasize some points that may help to enhance the validity of the findings.

The authors compared immunoassay and LC-MS/MS hormone values using a Wilcoxon test. However, this approach only assesses statistical variability between methods and does not evaluate their agreement among methods or interchangeability. For a correct method-comparison analysis, Bland–Altman plots or Passing–Bablok regression are recommended. As Bland-Altman analysis measures both bias and agreement limits, it provides a more comprehensive understanding of analytical consistency compared to simple significance testing.[2] Using such approaches would enhance the reliability and comparability of future results.

Another concern arises from variable androstenedione area under the curve (AUC) values for polycystic ovary syndrome (PCOS), reported in the abstract and results. This article reports androstenedione AUC as 0.949 in the abstract and 0.792 in the results section. Such variability suggests potential reporting or analytical error, producing confusion among the readers and raising concerns about data accuracy. Cross-checking data consistency across sections before publication would help in this regard. Another concern is the lack of information on standardized sampling conditions for hormone measurements; the study does not clarify whether measured factors were standardized or controlled during sample collection. Steroid hormone concentrations can vary with factors such as time of day, fasting, menstrual cycle, and pubertal stage.[3] In analytical endocrinology, such uncontrolled variability can not only imitate or exaggerate differences between assay methods but also affect diagnostic interpretation and compromise the validity of findings. Clarifying sampling procedures would therefore improve reproducibility and interpretability.

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Another relevant aspect relates to the authors' claim that electrochemiluminescence Immunoassay (ECLIA)-measured dehydroepiandrosterone sulfate (DHEAS) showed higher diagnostic performance for premature adrenarche. This overlooks the known tendency of immunoassays to overestimate DHEAS due to cross-reactivity with other sulfated steroids.[4] This means higher sensitivity might represent false positives rather than true accuracy. Future studies should confirm DHEAS results with LC-MS/MS and use method-specific reference ranges and confirmatory tests to improve diagnostic precision.

Overall, the efforts of the authors significantly contribute to pediatric endocrinology by addressing a major analytical problem. However, ensuring statistical agreement, data consistency, and control of pre-analytical variability will strengthen validity and applicability of findings to medical practice. Using robust analytical tools and LC-MS/MS confirmation would improve diagnostic reliability, prevent misinterpretation, and ensure medical decisions for diagnosis and prognosis depend on accurate and standardized hormone measurements.

Author contribution

The authors confirm contribution to the paper as follows: Designed and drafted the critique letter: RR; reviewed and revised the manuscript: RR, MR. All authors approved the final version and are responsible for its content.

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Conflict of interest

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Response to "Perspectives on 'Assessment of hormone measurement methods in girls with premature adrenarche, polycystic ovary syndrome, and non-classical congenital adrenal hyperplasia'"

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We would like to express our gratitude to the authors of the commentary for their careful evaluation of our article[1], and we would like to respond to the letter entitled "Perspectives on the Assessment of hormone measurement methods in girls with premature adrenarche, polycystic ovary syndrome, and non-classical congenital adrenal hyperplasia".[2] In this response, we endeavor to address each point raised in the letter.

Passing-Bablok regression and Bland-Altman analyses are statistical tools in method comparison studies.[3] The primary objective of our study was to evaluate the diagnostic performance of hormones measured by two different methods in clinically established diagnostic groups, rather than to assess interchangeability between the methods. The Wilcoxon signed-rank test was used to compare paired hormone measurements due to its capacity for analyzing dependent non-parametric data.[4] This evaluation facilitated the statistical analysis of measurement differences between assays, thereby providing background information for interpreting the results of the receiver operating characteristic (ROC) analysis.

