J BONE ONCOL 52 (2025) 100672

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

Research Paper

Pain in patients with multiple inherited osteochondromas: Incidence and potential prognostic factors. A retrospective cohort study

Morena Tremosini [a], Mattia Morri [a,*], Cristiana Forni [a], Elena Pedrini [b], Marina Mordenti [b], Maria Gnoli [b], Alessia Di Cecco [a], Alice Moroni [b], Luca Sangiorgi [b]

[a] Servizio di Assistenza Infermieristica Tecnica e Riabilitativa, IRCCS Istituto Ortopedico Rizzoli, 40136 Bologna, Italy
[b] Struttura Complessa Malattie Rare Scheletriche, IRCCS Istituto Ortopedico Rizzoli, 40136 Bologna, Italy

HIGHLIGHTS

- In 25 % of cases with inherited osteochondromas, pain is reported as moderate/severe.
- An increase in age is associated with a worsening of pain.
- Appropriate and specific pain therapy pathways must be implemented.
- Educational pathways for monitoring of pain symptoms must be encouraged.
- There is a lack of association between disease phenotype and pain score.

ARTICLE INFO

Keywords:
Pain
Multiple osteochondromas
Prognostic factors
Rare bone disease

ABSTRACT

Purpose: the purpose of this study was to describe the baseline characteristics, presenting phenotype and treatment interventions for patients diagnosed with multiple osteochondromas who presented with severe pain symptoms.
Methods: a retrospective single-centre cohort study was conducted at a Rare Skeletal Disorders Department. Pain symptomatology was measured at the first visit, pain level was reported, varying from 0, absence of pain to 10, maximum pain. Baseline characteristics, pathology phenotype using IOR classification and treatments performed/ongoing as medical, surgical and conservative therapies were collected.
Results: a total of 152 patients were enrolled, with a median pain score of 0 and the 25th and 75th percentiles of 0 and 4, respectively. A percentage of 25.7 % (95 % CI of 19.3–33.3) presented at the first visit with moderate/severe pain. Multiple logistic regression confirmed that age was the only factor to be significantly associated with moderate/severe pain and IOR classification was not able to provide a description of the pathology that was associated with a major pain score.
Conclusion: from the early stages of multiple osteochondromas diagnosis, pain symptoms must be carefully assessed. An increase in age is associated with a worsening of pain; IOR classification of the multiple osteochondromas phenotype does not currently allow an association between the various classes and pain. A re-evaluation of the classification in this light could be an important new element for clinical practice.

1. Introduction

Hereditary Multiple Osteochondromas (MO) is a condition characterised by the formation of osteochondromas, i.e. benign bone tumours covered by a cartilaginous cap, in the vicinity of two or more long bones of the skeleton as a result of genetic mutations in the *EXT1* and *EXT2* genes [1–3]. In patients affected by this condition, there is a dysregulation of the enchondral ossification process in the metaphyseal region of long bones. This alteration, during childhood and adolescence, results in abnormal bone growth. The prevalence of MOs is estimated to be approximately 1:50000; despite its rarity, it is one of the most common disorders affecting the musculoskeletal system [4–6]. The number and size of osteochondromas (OCs), which usually stop growing after puberty, can vary significantly from person to person [7,8]. The clinical

* Corresponding author.
E-mail address: mattia.morri@ior.it (M. Morri).

https://doi.org/10.1016/j.jbo.2025.100672
Received 4 February 2025; Received in revised form 7 March 2025; Accepted 10 March 2025
Available online 18 March 2025

problems and potential complications related to MO are manifold, such as skeletal deformities, reduced growth in stature, compression of neurovascular structures, limitations in daily life and quality of life [9,10], and even the potential malignant transformation of OCs into secondary peripheral chondrosarcoma, an event that occurs in about 5 % of cases. The clinical classification of this pathology and its evolution represent a challenge and imaging, such as MRI and X-rays, are not sufficient to capture its possible evolution and implications for patients' health [11,12]. Mordenti et al [8], describing the natural history of the pathology, showed the appearance of a new osteochondroma in 80.4 per cent of the cases, a new musculoskeletal deformity in 57.6 per cent, and a new joint functional limitation in 23.4 per cent. Overall, they reported pathology progression in 46.2 % of the patients over a mean observation period of 55.8 months. This description did not include pain symptoms and their progression. Pain is the most common indication for surgical treatment and the symptom most frequently reported by patients; Boarini et al. [13] reported it in 78.8 % of patients. Goud et al. [14] also pointed out that pain has an important influence on activities of daily living and on the social and psychological well-being of these patients.

