

ORIGINAL ARTICLE

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Fibrous dysplasia: clinical and pathologic characteristics, surgical approaches, and outcomes in a large Italian cohort

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Abstract

Fibrous dysplasia (FD) is a rare benign bone disease caused by postzygotic activating mutations in the *GNAS* gene, leading to replacement of normal bone with fibrous tissue. It may be monostotic or polyostotic, often asymptomatic but sometimes associated with pain, deformity, or fractures. Management is mainly surgical in symptomatic or complicated cases. This retrospective study analyzes a large FD cohort to identify determinants of treatment and outcomes, with a focus on pain and its evolution. The primary aim was to assess factors influencing surgical indication, while the secondary aim was to evaluate predictors of outcome in surgically treated patients, particularly symptom persistence at follow-up. A total of 227 patients were included. Mean age at diagnosis was 35.5 years (range 2–86 years); 79.3% had monostotic and 20.7% polyostotic FD. Pain was the most common presentation (62.6% at diagnosis; 78.4% during disease course), followed by incidental findings (21.6%), fractures (11.5%), and mass (4.4%). Surgery was performed in 51.6% of patients (127 lesions). Surgical patients were younger and had larger lesions and higher Mirels' scores (all $p < 0.001$), although Mirels' score showed only moderate predictive accuracy for surgery (area under the curve (AUC) 0.71). At a mean follow-up of 4.5 years, persistent pain was present in 24.1% of patients, with no significant difference between surgical and nonsurgical groups. Surgery was not an independent predictor of pain resolution in multivariable analysis. Postoperative complications occurred in 17.3% of procedures, with 7.1% requiring multiple revisions; rates were higher in polyostotic disease (21.3% versus 6.7%, $p = 0.004$). Our findings suggest that pain alone should not be used as an indication for surgery in FD, as it was not a reliable predictor of outcome in our study. Surgical decisions for pain relief should therefore be made with caution, and patients should be informed about the risk of persistent symptoms. Conservative, multidisciplinary management—including bisphosphonates, monoclonal antibodies, and psychological support—should be considered first-line, as it may improve symptoms and quality of life.

Keywords Fibrous dysplasia, McCune–Albright syndrome, Clinical features, Surgery, Treatment outcome, Pain, Rare bone disorder

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Introduction

First described in the late 1930s, fibrous dysplasia (FD; ORPHA:249) is a rare, benign, congenital, nonhereditary bone disorder characterized by replacement of normal bone with fibro-osseous tissue owing to abnormal osteoblastic differentiation [1, 2]. FD may present as a solitary lesion (monostotic FD (MFD)), accounting for 70–80% of cases, or as a more severe polyostotic form (polyostotic (PFD)) involving multiple skeletal sites and associated with deformities, fractures, scoliosis, and impaired mobility [3–5].

In some patients, FD is associated with extra-skeletal manifestations such as cafe-au-lait spots and hyperfunctioning endocrinopathies, defining McCune–Albright

syndrome (MAS) [6, 7]. The rare association of FD with intramuscular myxomas is known as Mazabraud syndrome [8, 9] (Fig. 1a–d).

FD is caused by postzygotic activating variants of the guanine-nucleotide binding protein alpha subunit stimulating activity polypeptide 1 gene (*GNAS*), leading to constitutive activation of Gas signaling and dysregulation of the cyclic adenosine monophosphate (cAMP) pathway [10]. Disease severity depends on the timing of the mutation during embryogenesis.

The estimated incidence is approximately 1:5000–10,000, without sex predilection [11, 12]. Pain, particularly involving the lower limbs and spine, affects up to 80% of adults and 50% of children, although

