

# 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.<sup>1,2</sup> It was first described by Gieldon et al. in 1972, as subacute and chronic 'symmetrical' osteomyelitis.<sup>3,4</sup> 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.<sup>3,5</sup> Although it has been classified in various ways over time, the term CNO is now widely used according to the most recent nomenclature.<sup>6-8</sup>

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.<sup>9</sup> Although the precise etiology remains unknown, accumulating evidence supports the central role of innate immune dysregulation and cytokine imbalance in disease pathogenesis.<sup>1</sup> 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.<sup>10-12</sup>

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.<sup>7,13-15</sup> 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.<sup>16</sup>

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.<sup>14,17</sup> The female

predominance observed in CNO contrasts with infectious osteomyelitis, which is more frequent in males.<sup>15,17-21</sup> 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%).<sup>22-24</sup>

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).<sup>8</sup>

## 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)-1 $\beta$ , IL-6, and Tumor necrosis factor alpha (TNF- $\alpha$ ), accompanied by a relative deficiency of IL-10.<sup>25,26</sup> This imbalance promotes recruitment of monocytes and neutrophils to the bone marrow, resulting in sterile inflammation and increased osteoclast activity.<sup>8</sup>

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.<sup>27</sup> Among the key mechanisms implicated, the receptor activator of nuclear factor- $\kappa$ B (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.<sup>25</sup> This was demonstrated in an adult CNO study, supporting the role of osteoclast dysregulation in disease pathogenesis.<sup>1,28</sup>

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.<sup>1,29,30</sup> 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.<sup>8</sup>

### 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).<sup>1,29</sup> 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- $\alpha$  blockade rather than conventional anti-inflammatory regimens.<sup>29</sup>

### 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.<sup>15</sup> 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.<sup>31,32</sup> 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.<sup>18</sup> 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.<sup>29,33</sup>

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.<sup>14,34</sup> 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.<sup>35</sup> 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.<sup>27,32</sup> 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.<sup>36</sup> Nearly 85% of cases present

with multifocal lesions, and the involvement is symmetrical in 25–40% of patients.<sup>37</sup> 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.<sup>11,35,38</sup> Pelvic lesions may occasionally present as unilateral sacroiliitis, while the small bones of the hands and feet are affected less commonly.<sup>32,39</sup>

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).<sup>6,16,34</sup>

#### *Extraosseous manifestations and associated inflammatory conditions*

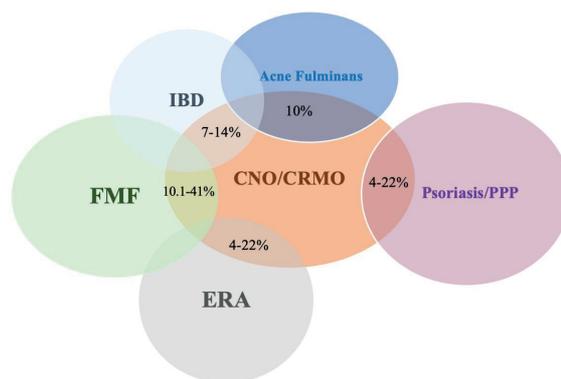
CNO can occur in association with other inflammatory conditions, and a positive family history of inflammatory or autoinflammatory diseases is common. Studies have shown that approximately 20% of patients have concomitant chronic inflammatory disorders such as JIA, spondyloarthropathies, inflammatory bowel disease (IBD), pyoderma gangrenosum, familial Mediterranean fever (FMF), and SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis).<sup>1,16</sup> 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).<sup>1,16,40-42</sup> The overlap between CNO and SAPHO syndrome has prompted some authors to suggest that CNO may represent a pediatric counterpart of SAPHO.<sup>30</sup> 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.<sup>17,41,43</sup>

#### **Laboratory and Histopathological Findings**

Routine laboratory tests usually provide non-specific findings, yet they remain essential for excluding alternative or secondary causes.<sup>29</sup> 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<sup>35</sup> (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.<sup>32</sup> 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, localization at skull and diaphysis periosteal elevation with subperiosteal hemorrhage	Malignancy, bacterial osteomyelitis, scurvy
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.