Darilek et al. [15] pointed out that moderate to severe pain was reported in 46 % of a population diagnosed with MO. This condition significantly interfered with daily activities, sleep, social life and mood in over 40 % of cases. The authors recognised complications related to MO and previous surgical interventions as two independent risk factors for pain. Awareness of pain in the early phase of the disease therefore becomes a central element of the treatment and prevention pathway for these patients, precisely in order to avoid chronic pain and limits its effects on quality of life.

Amajjar et al. [16] reported an average pain score of 3.2 on the Visual Analogue Scale (VAS) in an adult MO population, with significant differences between males and females. They also underlined the need for new studies focusing on the relationships between genotype, phenotype and clinical outcomes. The Rizzoli Multiple Osteochondromas Classification (RMOC), revised in 2021, allows precisely to describe the phenotype of individuals subject to MO. It distinguishes 3 classes based on the presence or absence of skeletal deformities and functional limitations. Each group is further divided into 2 subclasses based on the number of OCs, deformities functional limitations [17].

The aim of the present study was to describe patients experiencing moderate to severe pain symptoms at the beginning of their diagnosis and treatment pathway for MO at the Rizzoli Orthopaedic Institute (IOR). The study examined their baseline characteristics, the presenting phenotype of the pathology and the treatment interventions implemented (medical, surgical and conservative therapies).

2. Materials and methods

A retrospective single-centre cohort study was conducted at the Department of Rare Skeletal Disorders (Centro Malattie Rare Scheletriche, Ce.Ma.R.S.) of the Rizzoli Orthopaedic Institute (IOR). This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Area Vasta Emilia Centro with Protocol No. 800/2022/Oss/IOR evaluated on 15/11/2022. Due to the nature of the study, the collection of informed consent was exempted for the study.

Eligible patients were found through the IOR Registry of Multiple Osteochodromas (REM, cinicaltrails.gov NCT04133285) in which the patients of the Ce.Ma.R.S. outpatient clinic for whom the diagnosis of MO is confirmed are entered. Regarding access criteria, the Ce.Ma.R.S. outpatient clinic is accessed by persons with a suspected diagnosis of MO by referral from other doctors such as the general practitioners, community paediatricians, other healthcare centres, or through patient associations. The purpose of the first visit is to initiate care, involving the nursing and medical team (geneticists and orthopaedists), with an in-depth diagnostic examination and assessment of the care plan. The diagnosis of the pathology is mainly based on the clinical assessment and available diagnostic tests. In the absence of a molecular diagnosis, the patient with clinical suspicion of MO is offered a genetic test for the *EXT1* and *EXT2* genes to be performed on DNA extracted from peripheral blood or saliva with the aim of identifying the genetic variant responsible for the disease. The present study considered patients in the REM registry over a 5-year time frame from January 2017 to June 2022. No age or sex-related limitations or other reasons for exclusion from the study were identified in the observed cohort of patients.

2.1. Primary outcome

Pain symptomatology was measured at the first visit using different assessment instruments depending on the age of the patient: the FLACC scale in children 0–3 years, the VRS scale in children 3–6 years and the NRS scale for children and persons 7 years and older. For each person a pain level was reported, varying from 0, absence of pain to 10, maximum pain. Based on the score, two comparison groups were constructed, the group with no or mild pain with a scale score of 0 to 3 and a second group with moderate to severe pain with a pain score equal to or above 4.

Finally, for each pain greater than 3, a distinction was made as to whether it was a pain attributable to the site of one or more OCs present, a deformity or functional limitation associated with the pathology, or a generalised pain or pain in another site not directly related to the location of the OC.

2.2. Variables

During the first visit, a set of clinical data from the patients were collected and reported in the medical and nursing records according to a standardised procedure, covering the person's baseline characteristics, the phenotype of the pathology and any treatments performed or in progress.

Baseline patient characteristics included age, gender and body max index (BMI). As well as being reported in a timely manner, age allowed patients to be divided into four groups: pre-school children aged 2 to 5 years, school-age children aged 6 to 12 years, adolescents aged 13 to 17 years and finally young adults and adults over 18 years.