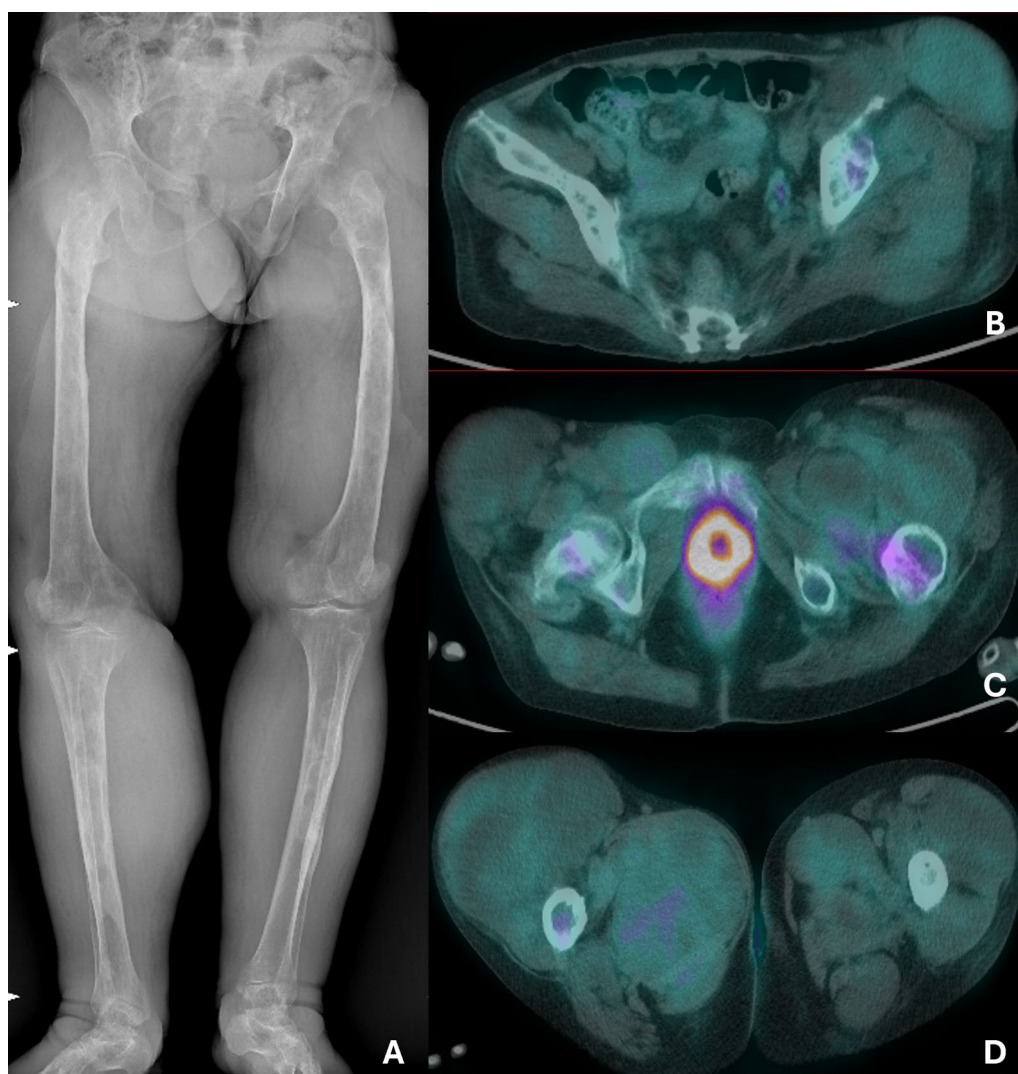


Fig. 1 A–D radiographic appearance of a female patient, 58 years old, with McCune–Albright/Mazabraud syndrome. **A** Long-standing lower limb radiographs show extensive involvement of both femurs, tibias, fibulae, and the pelvis. Axial positron emission tomography–computed tomography (PET–CT) slices demonstrate multiple intramuscular myxomas in the pelvis (predominantly on the left) (**B**), as well as in both hips (**C**) and thighs (**D**)

asymptomatic incidental lesions are not uncommon [3, 13]. Serum alkaline phosphatase (ALP) levels may be elevated, although findings remain inconsistent [14, 15].

The diagnosis of FD is generally well established and supported by imaging, histology, and molecular genetics. By contrast, although several treatment strategies have been proposed, clinical decision-making still largely relies on individual experience and patient-specific factors. In particular, pain management remains challenging, as the underlying mechanisms of pain in FD are still poorly understood [3]. Both nonsurgical approaches, such as bisphosphonates [16] and anti-receptor activator of nuclear factor kappa-B ligand (anti-RANKL) monoclonal antibodies including denosumab [17], and surgical treatments have been described. However, while surgery is essential for the treatment of fractures and progressive deformities, particularly in children and adolescents [18–21], its effectiveness in relieving pain and altering disease progression remains incompletely defined [22, 23]. Reliable predictors of outcome are still lacking, partly because most published series include small patient cohorts and are predominantly focused on proximal femoral involvement, especially the classic “shepherd’s crook” deformity [21, 24–26]. In this context, a more comprehensive understanding of the clinical course of FD, particularly in larger cohorts and among surgically treated patients, is essential.

This study analyzes a large cohort of patients with FD to identify clinical and surgical determinants of outcome, with a particular focus on pain persistence and symptom evolution. The primary aim was to determine which factors influence treatment decisions, particularly surgical indications. The secondary aim was, in the surgically treated subgroup, to evaluate which variables are associated with clinical outcomes, with specific attention to symptom persistence at follow-up. Overall, the study seeks to improve patient management and support more evidence-based clinical decision-making.

Materials and methods

Study design

We performed a retrospective observational study of the hospitalization and treatment of a large cohort of Italian patients affected by FD.

Consecutive male and female patients of all ages with a clinical and/or histological diagnosis of FD and available clinical and radiological data related to outpatient visits, hospitalizations, or surgical procedures were included. Patients with an unclear or unconfirmed diagnosis of FD, or without adequate clinical documentation at our institution, were excluded. This included patients with an initial diagnostic suspicion not confirmed at histology and patients lost to follow-up after the initial evaluation. All

patients were treated in the period between March 2006 and December 2024 at a tertiary referral center for rare bone diseases. Data were extracted from hospital electronic databases and the regional electronic health record system (a shared platform collecting longitudinal clinical data within the regional healthcare system, not available nationwide). Additional information was obtained from clinical charts and medical records, and all data were entered into a Microsoft Excel (Microsoft, Redmond, WA, USA) spreadsheet for cleaning and management.

