ORIGINAL ARTICLE

Bone involvement in sarcoidosis: Insights from a multicentre Italian cohort

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ABSTRACT

Background: Sarcoidosis is a multisystemic granulomatous disease that can involve the skeletal system, although bone manifestations are considered relatively uncommon and often underdiagnosed.

Objectives: To describe the prevalence, clinical characteristics, and treatment outcomes of bone involvement in a large multicenter Italian cohort of patients with sarcoidosis.

Methods: This retrospective, two-center observational study included 867 patients with histologically confirmed sarcoidosis followed at two Italian referral centers (2018–2025). Bone localization was identified by imaging (PET/CT, MRI, X-ray) and/or biopsy. Clinical, functional, laboratory, and therapeutic data were collected.

Results: Bone involvement was found in 46 patients (5.3%), predominantly women (58.7%), with mean age at diagnosis of 49.7 ± 12.2 years. Osseous lesions were most frequently localized in the axial skeleton, particularly pelvis (54.3%) and vertebrae (52.2%). Bone sarcoidosis was significantly associated with extra-thoracic lymphadenopathy, hepatic, and splenic involvement ($p < 0.001$), reflecting a pattern of clustered multi-organ disease. Osteoporosis and osteopenia were present in 15.2% and 13.0% of cases, respectively. Corticosteroid monotherapy was the most common initial treatment (56.5%), while 30.4% received combination therapy with csDMARDs or biologics. At one-year PET/CT re-evaluation, 56.5% showed a reduction of SUV at bone sites, with no significant correlation between therapeutic regimen and metabolic response.

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Conclusions: Bone involvement in sarcoidosis, though relatively rare, represents a clinically relevant phenotype strongly associated with hepatosplenic and lymphatic disease and characterized by a preferential axial skeleton localization. Recognition of this pattern is essential for diagnosis and management. Given the retrospective design and the limited follow-up sample, these findings should be interpreted with caution. Close radiological monitoring and tailored therapeutic strategies are warranted to improve outcomes.

Key words: sarcoidosis, bone sarcoidosis, osseous sarcoidosis, PET/CT, extrapulmonary sarcoidosis, multisystem disease

Introduction

Sarcoidosis is a chronic, multi-systemic inflammatory disease of unknown etiology, characterized by the presence of activated CD4+ T-helper lymphocytes and macrophages forming non-caseating epithelioid cell granulomas in affected tissues (1–3). Although the lungs are the most involved organ (in up to 90% of patients), the disease can affect nearly any organ in the body (4,5), including the skeletal system. Bone involvement, though traditionally considered rare, has been reported in approximately 1% to 13% and 3–5% of patients with sarcoidosis (6,7). However, this prevalence is likely underestimated due to its aspecific and/or asymptomatic clinical presentation (8). Historically, literature indicated that sarcoidosis mainly affects the small bones of hands and feet, likely due to the widespread use of plain radiography, while involvement of the spine, skull, knees, ribs, pelvis, and sternum was rarely reported. In recent years, the implementation of advanced imaging techniques such as MRI and PET/CT has significantly improved the detection and characterization of osseous lesions. Current studies suggest a greater involvement of the axial skeleton and pelvis compared to appendicular sites (6,9). Bone involvement presents a diagnostic challenge in clinical practice (10,11), as it can mimic a wide range of conditions, including inflammatory and autoimmune diseases (e.g., hyperparathyroidism, granulomatosis with polyangiitis, Sjögren's syndrome, psoriatic arthritis, eosinophilic granuloma, primary biliary cholangitis, granulomatous hepatitis, thalassemia), infections (e.g., tuberculosis, syphilis, brucellosis, histoplasmosis, coccidioidomycosis, leprosy), neoplasms and lymphoproliferative disorders (e.g., multiple myeloma, lymphoma, metastatic cancer, enchondroma, Castleman's disease) as well as exposure-related conditions (e.g., pneumoconiosis, chronic beryllium disease, hypersensitivity pneumonitis) or drug-induced diseases (TNF inhibitors) (12,13). In selected cases, bone biopsy may be necessary to confirm the presence of non-caseating granulomas and to exclude other conditions. However, recognition of typical cystic or punched-out lesions can be more straightforward in patients with established multisystemic sarcoidosis (14). To date, only case reports or small case series have been published on this topic (7,14,15). One study detailed a larger population, focusing on diagnostic and therapeutic algorithms (9). The need for further investigation arises from the necessity to better characterize this specific disease phenotype (1,16), as current guidelines provide limited information on therapeutic approaches for bone-localized sarcoidosis, despite its clinical significance and poorer response to treatment. Here, we present a population of patients with chronic sarcoidosis and bone involvement, observed at two Italian referral centers for lung diseases: the University Hospital of Siena and Bergamo Hospital. Our data revealed a specific phenotype frequently associated with splenic, hepatic, and extra-thoracic lymph node involvement—a pattern that, although scarcely reported in the literature, has been described in at least one other study (9). We provide follow-up data from these patients, highlighting the clinical complexity, differential diagnostic