The appearance of the disease phenotype was described by collecting the following data: the number of skeletal sites with OCs involved, the presence and location of skeletal deformities and functional limitations indicating the involvement of the limbs (upper, lower) and possibly the trunk. These characteristics were ascertained during the first clinical examination performed by the doctor and by viewing the available instrumental examinations such as X-rays, MRIs, CT scans and ultrasounds. Based on the number of skeletal sites involved, three groups were distinguished: up to five sites involved, between six and ten sites, and more than ten. Based on the data collected, the disease phenotype was classified according to the revised IOR classification with the distinction into 3 classes (I, II, III) and 2 subclasses (A and B) (Table 1.) [17].

Finally, to gain an overview of the patients' existing treatment, the

Table 1
Rizzoli multiple osteochondromas classification revised.

Criteria	Class	Subclass	
No deformities – no functional limitations	I	IA	<=5 sites with OC
		IB	>5 sites with OC
Deformities – no functional limitations	II	IIA	<=2 sites with deformities
		IIB	>2 sites with deformities
Deformites – functional limitations	III	IIIA	1 site with functional limitation
		IIIB	>1 site with functional limitation

current analgesic therapy, previous surgical therapy in a site related to the presence of an OC or in another unrelated site, and current conservative therapy such as physiotherapy and any orthoses used were recorded.

2.3. Data collection

Patient data were extracted from medical and nursing records and the REM Registry, then entered into a dedicated Case Report Form. The same data were then transferred to a pseudo-anonymised electronic database for statistical analysis. The research nurse of the rare disease genetics outpatient clinic was responsible for data collection and management.

2.4. Statistical analysis

The description of the pain was done by using the absolute frequency and percentage reported for the group with no/light pain and the group with moderate/severe pain, respectively. The point score of the pain was also reported using the mean and standard deviation or if necessary, the median and relevant percentiles. Similarly, the mean and standard deviation or median and percentiles (or interquartile range) along with absolute frequency and percentage were used, in accordance with the nature of the variables collected: continuous, dichotomous and categorical variables. The values of interest were reported in relation to the overall enrolled population, the group with no/light pain and the group with moderate/severe pain. In the descriptive analysis, a further analysis of the pain symptomatology was also performed in accordance with the 4 age groups (2–5 years, 6–12 years, 13–17 years and greater than 18 years) and in accordance with the 6 subclasses defined by the IOR classification of the MO.

In order to be able to investigate the association between pain symptoms (absent/light vs moderate/severe), used as the outcome of the model, and the 3 groups of collected variables related respectively to the baseline characteristics, to the phenotype of the disease and to the treatments carried out/ongoing, 3 different multiple logistic regression analyses were carried out, one for each group of variables considered. Where necessary, baseline characteristics of the sample could also be used as correction factors for the other logistic regressions performed: the association between phenotype and pain and between treatments performed/ongoing and pain. In all analyses performed, a significance threshold for p-Value of 0.05 was accepted. Statistical analysis was conducted with the statistical software StataMP v.18 [18].

2.5. Sample size

Given the rarity of the disease, it was planned to collect a sample consisting of all patients attending the Ce.Ma.R.S. outpatient clinic with a diagnosis of MO. Assuming a convenience sample of 150 patients, considering an incidence of patients with moderate/severe pain of 46 % equivalent to 69 events, it was possible to estimate the incidence of the primary outcome with a 95 % confidence interval of 16.5 percentage points. According to the rule of thumb, which provides for 1 factor per 10 events, up to 7 covariates can be included in the multiple regression model, limiting the biasing effects of the model.

3. Results

During the study period, 168 first visits were recorded for persons with suspected MO. Of these, 15 did not have diagnostic confirmation of the disease and were therefore excluded from the study, while for one person no clinical documentation could be found. Therefore, a total of 152 patients were enrolled and analysed. The pain symptoms recorded in a precise way had a 25th, 50th and 75th percentiles of 0–0-4, respectively. A percentage of 25.7 % (95 % CI of 19.3—33.3) presented at the first visit with moderate/severe pain.

3.1. Baseline characteristics

The median age was 11.2 years (IQR = 25.0) and the patients were equally distributed by gender. Looking at the median pain score stratified into the four age-related groups (Table 2.), an upward trend in pain score percentiles emerged, ranging from 0 - 0–0 in the preschool group to 2–4–6.5 in the young adult/adult group. Logistic regression confirmed that age was the only factor to be significantly associated with moderate/severe pain, with each additional year of age increasing the risk of experiencing moderate/severe pain by 5 % (OR = 1.05; p-value = 0.001) (Table 3.). A further sub-analysis conducted only for patients over 18 years of age showed that none of the baseline characteristics were significantly associated with pain symptoms (supplementary material –S1).