The present study was approved by the Institutional Ethics Committee (Area Vasta Emilia Centro Ethics Committee-CE-AVEC) in February 2021 (294/2022/Sper/IOE) and the research was conducted according to the Declaration of Helsinki and the guidelines for Good Clinical Practice.

Patient characteristics

We took into consideration demographic characteristics (gender, age at diagnosis), reason for admission, diagnosis, comorbidities, clinical manifestations and radiological aspects, number and localization of the lesion, presence/absence of pain at lesion site (at baseline and 1-year follow up), and serum alkaline phosphatase (ALP)—a marker of osteoblastic activity. Surgical variables included procedure type, number and location of skeletal segments treated, and perioperative complications. According to the modified Clavien–Dindo–Sink (mCDS) classification [27, 28], complications were grouped as minor (< grade II) and major (> grade II), with only the latter considered in the analysis.

Radiographic evaluation

On radiographs, lesion location, size, and associated deformities were described. The Mirels’ score was calculated *a posteriori* to explore its association with surgical treatment. The Mirels’ score is a clinical–radiological system used to estimate the risk of impending pathological fracture in long bones, primarily in patients with metastatic disease [29, 30]. It is based on four parameters (site of lesion, pain, radiographic appearance, and lesion size) each scored from 1 to 3, yielding a total score from 4 to 12. Higher scores indicate greater fracture risk, and a score > 9 supports consideration of prophylactic surgical fixation, whereas lower scores generally favor conservative management and surveillance. Although primarily used in the assessment of metastatic bone lesions, it has also been proposed for benign conditions such as bone cysts and FD [31, 32].

All patient data were independently reviewed by two observers (a senior orthopedic surgeon with > 20 years of experience and a junior resident trained in image interpretation). For interobserver reliability of lesion

size measurements, FD images were randomly selected from the initial cohort. *A priori* sample size calculation was performed using G*Power 3.1.9.7 (bivariate normal correlation model, exact test), assuming a minimum acceptable intraclass correlation coefficient (ICC) of 0.60, an expected ICC of 0.80, $\alpha=0.05$, and 80% power, resulting in a required sample size of 51 images. This was increased by 20% to account for potentially incomplete or nonassessable images, yielding a final sample of 60 images. Minor discrepancies were resolved by consensus and, when necessary, adjudicated by a third senior orthopedic surgeon with extensive expertise in monostotic and polyostotic fibrous dysplasia.

Missing data handling

Missing data were first evaluated to determine their underlying mechanism, classified as missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR) [33]. The handling strategy was predefined according to the proportion and presumed mechanism of missingness. Complete-case analysis was used when missing data were < 5%. For missing rates between 5% and 40% with plausible MCAR/MAR mechanisms, multiple imputation by chained equations (MICE) was considered. When data were suspected to be MNAR, or when missing outcome data exceeded 40% in a relatively small retrospective dataset (< 1000 cases), formal imputation was considered unreliable; therefore, complete-case analysis with sensitivity analyses was adopted. Best-/worst-case scenarios were used for binary outcomes, while extreme-value analyses based on clinically plausible ranges were applied for continuous outcomes [34].

Statistical analysis

All demographic, epidemiological, and statistical analyses were performed using Jamovi (version 2.3.28) and SPSS (version 25.0; IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate.

For continuous variables, comparisons between two groups were performed using the Student's *t*-test or the Mann–Whitney *U* test, depending on data distribution. When more than two groups were compared, one-way ANOVA or the Kruskal–Wallis test was applied accordingly. Correlations were assessed using Pearson or Spearman correlation coefficients on the basis of data normality.

To explore factors associated with the outcomes of interest, univariate analyses were first performed. Variables considered clinically relevant and/or statistically

significant in univariate analyses were subsequently entered into multivariate binary logistic regression models to identify independent predictors. In addition, all variables with potential biological or clinical relevance were considered for inclusion in the multivariable models.

Model results are reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Model interpretation was based on the identification of independent associations after adjustment for covariates, with emphasis on the magnitude and direction of effect estimates, as well as the precision of estimates as reflected by the width of the confidence intervals. Narrow confidence intervals were interpreted as indicating more stable estimates, whereas wide confidence intervals suggested greater uncertainty, often related to small sample size or low event frequency.

Statistical significance was set at $p < 0.05$.

Results

Patient characteristics and clinical presentation

A total of 227 patients were enrolled (121 females, 53.3%), predominantly Caucasian (94.7%). Age at diagnosis ranged from 2 to 86 years (mean 35.5 years). A total of 44 patients (19.4%) were diagnosed before age 18 years. MFD was present in 180 patients (79.3%) and PFD in 47 (20.7%). Among PFD cases, seven (3.1%) were affected by McCune–Albright syndrome, 1 (0.4%) by Mazabraud syndrome, and 2 (0.9%) by both. Additionally, 33 patients reported heterogeneous comorbidities: 10 (4.4%) had oncological conditions and 23 (10.1%) had various diseases affecting different systems and tissues. The most common reason for admission was pain, reported in 142 patients (62.6% at presentation and 78.4% during the disease course), with an almost equal sex distribution (84 males and 94 females). This was followed by incidental imaging findings (49 patients, 21.6%), pathological fracture (26 patients, 11.5%), and palpable mass (10 patients, 4.4%).