challenges, and therapeutic strategies associated with this rare manifestation of sarcoidosis.

Materials and Methods

Population

A cohort of 867 patients diagnosed with sarcoidosis (F/M: 464/382; mean age 55.83 ± 13.05 years) between 2018 and 2025 at two Italian referral centers for rare lung diseases—the University Hospital of Siena and Bergamo Hospital—was retrospectively enrolled in the study. A diagnosis of sarcoidosis in accordance with American Thoracic Society (ATS) diagnostic guidelines was required to be included in the study (17). Subjects with only a probable diagnosis or suspected alternative causes such as infections, malignancies, or other granulomatous diseases were excluded. Organ involvement was evaluated according to the WASOG organ assessment instrument (18) and deemed present if documented at any stage of the disease course. As part of the standard diagnostic work-up at our centers, PET/CT was routinely performed at the time of sarcoidosis diagnosis in all patients to assess disease localization and inflammatory activity. Bone involvement was identified primarily on PET/CT based on focal or multifocal areas of increased tracer uptake within the skeleton, not attributable to alternative causes and judged clinically compatible with sarcoidosis (10). PET/CT interpretation was qualitative, and no predefined SUV cut-off values were applied. Conventional imaging modalities (X-ray or MRI) were used as supportive tools, particularly to further characterize morphological features of bone lesions or to evaluate PET-positive findings. Bone biopsy was performed only in selected cases with atypical or equivocal imaging findings, particularly when a differential diagnosis with malignancy or other bone diseases could not be confidently excluded. Image interpretation was performed locally at each center by experienced radiologists and nuclear medicine physicians involved in the routine clinical management of sarcoidosis patients, according to standard clinical practice. Demographic data, clinical manifestations, pulmonary function tests, laboratory findings, imaging features, and treatment history were retrospectively collected from medical records and recorded anonymously in a dedicated database for statistical analysis. All participants provided written informed consent. The study protocol was approved by the Local Ethics Committees (CTET-6, CEAVSE; approval codes: 180712 and Markerlung 17431). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Lung function tests

Lung function tests were conducted following ATS/ERS guidelines (19), using a body plethysmograph with corrections for temperature and barometric pressure, measuring: forced vital capacity (FVC), forced expiratory volume in 1s (FEV1), FEV1/FVC, total lung capacity (TLC), residual volume (RV), lung diffusion capacity for carbon monoxide (DLCO). We recorded the results only in patients who performed lung function tests at the time of diagnosis before starting any type of treatment.

Bronchoscopy and bronchoalveolar lavage

Patients who underwent bronchoscopy signed informed consent before the procedure, received intravenous Fentanyl and Midazolam 15-30 min before undergoing the procedure, Lidocaine was instilled topically for local anesthesia. Bronchoalveolar lavage (BAL) was obtained following technical recommendations and guidelines for BAL (20).

Chest X-ray

Chest X-Ray images obtained at the time of diagnosis were classified using the Scadding staging score (1,21): Stage 0, normal; stage 1, bilateral hilar adenopathy without parenchymal involvement; stage 2, hilar adenopathy and parenchymal infiltration; stage 3, parenchymal infiltration without hilar adenopathy, and stage 4, pulmonary fibrosis.

Vitamin D and calcium metabolism

Serum levels of 25-(OH) D and 1,25(OH) 2 D, calcium, phosphate were measured in 23 using

standard automated laboratory techniques. Urinary calcium, phosphate, and creatinine were determined in 24h urine samples. Patients already in treatment for osteoporosis before the diagnosis of sarcoidosis or on vitamin D/Calcium supplementation and/or affected by disorders that can influence Vitamin D and Calcium metabolism other than sarcoidosis were not included.