3.2. Pathology phenotype

At the time of the first visit, according to the IOR classification, class I, in the absence of deformity and functional limitations, was the most numerous with 43 % of patients (Table 2.). At the same time, it was possible to record the presence of significant pain symptoms compared to the other subclasses with pain percentiles of 0–2–4, for subclass IB. Only class III had similar pain percentiles, in subclass IIIA equal to 0–2–3 and in subclass IIIB equal to 0–1–6. Class II, comprising 34.8 % of patients, had lower pain levels as percentiles.

In the majority of the patients, with a percentage of 42.8 %, 6 to 10 OCs were present and in 53.3 % of the cases, in addition to the limbs, which were always involved, OCs also affected the trunk. Multiple linear regression showed that it was impossible to identify an association between phenotype and pain symptoms (Table 4.). The IOR classification was not able to provide a description of the pathology that was associated with a major pain score. The multiple logistic regression conducted by including age as a correction factor did not lead to a change in the results, confirming that age was the only independent predictor of moderate/severe pain (supplementary material –S2).

3.3. Treatments performed/ongoing

Patients suffering from MO presented themselves at the first visit having already undergone medical therapies for pain in 20 % of the cases, conservative therapies in a further 20 % of the population or having already undergone surgery, which in 8 % of the cases was attributable to a painful OC site (Table 5.). In the 31 patients for whom analgesic therapy was registered, paracetamol was used in 22 cases and a drug of the NSAID type in 9 cases. Multiple logistic regression showed a significant association (OR = 13.53; p-value < 0.001) between analgesic medical therapy and pain symptoms. Patients undergoing treatment were 13 times more likely to report moderate/severe pain than those not undergoing antalgic treatment. The other treatments

Table 2
Pain score stratified into the four age-related groups and Rizzoli Multiple Osteochondromas Classification.

Variable	N (%)	Percentil		
		25°	50°	75°
Age				
2–5 year	38 (25.0)	0	0	0
6–12 year	42 (27.6)	0	0	2
13–18 year	16 (10.5)	0	2	4
>18 year	56 (26.9)	2	4	6.5
IOR Classification				
IA	27 (17.8)	0	0	4
IB	39 (25.7)	0	2	4
IIA	37 (24.3)	0	0	3
IIB	16 (10.5)	0	0	3
IIIA	19 (12.5)	0	2	3
IIIB	14 (9.2)	0	1	6

Table 3
Pain score description and multiple logistic regression by baseline characteristics.

	N = 152	Absent/ mild pain (N = 113)	Moderate/ severe pain (N = 39)	Multiple logistic regression OR	CI 95 %	pvalue
Age, median (IQR)	11.2 (25.0)	8.2 (12.3)	31.0 (21.2)	1.05	1.02; 1.09	0.001
BMI, median (IQR)*	18.4 (6.9)	17.2 (6.4)	22.0 (5.5)	1.05	0.93; 1.19	0.397
Female, n (%)	73 (48.0)	55 (48.7)	18 (46.2)	0.85	0.35; 2.08	0.733

*12 missing.

considered had no significant associations. The age-adjusted regression of the population confirmed this result. Antalgic treatment had a reduced OR of 8.12 with a p-value < 0.001, while age was the only other significant factor with an OR of 1.05 and p-value of 0.002 (supplementary material – S3).

4. Discussion

The aim of the present study was to investigate and describe the pain symptoms of patients referred to Ce.Ma.R.S. for the diagnosis of MO. In 25 % of the cases, the pain was found to be of moderate/severe intensity. With respect to baseline characteristics, age was identified as an independent risk factor, with a particularly significant increase in pain in patients over 18 years of age. The IOR classification, based on the disease phenotype, showed no significant association with pain, while ongoing antalgic treatment was associated with a higher pain score.