A total of 360 bone lesions were identified, with nearly one-third located in the proximal femur, which also represented the most common site of surgical intervention (Table 1). PFD involved a number of skeletal sites varying from 2 to 20, with a mean of four lesions per patient.

BMI was calculated for 94 patients, on the basis of the availability of both height and weight. Mean BMI was 23.5 ranging from 14.3 to 36.0. More than half of patients (49 subjects, 52.1%) had a normal BMI, followed by 27 overweight subjects (28.7%); obese, underweight, and very underweight groups were poorly represented (8, 4, and 6 subjects, respectively).

Table 1 Distribution of lesions per anatomic area considering the overall population and the surgical patients

Localization in lower and upper limbs	N (%)	Surgical treatment (%)
Overall	360	127 (35.3)
Proximal femur	100 (27.8)	70 (55.1)
Proximal tibia	33 (9.2)	7 (5.5)
Proximal humerus	15 (4.2)	7 (5.1)
Distal tibia	17 (4.7)	4 (3.1)
Distal humerus	12 (3.3)	4 (3.1)
Proximal ulna/radius	15 (4.2)	5 (3.9)
Distal femur	19 (5.3)	4 (3.1)
Foot	9 (2.5)	0
Distal ulna/radius	5 (1.4)	2 (1.6)
Ribs and sternum	53 (14.7)	9 (7.1)
Spine	24 (6.7)	9 (7.1)
Craniofacial	7 (1.9)	0
Hand	6 (1.7)	2 (1.6)
Fibula	8 (2.2)	0
Pelvis	34 (9.4)	3 (2.4)
Scapula	3 (0.8)	1 (0.8)

Imaging and laboratory evaluation

Radiologic documentation was available for 218 patients (96.0%), predominantly consisting of computed tomography (CT) scans (180 patients), plain radiographs (172 patients), and magnetic resonance imaging (MRI) scans (120 patients). Whole-body bone scintigraphy, PET-CT, bone-scintigraphy, and ultrasound were available in 20, 9, and 5 patients, respectively. Interobserver reliability analysis demonstrated an excellent level of agreement, with a mean-measures ICC of 0.994 (95% CI 0.990–0.996), confirming the excellent reliability of lesion size measurements between observers.

Biopsy was performed at our institution in 176 patients (77.5%), while the remaining diagnoses were established on the basis of imaging and clinical history, supported by histological confirmation conducted externally. All evaluated specimens showed histological features consistent with FD, in line with imaging findings.

The maximum lesion diameter, assessed on available imaging, ranged from 5 mm to 215 mm (mean 60.5 mm). The Mirels' score, calculated in 154 patients with appendicular lesions, had a mean of 8.5 (range 4–12) and showed a weak correlation with age (Spearman's $r=0.25$, $p=0.001$). Overall, 79 patients (50.6%) had a Mirels' score >8 .

Serum alkaline phosphatase (ALP) data were available for 76 patients. In the majority of patients (66 subjects, 87%), the ALP concentration was normal with respect

to the age and gender ranges (Mayo Clinic Laboratories indications, Mayo Clinic Laboratories, Rochester, MN, USA). In all the ten subjects with an elevated ALP level, only one male subject had a very high ALP level, while the remaining nine subjects had slightly or moderate elevated levels (Table 2).

Surgical treatment

A total of 127 lesions (35.3%) in 117 patients (51.6%) were treated surgically at our institution.

Surgical patients were significantly younger (mean difference = 9.5 years; 95% CI 5.0–14.1 years; $p<0.0005$). Similarly, size of the lesion and Mirels' score were significantly higher in patients undergoing surgery (mean difference = 16.5 mm; 95% CI 6.8–26.3 mm; $p=0.001$ and mean difference of 1.6 points; 95% CI 1–2.2 points; $p<0.0005$, respectively). In particular, the Mirels' score showed only moderate accuracy in predicting need for surgery (AUC 0.71; 95% CI 0.63–0.79 $p<0.0005$).

The main surgical treatments were osteosynthesis or curettage (see Table 3). Osteosynthesis involved femur in

Table 2 List of ALP levels of the ten patients with an altered value and normal ranges of ALP value depending on age and gender according to Mayo Clinic Laboratories indications

ALP (U/L)	ALP normal range (U/L) (per age and gender)
167	50–117
343	142–335
523	142–335
107	35–104
118	35–104
109	35–104
146	40–129
127	35–104
149	40–129
111	35–104

Table 3 Number and frequency of subjects who underwent surgical treatment

Type of surgical treatment	Number (%) of subjects
Fixation	51 (40.2)
Curettage	38 (29.9)
Osteotomies	12 (9.4)
Resection	11 (8.7)
Others	11 (8.7)
Injection	4 (3.1)

the majority of cases (42 cases) while tibia and humerus were synthesized in five and four patients respectively. Osteosynthesis was achieved by intramedullary nails (33 patients), screw plates (11 patients), and blade plate (7 patients). Bone allografts (cancellous and/or strut cortical) were used in 47 patients especially after curettage: 68% of the curettages were filled with bone allograft, while cortical or strut bone allografts were used in 38.9% of osteosynthesis and/or osteotomies; bone cement was used in four cases of curettage. Demineralized bone matrix with platelet-rich plasma and bone marrow centrifugate was injected into four lesions.