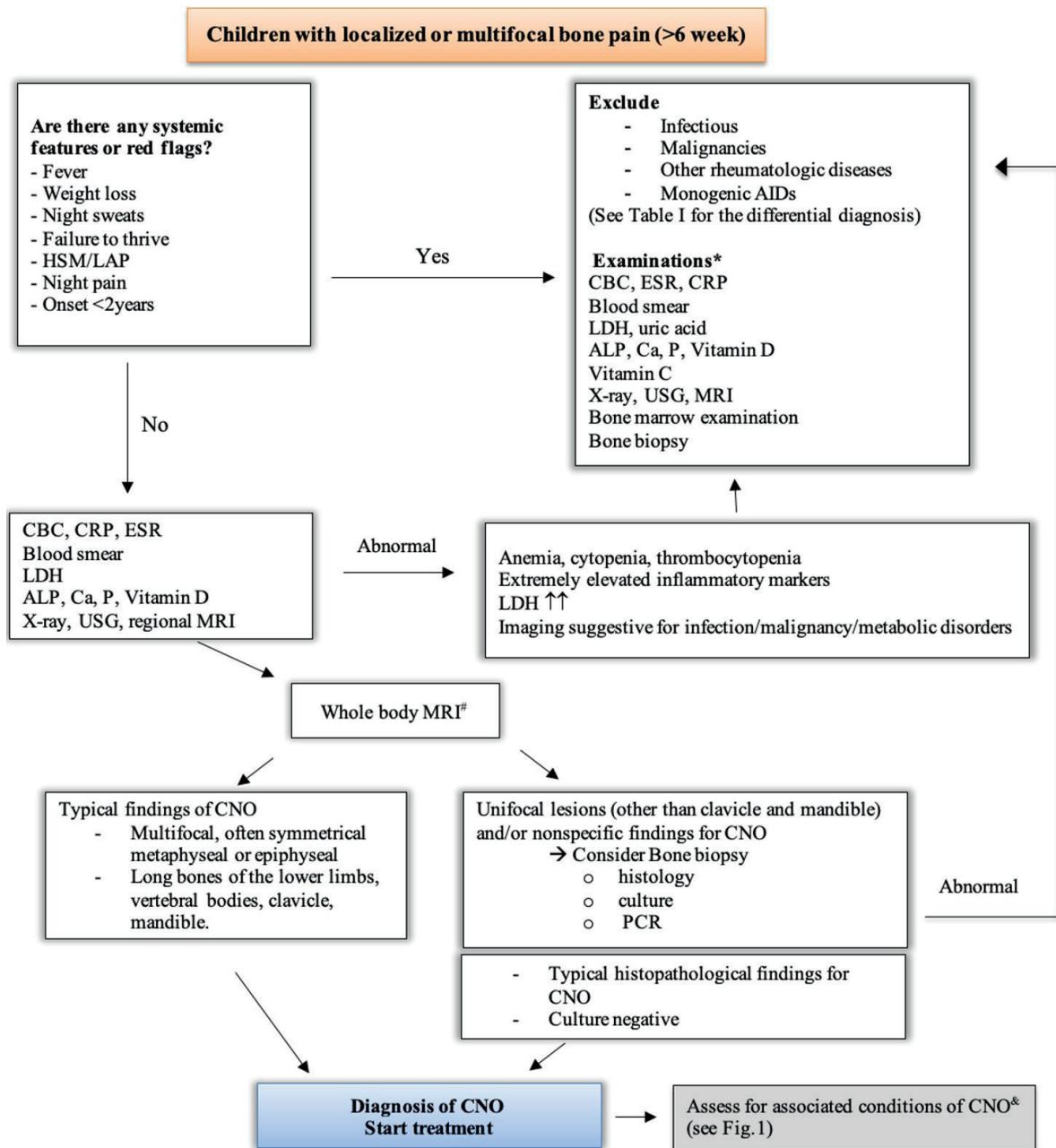
AIDs: autoinflammatory diseases, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, HSM: hepatosplenomegaly, LAP: lymphadenopathy, LDH: Lactate dehydrogenase, NSAIDs: nonsteroidal anti-inflammatory drugs

49% and 80%. Markedly increased values (for example, threefold above the upper limit of normal) should raise suspicion for other underlying conditions.<sup>29,44</sup> Autoantibodies, including antinuclear antibodies (ANA) and HLA-B27, may rarely be detected in some individuals, but these lack diagnostic specificity.<sup>16-18,29,37,45-47</sup> 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.<sup>43</sup>