In the studies by Amajjar et al. and Darilek et al. [15,16], moderate/severe pain levels were reported in higher percentages, 46 % and 42 % of patients, respectively. This diversity of results could be explained by baseline characteristics of the study population with a difference in the ages of the patients enrolled and the stage of the disease the patients were in. Amajjar et al. [16] considered an adult population older than 18 years, whereas Darilek et al. reported a population in which only 40 % of patients were younger than 20 years. [15] In the present study, 63 % of the population was younger than 18 years and the patients enrolled were at an early stage of the disease that had yet to be diagnosed with certainty. In the population of pre-school children, moderate/severe pain was reported for none, while a significant point of change was the age at 18 years. Considering only this group of patients, moderate/severe pain was reported in 53 % of the cases. In the univariate analysis the same association was reported by Darilek et al. [15] who, precisely in order to make the sample more homogeneous, excluded the population under 10 years of age from the multiple regression analysis.

In an attempt to draw a hypothesis of the evolution of pain symptoms linked to the evolution of the pathology itself over time, by correlating the various studies, one could hypothesise a negative trend for pain that appears from the very beginning of the treatment pathway and that tends to worsen over time. In order to make this suggestion more concrete, it will be necessary to carry out prospective studies evaluating the evolution of pain over time and how these changes following the various treatments implemented. From the clinical point of view, the message that emerges is the need for careful monitoring of pain from the earliest stages of treatment in order to avoid its worsening over time and the risk of chronicity, also highlighted by Amajjar [16]. Clinical pathways, aimed at patient education in pain management and monitoring, should be encouraged and structured appropriately within the referral centres for the treatment of patients with rare skeletal diseases. Amajjar et al. [16] in the adult population also reported an association between pain and female sex, unlike the present study in which no such association emerged. Even the analysis of the adult population alone, aged over 18 years, in the present study did not confirm the association between sex and pain. In subsequent studies, it will be necessary to clarify whether sex may play an important role in the development of pain symptoms during the clinical evolution of the disease itself.

The classification of the phenotype proposed and reviewed by the IOR [17] revealed precisely a heterogeneity of pathology presentation that was important and the data presented showed that the early classification did not allow an association between the pain symptoms and the different subclasses. Class IB patients, who had no skeletal deformities and functional limitations but a number of OCs greater than 5, were the patients with the most pain symptoms. In the initial phase, the pain would appear to be linked not so much to the complications that OCs cause on joints with the appearance of limitations and deformities, but rather to intrinsic aspects of the pathology such as the mechanical compression exerted on adjacent structures. The number of sites involved did not confirm its association with pain symptoms when

Table 5
Pain score description and multiple logistic regression by treatments performed/ ongoing.

	N = 152	Absent / mild pain (N = 113)	Moderate / severe pain (N = 39)	Multiple logistic regression OR	CI 95 %	pvalue
Ongoing antalgic therapy	31 (20.4)	9 (8.0)	22 (56.4)	13.53	5.24; 34.93	<0.001
Surgery in the site of pain	13 (8.6)	7 (6.2)	6 (15.4)	1.30	0.31; 5.47	0.724
surgery at a site other than that of pain	42 (27.6)	26 (23.0)	16 (41.0)	1.55	0.60; 3.98	0.364
Physiotherapy / orthoses / brace / other	31 (20.4)	24 (21.2)	7 (18.0)	0.87	0.28; 2.68	0.808

Table 4
Pain score description and multiple logistic regression by pathology phenotype.

			N = 152	Absent / mild pain (N = 113)	Moderate/severe pain (N = 39)	Multiple logistic regression OR	CI 95 %	pvalue
Rizzoli classification, n (%)	I	A	27 (17.8)	20 (17.7)	7 (18.0)	–		
		B	39 (25.7)	26 (23.0)	13 (33.3)	1.07	0.26; 4.28	0.928
	II	A	37 (24.3)	29 (25.7)	8 (20.5)	0.57	0.14; 2.26	0.421
		B	16 (10.5)	13 (11.5)	3 (7.7)	0.40	0.07; 2.34	0.312
	III	A	19 (12.5)	15 (13.3)	4 (10.3)	0.58	0.12; 2.79	0.494
		B	14 (9.2)	10 (8.9)	4 (10.3)	0.80	0.15; 4.18	0.792
Number of affected skeletal sites, n (%)		1–5	53 (34.9)	42 (37.2)	11 (28.2)	–		
		6–10	65 (42.8)	46 (40.7)	19 (48.7)	2.02	0.69; 5.94	0.197
		>10	34 (22.4)	25 (22.1)	9 (23.1)	1.70	0.50, 5.84	0.396
Exostosis localization, n (%)		Upper/ lower limbs	71 (46.7)	50 (44.3)	21(53.9)	–		
		Limbs and trunk	81 (53.3)	63 (55.8)	18 (46.2)	0.59	0.27; 1.28	0.182