Follow-up

A total of 94 patients (41.4%) were lost to 1-year follow-up; among the remaining cohort, mean follow-up was 4.5 ± 3.7 years (range 1.0–19.4). Missing data were more frequent in MFD than PFD (46.7% versus 21.3%, $p=0.002$) and associated with older age (mean difference = 10.1 years; $p=0.001$, $p<0.0005$), smaller lesions (mean difference = -14.1 mm; $p=0.001$), and nonsurgical management (50.9% versus 32.5%, $p=0.007$), suggesting a likely MNAR “missing-better” mechanism.

Overall, 1-year follow-up data were available for 133 patients (58.6%). At the latest follow-up, persistent pain was reported in 32/133 patients (24.1%), including 20/79 (25.3%) surgically treated and 12/54 (22.2%) nonsurgically treated patients. Among 107 patients presenting with pain at diagnosis, 69 (64.5%) underwent surgery, leading to pain resolution in 53 cases (76.8%), while spontaneous pain resolution was observed in 27 out of 38 nonoperatively managed patients (71.1%). Conversely, among 26 initially asymptomatic patients, 11 (42.3%) developed pain during follow-up; of them, 10 patients subsequently underwent surgery, although persistent pain remained in four cases. Among the 16 patients (61.5%) who remained nonoperative, only 1 reported pain at follow-up. Extreme-case MNAR sensitivity analysis yielded a plausible range for pain prevalence at latest follow-up of 17.1–49.6% in the surgical group and 10.9–61.8% in the nonsurgical group. The observed distribution was more consistent with the lower bound (“missing-better” scenario), suggesting a potentially lower true prevalence of pain among patients with missing outcome data.

Pain at follow-up was associated with age at diagnosis (mean difference = -7.9 years; $p=0.015$) and follow-up duration (mean difference = 1.2 years; $p=0.049$). Multi-variable analysis including all candidate variables showed borderline overall significance (Omnibus $p=0.063$; Nagelkerke $R^2=0.37$; Hosmer–Lemeshow $p=0.204$), suggesting limited model stability.

A reduced model including only variables significant at the univariate analysis improved overall fit (Omnibus

$p=0.02$; Hosmer–Lemeshow $p=0.786$), although explanatory power remained low (Nagelkerke $R^2=0.09$), indicating that the available variables only partially accounted for pain persistence. Similarly, logistic regression analysis did not demonstrate a significant independent effect of surgery on pain resolution.

Postoperative complications were reported in 22 of 127 surgical procedures (17.3%) and included lesion recurrence with persistent pain or refracture requiring reoperation, progressive deformity, intra-articular hardware migration (“cut-out”), and other mechanical failures. Overall, 22 of 127 patients (17.3%) required at least one revision procedure, while 9 patients (7.1%) underwent more than two surgeries owing to complications or sub-optimal outcomes. The complication rate was significantly higher in patients with polyostotic FD compared with those with the monostotic form (21.3% versus 6.7%, $p=0.004$). A representative case is illustrated in Fig. 2A–I.

Discussion

In this study, we reported clinical and surgical data from a large single-center Italian cohort of patients with fibrous dysplasia collected over an 18-year period, exploring the relationship between disease presentation, treatment indications, and clinical outcomes. To the best of our knowledge, this represents one of the largest single-center cohorts reported in the literature.

Consistent with previous large surgical series, our findings confirm that only approximately one-third of lesions ultimately require surgery, most commonly for pathological fractures and progressive deformities, particularly of the proximal femur [35]. However, in our cohort we were not able to demonstrate a clear or definitive benefit of surgery in patients presenting with pain alone, underscoring the uncertainty of surgical indications in patients with pain as the sole clinical manifestation.

Patient characteristics and clinical presentation

In the present cohort, MFD are predominant over the PFD, with a ratio in line with some case series reported in literature, [3, 22, 36, 37]. Interestingly, the proportion of PFD/MAS cases in our series was lower than that reported in the Danish national registry, which identified more than 30% PFD/MAS cases among 408 patients collected over 25 years [6]. This difference may reflect the orthopedic referral nature of our institution, potentially underrepresenting craniofacial and endocrine-related forms, as well as the low rate of systematic whole-body imaging in our cohort (29/227 patients, 12.8%), which may have contributed to underdiagnosis of polyostotic disease. Importantly, there are still no universally established recommendations regarding routine whole-body