Statistical analysis

Statistical analysis Data is reported as mean ± standard deviation, unless otherwise reported. Statistical analyses for comparison of continuous and categorical variables were conducted through non-parametric tests. A p-value < 0.05 was considered statistically significant. A multivariate logistic regression analysis was performed to identify variables independently associated with bone involvement, and results are reported as odds ratios with 95% confidence intervals. To account for multiple comparisons across organ localizations, false discovery rate correction was applied using the Benjamini–Hochberg procedure. All statistical analysis and graphic representation of the data were performed by Jamovi 2.5.6 software.

Results

Study population

We enrolled a cohort of 867 patients with sarcoidosis (F/M: 464/382; mean age 55.83 ± 13.05 years) followed at the University Hospital of Siena and Bergamo Hospital (Table 1).

The distribution of extra-pulmonary organ involvement in the overall cohort is presented in Table 2. Among the entire study population, 46 (5.3%, F/M: 27/19; mean age at diagnosis 49.7 ± 12.2 years) had evidence of bone involvement.

Overall, bone involvement was diagnosed based on imaging findings alone in 39 patients, while histological confirmation was obtained in 7 patients following bone biopsy (Figure 1). Bone biopsy was performed only in selected cases with atypical or equivocal imaging features, when imaging alone was insufficient to exclude alternative diagnoses, including malignancy. In five of these seven patients, histological examination—initiated due to suspicion of other bone diseases—led to a definitive diagnosis of sarcoidosis. In two additional cases, osseous sarcoidosis was diagnosed incidentally through postoperative histological analysis. In the first case, non-caseating granulomas consistent with sarcoidosis were identified in bone tissue removed during lumbar disc herniation surgery. In the second, the diagnosis was made following histological evaluation of bone tissue obtained during a right hip arthroplasty.

Table 1. Characteristics of sarcoidosis population

	N (%) or mean (SD)
Gender F/M	F 464 (53.8%) / M 382 (44.3%)
Age, years	55.83 (13.05)
BMI, kg/m2	24.75 ± 3.99
Smoking habits	
Current smoker	32 (3.7%)
Ex smoker	134 (15.4%)
Not smoker	701 (80.9%)
Ethnicity	
Caucasian	837 (96.5%)
North African *Center African*	23 (2.7%) 4 (0.5%)
South American	3 (0.3%)

Table 2. Sarcoidosis localizations in our population

	N (%) **(Total 867)**
Extra-pulmonary localizations	
Extra-thoracic lymph nodes	125 (14.4%)
Heart	37 (4.3%)
Skin	174 (20.1%)
Eyes	33 (3.8%)
Central nervous system	14 (1.6%)
Kidney	5 (0.6%)
Spleen	71 (8.2%)
Liver	58 (6.7%)
Bone	46 (5.3%)