considering all patients in all classes. Further studies could propose a re-examination of the classification of MO and its phenotype taking into account pain intensity to provide a useful tool in clinical practice for the management of patients' symptoms. In the literature, there were different types of classifications for patients with MO, based on age of the patients, the time of onset of the disease, functional aspects and the presence of deformities, but in none of the classifications was the aspect of pain symptomatology included [19–22]. Age was confirmed as the only factor able to explain, at least partially, the painful symptomatology within the different classes and in relation to the characteristics of the phenotype. Correct identification of patients most at risk of developing pain would make it possible to propose treatments and pain management more oriented to specific patient characteristics.

When looking at the therapies implemented or already performed by patients, a paradoxical effect emerged in connection with the association between medical therapy and the presence of pain symptoms. If it is easy to understand why patients who present with greater pain are also the patients who are most likely to resort to analgesic therapy, at the same time it is less intuitive to explain the association in the opposite direction, i.e. why patients who have medical therapy continue to have such significant pain. In order to explain this, it should be borne in mind that in the initial phase, patients with pain had a therapy that was mainly based on drugs such as fans and paracetamol. From the data collected in this cohort of patients, it can be assumed that the therapy implemented was insufficient to provide real relief for the patient. In clinical practice, this should be translated into the need to set up a course of pain therapy from the moment of diagnosis in order to provide the patient with adequate support. In the present study, surgical intervention at the site of OCs, reported in 8 % of patients, did not show an association with pain symptoms, in contrast to the findings of Darilek et al., in which this type of treatment was, however, reported in over 80 % of patients.

4.1. Limitations

The study has some limitations. Firstly, the IOR classification of the phenotype is built on 6 classes, which would require a larger sample size in order to be investigated more thoroughly. To the authors' knowledge this is the first attempt at an association between the phenotype of MOs and a relevant clinical outcome such as pain.

In addition, the sample size was lower than expected, the incidence of the event being 25 % lower than the 46 % assumed on the basis of literature data. According to the authors, this did not lead to distorting effects in the regression models constructed in which the number of factors considered was limited. The retrospective nature of the study may have introduced a population selection bias. On the other hand, the entire population that consecutively addressed the study's promoter rare disease centre was enrolled, reducing this risk.

Finally, the present study does not relate pain to other elements of people's quality of life. This aspect calls for further studies with prolonged follow-up over time that will make it possible to understand the evolution of pain symptoms also in relation to the quality of life and the different treatment courses implemented. The present study represents a first step in this area to understand the role of pain from the earliest stages of MO diagnosis.

5. Conclusions

Pain symptoms must be carefully assessed and monitored from the early stages of MO diagnosis. An increase in age is associated with a worsening of pain; for patients under the age of 18 years, educational pathways with respect to the correct management and monitoring of pain symptoms must be encouraged, while for patients over the age of 18 years, appropriate and specific pain therapy pathways must be implemented. The IOR classification of the MO phenotype does not currently allow an association between the various classes and pain. A re-evaluation of the classification in this light could be an important new element for clinical practice.

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Area Vasta Emilia Centro with Protocol No. 800/2022/Oss/IOR evaluated on 15/11/2022. Due to the nature of the study, the collection of informed consent was exempted for the study.

CRediT authorship contribution statement

Morena Tremosini: Methodology, Data curation, Conceptualization. **Mattia Morri:** Writing – original draft, Methodology, Formal analysis. **Cristiana Forni:** Writing – review & editing, Data curation, Conceptualization. **Elena Pedrini:** Writing – review & editing, Methodology. **Marina Mordenti:** Methodology, Formal analysis. **Maria Gnoli:** Formal analysis, Data curation. **Alessia Di Cecco:** Data curation, Conceptualization. **Alice Moroni:** Methodology, Data curation. **Luca Sangiorgi:** Supervision, Conceptualization.

Funding

This work has been supported by "*Department of Rare Skeletal Disorders*" – IRCCS Istituto Ortopedico Rizzoli for open access article processing charge (APC).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We acknowledge the patients for their participation in this study. Authors of this publication are members of the ERN BOND—the European Reference Network for Rare Bone Diseases "https://ernbond.eu/".

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbo.2025.100672.

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