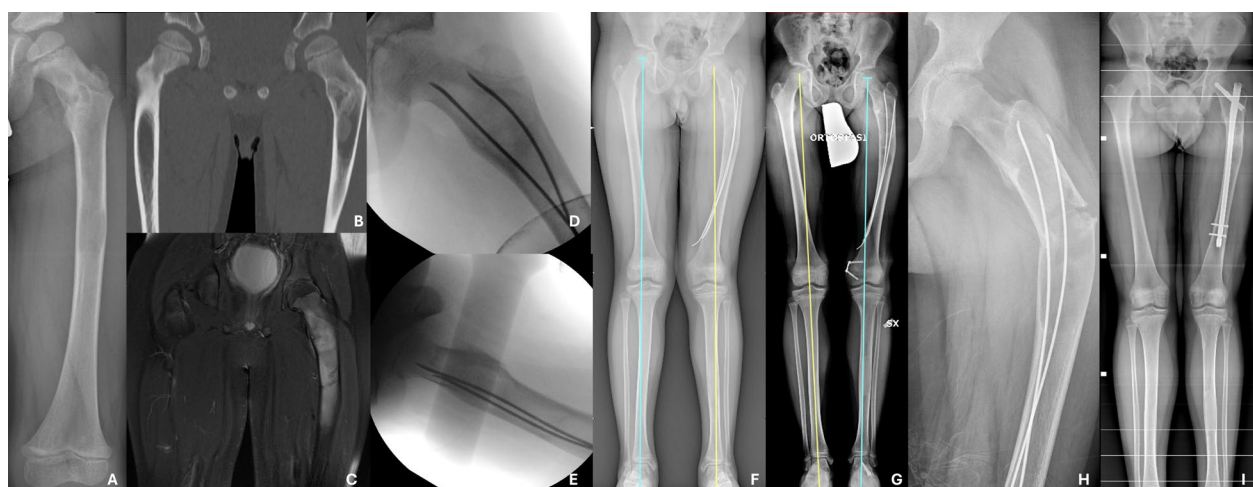


Fig. 2 **A–I** Case presentation of a 4.6-year-old male with polyostotic fibrous dysplasia involving the left femur and tibia. **A** initial radiograph showing a mixed-type lesion affecting the femoral neck and proximal shaft. **B** coronal CT reconstruction, and **C** MRI confirming lesion characteristics. **D, E** at age 9.5, the patient underwent intramedullary fixation with elastic nails. **F** follow-up at 11.5 years showing lesion progression, 15 mm limb length discrepancy, and increasing knee valgus. **G** medial femoral hemiepiphyseal stapling and subtalar arthroereisis with calcaneal stop screw were performed. **H** at 14 years, a proximal femur fracture occurred and was treated with closed reduction and intramedullary nailing. **I** at 2-year follow-up, the patient (now 16 years old) remains under clinical observation

screening or the optimal imaging modality for excluding PFD/MAS following the incidental detection of MFD lesions, although some expert consensus statement has suggested the use of whole-body imaging in patients with MFD older than 5 years of age [23, 38].

Evaluations on gender-confirmed previously published studies, highlighting an almost equal distribution between sexes [6, 19, 39]. The mean age (35.5 years) of the present cohort is in line with the literature, considering that it varies notably (22.1–45.1 years) from study to study [6, 19, 40].

Albeit this feature has been less evaluated in the FD literature, the mean BMI is similar to study of Liu [41]. In addition, our data showed that most of the patients were of normal weight (52.1%), although overweight and obese patients represented almost 37.2%, while underweight and very underweight patients were poorly represented in the cohort, taking into consideration that data pertaining to 125 patients were missing. This aspect needs to be investigated further in future studies, particularly given that weight is a crucial factor in orthopedic disorders and can affect pain, especially in cases of lower limb involvement, that are known to be the most common lesion site.

In literature, the femur, and more specifically the proximal femur, is the most common bone affected by FD lesions [22, 36]. Our results confirmed this, also highlighting the lower limbs as the most involved sites in both MFD and PFD. Although FD lesions are incidentally detected in fewer than one-quarter of asymptomatic patients, 62.6% of our cohort presented with pain at first

evaluation, and an additional 19% developed pain during follow-up owing to progressive deformity or impending fracture, consistent with previous reports [22, 42]. The psychological dimension of pain in FD has recently gained attention, as disease awareness, even when incidentally diagnosed in minimally symptomatic patients, may amplify pain perception and influence treatment decisions, including surgical requests. Bulaicon et al. reported pain (mild-to-severe) in 85.6% of 167 patients assessed with the 36-item short form survey (SF-36), and observed that over 2 years, 27.4% of patients with absent or mild pain developed or worsened symptoms, whereas those with moderate-to-severe pain generally showed persistence rather than improvement, suggesting chronic adaptation rather than resolution [43].

Hagelstain-Rotman et al. mentioned that patients with FD face a higher risk of malignancies [36]. We screened our entire cohort for oncological and nononcological comorbidities. Malignancy rates were lower than in that study and in line with the largest Italian series, but still more than six-fold higher than the 0.7% prevalence in the general population [44, 45]. This is due to the postzygotic mosaic nature of FD and the presence of *GNAS* gene mutations not only in osteogenic cell lines, but in other cell lineage, leading to a varying clinical aspect [46].