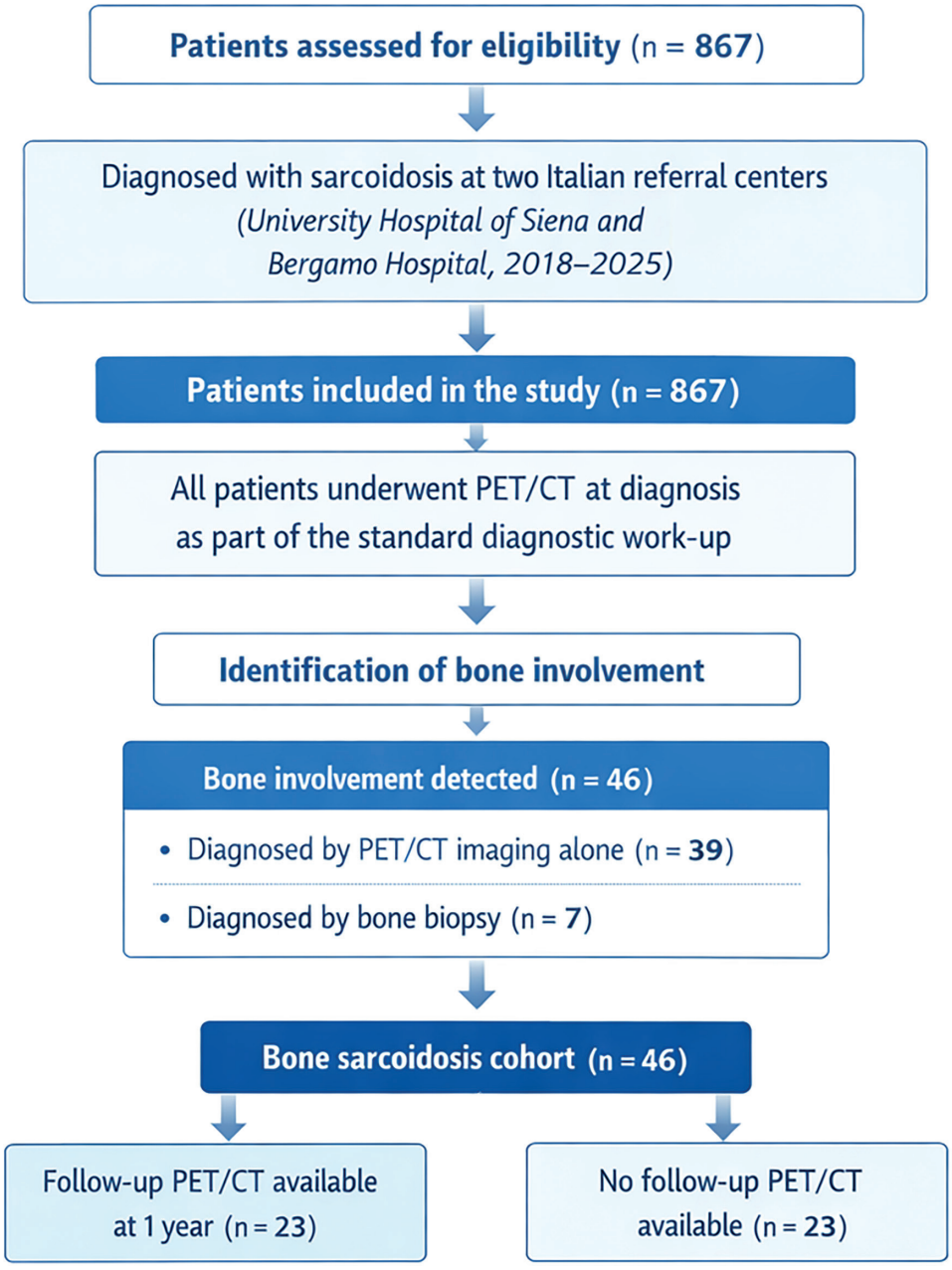

Figure 1. STROBE-style flowchart illustrating cohort selection, diagnostic work-up, identification of bone involvement, and availability of PET/CT follow-up. All patients with sarcoidosis diagnosed at two Italian referral centers underwent PET/CT at baseline as part of the standard diagnostic evaluation. Bone involvement was identified in 46 patients, based on PET/CT findings alone or confirmed by bone biopsy in selected cases. Follow-up PET/CT at one year was available in 23 patients of the bone sarcoidosis cohort.

Characteristics of the bone sarcoidosis subgroup

Of the 46 patients with bone sarcoidosis, 27 (58.7%) were female. The mean age of the cohort was 49,7 ± 12,2 years at diagnosis. Baseline pulmonary function tests were within normal limits. Evaluation of bone metabolism revealed a moderate reduction in serum 25-hydroxyvitamin D [25(OH)D] levels, with a mean value of 20.2 ± 11.9 ng/mL. In contrast, levels of activated vitamin D (1,25-dihydroxyvitamin D), serum calcium, and 24-hour urinary calcium excretion were within the normal range. Among the patients with bone involvement, 7 individuals (15.2%) had a prior diagnosis of osteoporosis confirmed by Dual-Energy X-ray Absorptiometry (DEXA), while 6 patients (13.0%) had a diagnosis of osteopenia. Baseline demographic and clinical characteristics of the bone sarcoidosis subgroup are reported in Table S1. In this subgroup, the most frequently observed extra-pulmonary localizations were cutaneous and systemic lymph node involvement. Notably, a statistically significant association was observed between bone sarcoidosis and the presence of extra-thoracic lymphadenopathy, as well as hepatic and splenic involvement (Table 3, $p < 0.001$). A highly significant correlation was found between bone involvement and hepatic, splenic, and concurrent hepato-splenic disease ($p < 0.001$). After false discovery rate correction using the Benjamini–Hochberg procedure, the associations between bone involvement and liver involvement, spleen involvement, and the composite hepatosplenic involvement (defined as liver and/or spleen involvement), as well as extra-thoracic lymphadenopathy and the overall burden of extra-thoracic involvement, remained statistically significant, whereas no other organ localizations showed significant associations. In multivariate logistic regression analysis adjusting for sex, smoking status, disease duration, and referral center, hepatosplenic involvement emerged as a strong independent predictor of bone sarcoidosis (odds ratio [OR] 8.17, 95% confidence interval [CI] 2.80–23.87; $p < 0.001$). Disease duration showed a non-significant trend toward association with bone involvement (OR 1.03 per year, 95% CI 0.99–1.07; $p = 0.158$). Sex, smoking status, and referral center were not significantly associated with the presence of bone disease. These findings confirm that the association between bone involvement and hepatosplenic disease persists after adjustment for potential confounders, supporting the systemic nature of sarcoidosis with clustered organ involvement. In terms of clinical presentations in this subgroup, 28.26% of subjects (13 patients) reported arthralgia or bone pain during medical evaluation. However, bone sarcoidosis was determined to be the cause in only 23.07% of these instances, frequently without a clear correlation in terms of pain localization.