Recent investigations have identified elevated levels of several cytokines and chemokines in CNO, such as TNF- $\alpha$ , IL-6, IL-12, monocyte chemoattractant protein-1 (MCP-1), C-C motif ligand 11 (CCL11), CCL5, collagen 1 $\alpha$ , and the soluble IL-2 receptor (sIL-2R).<sup>37,48,49</sup> 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.<sup>43</sup> 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.<sup>50</sup>

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.<sup>1,35,51</sup> 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.<sup>27</sup> 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.<sup>10,13,35,52,53</sup>



**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.<sup>11,54</sup> 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.<sup>33</sup>

### *Lesion characteristics in imaging*

#### *Radiographs and CT*

Radiographs and CT reveal round or ovoid osteolytic bone lesions centered at physal 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.<sup>11,33</sup>

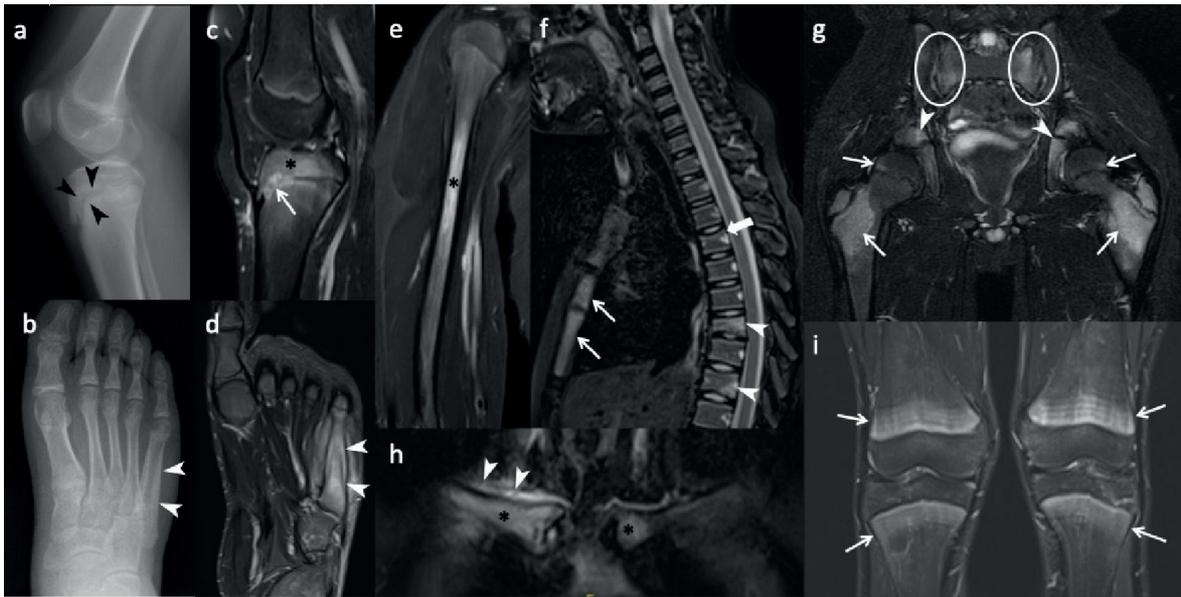
In addition to the initial work-up, radiographs are essential for follow-up of complications. Due to physitis, early physal closure may occur through the formation of a physal bridge or bar. Radiographs can demonstrate the characteristic "physal tongue," which appears as a lytic or sclerotic tubular 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.<sup>39</sup>

#### *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).<sup>54</sup> 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).<sup>11,54</sup> 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).<sup>39</sup> 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.<sup>39,55</sup> 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).<sup>33</sup>

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 physal 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.