Imaging and laboratory valuation

In the entire cohort of both MFD and PFD patients, we identified 360 lesions, the maximum diameter ranging from 0.5 to almost 44 cm, from a very small lesion

detected as an incidental finding to wide and disabling lesion. Of these, only 127 lesions in 117 patients were treated surgically at our institution. This is likely due to multiple, nonmutually exclusive factors, including referral patterns to our tertiary national center, where many patients are evaluated primarily for diagnostic confirmation and reassurance rather than long-term management. Subsequent follow-up is often performed closer to patients' homes, particularly in cases of initially asymptomatic or spontaneously improving lesions. In addition, spontaneous partial regression of FD lesions over time, especially in monostotic forms, has been previously reported [47]. Overall, the high rate of loss to follow-up may reflect a predominantly benign disease course in a substantial proportion of patients.

Ma et al. refer that patients with FD often show higher ALP concentration and that this value can be used as a prognostic marker particularly for PFD [48]. In our cohort, considering ALP concentration, only one patient with MFD, high Mirels' score (11 points), and a large lesion (> 17 cm) presented a very high level. Most cases had a normal ALP level, and few presented slightly higher. The role of ALP as a prognostic factor for FD progression is a debated topic in literature, particularly given that ALP levels are influenced by skeletal maturity and physiological bone metabolism. The results from the present study do not clearly indicate role of ALP as a FD prognostic factor.

Surgical treatment and pain evaluation

Surgical patients were significantly younger (by approximately 12 years) and more frequently presented with larger lesions, higher Mirels' scores, and indications for surgery such as pathological fracture or progressive deformity compared with nonsurgical patients. Although surgical indication was mainly based on surgeon experience and preference, younger age was more frequently associated with operative management, potentially reflecting more active disease biology. As previously reported, growth-related factors, higher physical activity, and hormonal influences in pediatric patients may contribute to lesion progression, pain, deformity, and ultimately a greater likelihood of surgery [49]. Functional and psychosocial concerns may further lower the threshold for intervention in children and adolescents [23]. Notably, our findings are consistent with a recent multicenter pediatric study on femoral FD lesions in patients younger than 16 years, in which 78% of cases underwent surgical treatment (most commonly curettage with or without internal fixation) while only 22% were managed conservatively [50]. Similarly, in our cohort, approximately 75% of children under 16 years with lower-limb involvement underwent surgery,

supporting the tendency toward more aggressive management in younger and weight-bearing patients. By contrast, in adults FD lesions often become more quiescent, with fewer fractures and more sclerotic radiographic patterns, although pain may persist owing to secondary degenerative changes. In long-standing disease, adaptive coping mechanisms may also modulate pain perception [43]. Majoor et al. reported pain in 46% of adult patients [3], a lower prevalence than in our younger cohort. However, these observations remain speculative and require further investigation.

Mirels' score has been widely used in orthopedic oncology for its simplicity and clinical utility in predicting the risk of fracture in metastatic lesion of the long bone [30, 51, 52]; its applicability to benign lesions such as fibrous dysplasia has not been completely validated [31, 32]. In our study, the score was calculated retrospectively from available clinical and radiographic data, and treatment decisions were made independently of the Mirels' score. While a moderate association was observed between higher scores and the likelihood of surgical intervention, its predictive value in this cohort appears limited, owing to the retrospective design and lack of prospective validation.

The surgical approach is typically tailored to clinical and imaging findings, the patient's age, and the location and number of lesions [19]. It mainly involves curettage, osteosynthesis, and corrective osteotomies, sometimes combined with guided growth or lengthening procedures in cases of severe bone deformities [20, 21, 23]. Other reported options range from intralesional injections and bone resection to prosthetic replacement [18].

In the present study, surgical approach solved the pain and functional deficit in the vast majority of patients, still representing the main treatment for FD. The most common surgery on the entire cohort was osteosynthesis, followed by curettage. Curettage was performed in only in two patients < 15 years (associated with the filling of the lesion with morcellized bone or with bone grafts) as treatment, while it appears to be a more common intervention in patients between 15 and 30 years of age (10 cases), and the most used surgical approach in patients > 30 years (25 cases). Historically, the curettage of the lesion was the surgical treatment of choice to cure patients with FD [53]. However, its effectiveness has been questioned owing to high recurrence rates, leading to a large reduction as a standalone treatment and favoring more comprehensive surgical approaches [23]. In addition, in the < 15 age group, 75% of the interventions were osteosyntheses and corrective osteotomies, confirming that pediatric FD management primarily focuses on mechanical stabilization and deformity correction rather than isolated lesion excision.

Based on this study and its findings, and taking all limitations into account, the presence or absence of pain as the sole presenting symptom cannot, in itself, be used as a criterion for selecting surgical treatment. Moreover, our results do not provide reliable predictive information regarding outcomes. Therefore, the indication for surgery aimed at pain relief should be considered with caution. Patients should be informed about the possibility of persistent symptoms even after surgical intervention, and conservative treatment options, such as bisphosphonates [16] and monoclonal antibodies [17], should be considered as first-line approaches within a multidisciplinary team including orthopedic surgeons, endocrinologists, and psychologists. Such integrated management has been shown to improve both symptoms and quality of life in patients with FD [54].

Limitations

While this study offers valuable insights into the clinical spectrum and treatment outcomes of a large Italian cohort with FD, several limitations must be acknowledged.