Table 3. Sarcoid localizations in the overall population, comparison between patients with and without bone involvement

	Bone localization (n=46)	No bone localization (n=821)	p-value
Extra-thoracic lymph nodes	39	86	<0.001
Intra-thoracic lymph nodes	34	583	0.648
Lung	38	656	0.714
Heart	3	34	0.960
Skin	8	166	0.741
Eyes	0	33	0.327
Central nervous system	0	14	0.528
Kidney	0	5	0.771
Spleen	15	56	<0.001
Liver	15	43	<0.001
Liver and Spleen	11	29	<0.001
Mean number of extra-thoracic localizations	2.74	0.56	<0.001

Extra-thoracic involvement

In addition to bone involvement, various extra-thoracic organ manifestations were observed in this subgroup (Table 3). The most frequently affected site was the lymphatic system, with lymph node involvement documented in 39 patients (84.8%). Hepatic and splenic involvement were each identified in 15 patients (32.6%), while cutaneous manifestations were observed in 9 patients (19.6%). Cardiac sarcoidosis was present in 5 patients (10.9%). Notably, no cases of ocular, renal, or central nervous system involvement were detected in this subgroup. A substantial proportion of patients (n = 20; 43.5%) presented with multiple concurrent extra-thoracic localizations. These most involved combinations of lymph nodes, liver, and spleen. Specifically, 11 patients exhibited simultaneous involvement of all three sites, while 9 patients had dual involvement of lymph nodes with either the liver (n = 4) or the spleen (n = 5).

Bone localizations in sarcoidosis

Among our patients, PET analysis showed that the most frequent bone localizations were in the axial skeleton (Figure 2), primarily involving the pelvis and vertebrae, which were affected in over half of the cohort (Table 4).

Six patients (13,0%) had involvement of the ribs. Additionally, 5 patients (10.9%) presented with scapular involvement, and another 5 patients exhibited sternal involvement. Long bone involvement, specifically of the humerus and femur, was found in 4 patients (8,7%). The lowest prevalence of the disease was observed in the skull**,** olecranon, and hand.

Treatment strategies at diagnosis

At the time of diagnosis, monotherapy was initiated in 32 patients (69.6%). Among these, 26 patients (56.5%) received corticosteroid therapy, while 6 patients (13.0%) were treated with methotrexate alone. Combination therapy, consisting of corticosteroids and additional immunosuppressive agents, was administered to 14 patients (30.4%). Of those receiving combination treatment, 13 patients were prescribed corticosteroids in conjunction with immunosuppressants, primarily methotrexate, and in one case, azathioprine. One patient was treated with a combination of corticosteroids and a biologic drug, specifically infliximab. The number of organ localizations was the primary factor influencing the initiation of combination therapy (p = 0.046). Other clinical features, including pulmonary involvement, did not significantly affect treatment choice. The mean initial dose of prednisone was 35.5 ± 15.7 mg/day, with a mean duration of corticosteroid therapy of 28.6 ± 16.7 months.

Table 4. Bone localizations of sarcoidosis lesions

	N (%)
Axial skeleton	
Pelvis	25 (54,3)
Vertebrae	24 (52,2)
Rib	6 (11,03)
Scapula	5 (10,9)
Sternum	5 (10,9)
Peripheral skeleton	
Humerus	4 (8,7)
Femur	4 (8,7)
Skull	2 (4,5)
Olecranon	1 (2,2)
Hands	1 (2,2)

Follow-up and treatment response assessment

At one-year follow-up, PET was available in 23 patients. All patients were receiving active treatment at the time of follow-up imaging; specifically, 16 patients were treated with oral corticosteroids alone, while 7 patients were receiving combination therapy with oral corticosteroids and methotrexate.