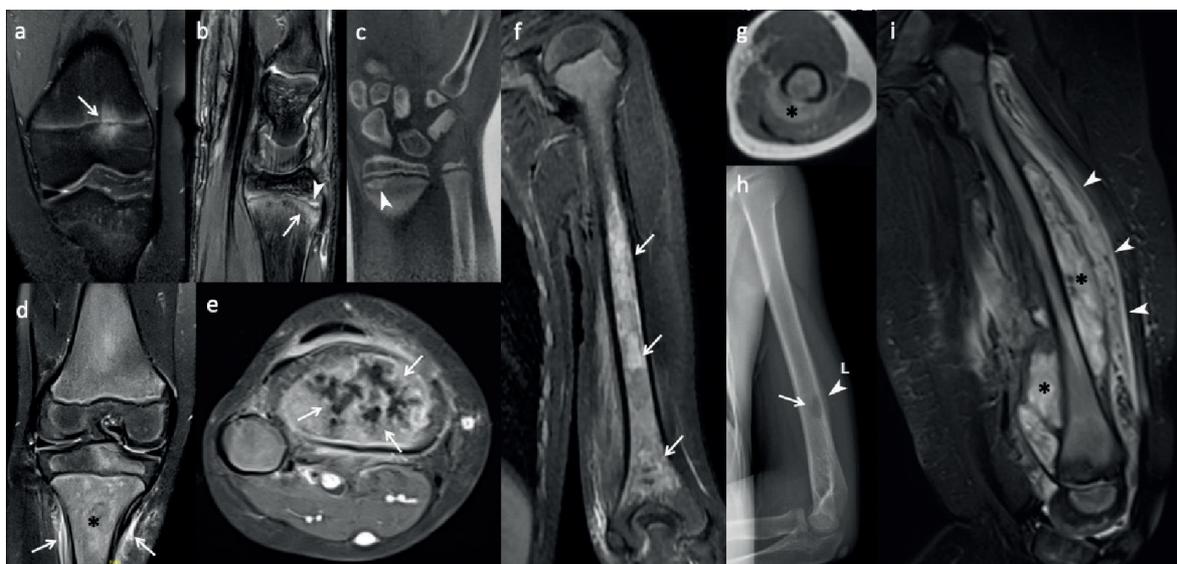
bisphosphonate treatment is the presence of bilateral symmetric bright metaphyseal bands on STIR. These high-signal bands can mimic disease relapse, and their abrupt demarcation in relation to the adjacent metadiaphysis can be a key feature for differentiating them from true osteitis (Fig. 3i).<sup>54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

### *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 physal closure period (Fig. 4a). Bone contusions, physal 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 physal enlargement of the distal radius at the dorsal side which is surrounded by osteitis consistent with physal 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).<sup>33,54</sup>

### 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.<sup>3</sup> 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.<sup>13</sup> 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.<sup>10,37</sup> 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.<sup>11,13</sup> 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).<sup>56</sup> 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.<sup>11,57</sup> 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.<sup>57</sup> 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.<sup>57</sup>

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.<sup>1,30</sup> 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.<sup>29,51</sup>

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.<sup>56</sup>**Step 1, Verify entry criteria (all should be present):**

1. Bone pain and/or musculoskeletal functional limitation  $\geq 6$  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<sup>3</sup>;
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  $\geq 55$  is required to classify a patient as CNO.

Criteria domains / levels	Score
Bone biopsy	
Signs of inflammation <sup>†</sup> 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	
$\geq 3$ 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 $\geq 2$ 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  $\geq 700$  IU or > 2 times of the upper normal limit may be considered pathological.

<sup>†</sup>Defined as the presence of immune cells including neutrophils, monocytes, lymphocytes and/or plasma cells.

<sup>‡</sup>Axial arthritis is defined as imaging confirmation of inflammation within the sacroiliac joint or intervertebral joint.

<sup>§</sup>Cutaneous conditions include psoriasis, palmoplantar pustulosis, pyoderma gangrenosum, acne fulminans, and hidradenitis suppurativa.

**Table II.** Continued.<sup>56</sup>

Criteria domains / levels	Score
Coexisting conditions prior to the diagnosis of CNO	
Inflammatory bowel disease (IBD)	9
Cutaneous condition <sup>§</sup> without IBD	8
Axial arthritis <sup>¶</sup> 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-arthritis 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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\*\*\*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.

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

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.<sup>51</sup>

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.<sup>25,29,50,58,59</sup> 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.<sup>51</sup>

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.<sup>60,61</sup> The limited efficacy observed may be attributed to pathophysiological heterogeneity and tissue-level differences in therapeutic response.<sup>1,30</sup>

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.<sup>30</sup> 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.<sup>11,62,63</sup> Nevertheless, further studies are required to establish their safety profile and clinical efficacy in this population.<sup>11</sup>

### 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.<sup>17,18,43</sup>

In a cohort of 178 patients followed for an average of four years, 57% remained non-remissive, and 26% developed permanent sequelae.<sup>17</sup> 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.<sup>7,18,43,51,53</sup>

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.<sup>35,52</sup>

### 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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