This study is limited by its retrospective, real-world design and substantial loss to follow-up (>40%), which was unevenly distributed between groups. Given that FD is often an isolated, benign, and asymptomatic condition, frequently managed conservatively or incidentally detected, we considered a “missing-better” scenario in which patients lost to follow-up were more likely to be asymptomatic, although attrition bias cannot be excluded. As the study is primarily descriptive, results should be interpreted without inferential claims regarding treatment effects.

Most patients did not undergo whole-body MRI or skeletal surveys, potentially missing occult lesions.

Because of the retrospective design of the study, no standardized protocol with predefined inclusion or exclusion criteria for surgical treatment was applied, and both the indication for surgery and the choice of procedure were on the basis of surgeon experience and shared decision-making with patients and their families. In general, surgical indications included pathological fractures, progressive deformities or angular deviations, and pain. The study includes 127 surgical procedures performed by 14 surgeons with expertise in pediatric and/or orthopedic oncology surgery. Therefore, the observed variability in surgical decision-making reflects real-world clinical practice rather than the application of standardized treatment protocols.

The lack of significant independent predictors of outcome, particularly regarding pain, may reflect the multifactorial nature of pain persistence in FD, as well as

limited statistical power owing to the relatively small number of outcome events and incomplete longitudinal follow-up.

Clinical and functional outcomes were also limited. Pain was documented only as a categorical variable, with no standardized scales (e.g., Visual Analogue Scale (VAS)/Numerical Rating Scale (NRS)), and no Patient-Reported Outcome Measurements (PROMs) or quality-of-life measures were collected at baseline or follow-up. Additionally, data on pharmacological treatment were excluded owing to inconsistent reporting on drug type, duration, and timing, despite the potential impact of therapies such as bisphosphonates on disease progression.

Finally, selection bias may have affected representation of craniofacial FD, as a regional maxillofacial referral center outside our institution likely received the majority of such cases.

Conclusions

Fibrous dysplasia is a complex and heterogeneous condition, and not all lesions necessarily follow the same course and evolution or exhibit the same behavior. Consequently, a consensus on the optimal surgical approach for addressing FD lesions remains challenging. Based on our findings and their limitations, pain alone should not be used as an indication for surgery, nor do our results provide reliable predictors of outcome. Therefore, surgery for pain relief should be approached with caution, and patients should be informed that symptoms may persist postoperatively. Treatment decisions should instead rely on a comprehensive, multidisciplinary assessment, including deformity progression, functional impairment, response to medical therapy, and the overall risk–benefit profile.

As the understanding of FD continues to evolve, further research and long-term studies will be valuable in providing more insights into the natural history of the disease and the most effective treatment strategies. Nevertheless, in line with the results of the present study, individualized patient management based on their specific characteristics, disease presentation, and symptoms is imperative, and orthopedic surgeons must adopt an accurate and personalized strategy on the basis of several complex evaluations.

The development of clear guidelines for surgical intervention, taking into account factors such as patient age, lesion characteristics, and outcomes, would be highly beneficial for clinicians and patients, as it would facilitate informed decision-making regarding their treatment.

Lay summary

Fibrous dysplasia is a rare bone disorder where normal bone is replaced by fibrous tissue, weakening affected areas. It may involve one bone (monostotic) or several (polyostotic), causing symptoms such as pain, fractures, or deformities, though some patients remain asymptomatic. Surgery is the main treatment. This study examined 227 Italian patients, about half undergoing surgery to relieve pain, correct deformities, or repair fractures. The authors analyzed indications for admission, surgical management, complications, and the impact of disease subtype and lesion location on outcomes. Post-operative complications and persistent pain were not negligible. Overall, the findings highlight the importance of individualized surgical decision-making and a tailored multidisciplinary approach to patient care.

Acknowledgements

We would thank the patients and their families for their participation in this study.

Several authors of this publication are members of the European Reference Network for rare Bone Diseases (ERN BOND)—<http://ernbond.eu/>. We are also grateful to "5x1000 2022 redditi 2021" project.

Author contributions

MM and GT conceptualized the study, defined the methodology, supported the curation of the dataset, and performed statistical analyses and interpreted the results, also supervising other authors. In addition, MM and GT were the major contributors in writing the manuscript and in the revision process. AM supported the definition of methodology and the results interpretation. AM participated in the original draft preparation and in the subsequent reviewing process. SCP and SN prepared and integrated the dataset. Moreover, they were involved in manuscript editing. ELS participated in the conceptualization of the study, supported methodology and data curation. He also participated in data interpretation and in draft preparation and editing. AR and MG supported the preparation of the dataset and reviewed and edited the manuscript. DMD and LS supported the conceptualization of the study, oversaw the study's progress, and reviewed the draft. In addition, LS secured funding. All authors read and approved the final manuscript.

Funding

This work has been supported by Department of Rare Skeletal Disorders—IRCCS Istituto Ortopedico Rizzoli (internal funding).

Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The present study was approved by the Area Vasta Emilia Centro Ethics Committee (CE-AVEC). Approval No. 294/2022/Sper/IOE (May 2022). According to Italian regulations (art. 110bis of D.Lgs. n.196/2003), explicit consent was not required for retrospective chart reviews and publication of the aggregated data.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 22 September 2025 Accepted: 5 June 2026

Published online: 05 July 2026

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