We would like to express our appreciation to the authors for highlighting the discrepancy between the area under the curve (AUC) value of androstenedione for polycystic ovary syndrome (PCOS) reported in the abstract (AUC: 0.949) and the value presented in the results section (AUC: 0.792). This difference arose from an earlier version of ROC analysis, which was subsequently updated after adjustments for age and Tanner stage. The correct AUC value is 0.792, as reported in the results and depicted in Figure 2. The value in the abstract represents a typographical oversight. Therefore, we are publishing a corrigendum to correct this mistake.[5]

Pre-analytical variables are known to influence steroid hormone measurements, and the retrospective design of the study limited our ability to standardize all aspects of sample collection. However, in PCOS cases, blood sampling was consistently performed on the third day of menstruation, as outlined in the methods section. Additionally, in our center, steroid hormone analyses are routinely carried out in the early morning after an overnight fasting period of 8-10 hours. A regression analysis was specifically designed to mitigate

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variability stemming from different pubertal stages. It is clear that future prospective studies should incorporate enhanced control for these factors.

We thank the authors for highlighting the well-recognized issue of immunoassay cross-reactivity in the measurement of DHEAS. Indeed, the findings of our study demonstrated that electrochemiluminescence immunoassay (ECLIA) yielded higher dehydroepiandrosterone sulfate (DHEAS) values compared with those obtained by liquid chromatography – tandem mass spectrometry (LC-MS/MS) across all diagnostic groups. It was observed that the DHEAS levels measured by the ECLIA method exhibited a higher AUC, while maintaining a low level of specificity. As previously mentioned in the discussion, DHEAS is not a biologically active androgen, its association with clinical premature adrenarche (PA) is weak, and its diagnostic value is limited despite higher sensitivity. Consequently, this study does not provide evidence that immunoassay-based DHEAS is superior to other methods. Instead, these findings suggest that DHEAS is an unreliable marker for PA and should be interpreted with caution. Furthermore, we concur that LC-MS/MS-derived 11-ketotestosteron has the potential to serve as a promising biomarker, and we have cited this evidence accordingly in the manuscript.[1]

We extend our gratitude to the authors for their meticulous review. It is our hope that the aforementioned clarification will adequately address each point raised.

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Conflict of interest

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Corrigendum

Author Correction to: "Assessment of hormone measurement methods in girls with premature adrenarche, polycystic ovary syndrome, and non-classical congenital adrenal hyperplasia." [Turk J Pediatr 2025; 67: 692-699.]

Mert Uçar[1], Aysun Ata[2], Burcu Barutçuoğlu[3], Güneş Ak[3], Sara Habif[3], Zühal Parıldar[3], Damla Gökşen[2], Şükran Darcan[2], Samim Özen[2]

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Correction to: Turk J Pediatr 10.24953/turkjpediatr.2025.5939 (published October 20, 2025).

In the abstract of the paper "Uçar M, Ata A, Barutçuoğlu B, et al. Assessment of hormone measurement methods in girls with premature adrenarche, polycystic ovary syndrome, and non-classical congenital adrenal hyperplasia. Turk J Pediatr 2025; 67: 692-699. https://doi.org/10.24953/turkjpediatr.2025.5939", the area under curve (AUC) value of androstenedione in the receiver operating characteristic (ROC) analysis performed in cases with polycystic ovary syndrome (PCOS) was inadvertently reported as 0.949 instead of the correct value of 0.792. The authors apologize for any inconvenience and confusion caused by this typographical error.

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Corrigendum

Author Correction to: "Turkish pediatricians' knowledge, attitudes, and awareness of respiratory syncytial virus (RSV) infection and immunization strategies: a cross-sectional study." [Turk J Pediatr 2025; 67: 153-161.]

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Correction to: Turk J Pediatr 10.24953/turkjpediatr.2025.5528 (published May 2, 2025).

In the article entitled "Turkish pediatricians' knowledge, attitudes, and awareness of respiratory syncytial virus (RSV) infection and immunization strategies: a cross-sectional study" published in the Turkish Journal of Pediatrics. 2025; 67(2): 153-161, an affiliation of Osman Yeşilbaş was incomplete.

In the published version, Osman Yeşilbaş was listed as:

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CASE REPORTS

LETTERS TO THE EDITOR

CORRIGENDA

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