All patients undergoing follow-up PET/CT had received oral prednisone as first-line therapy, with a comparable initial dose across the cohort (mean initial dose 33.4 ± 14.3 mg/day). Follow-up PET/CT was performed after treatment initiation, typically within the first year, with variability in both the duration and tapering of corticosteroid exposure reflecting routine clinical practice. At this time point, 13 (56.5%) showed a reduction in Standardized Uptake Value (SUV) levels at the site of bone involvement, whereas in 10 cases,

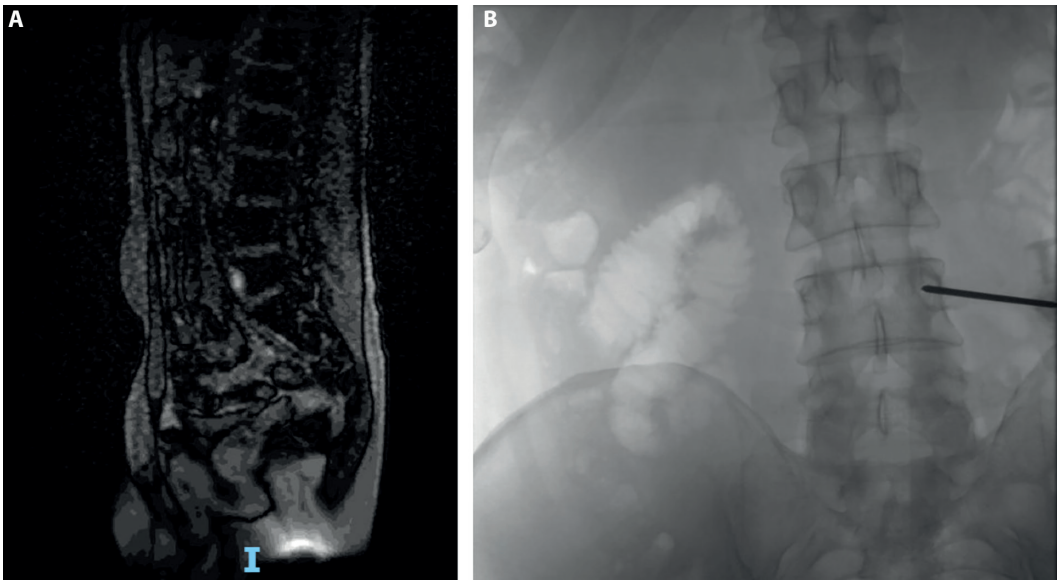

Figure 2. Representative imaging of axial bone sarcoidosis. (A) Magnetic resonance imaging showing focal bone marrow involvement of the lumbar spine, characterized by altered signal intensity consistent with granulomatous infiltration. (B) Fluoroscopic (X-ray–guided) image obtained during percutaneous bone biopsy, illustrating needle positioning at the site corresponding to the MRI-detected lesion. Histological examination confirmed non-caseating granulomas consistent with sarcoidosis.

SUV remained unchanged or increased. Given the limited sample size, no significant differences were observed in SUV changes between different bone locations or between monotherapy and combination therapy groups (p=0.776). These results should be interpreted with caution, particularly in light of the small number of patients receiving combination therapy and the descriptive nature of the follow-up analysis. Furthermore, the number of extra-thoracic manifestations did not correlate with the response to therapy (p=0.153). Pulmonary function tests performed at follow-up did not show significant differences compared with baseline values, and changes in pulmonary function were not associated with reductions in SUV at bone lesions.

Discussion

Sarcoidosis is a systemic granulomatous disease of unknown etiology, characterized by the formation of non-caseating granulomas. Bone involvement is relatively uncommon, with a reported prevalence ranging from 3% to 13%, depending on the diagnostic methods employed (12). In our study, bone involvement was observed in 5.3% of patients, a rate consistent with the findings reported by Wilcox et al. Although rare, osseous sarcoidosis represents a clinically relevant and potentially underdiagnosed condition, particularly in patients with atypical or persistent musculoskeletal symptoms, warranting careful diagnostic evaluation. In our cohort, osseous manifestations were predominantly localized to the axial skeleton, particularly the pelvis and vertebrae. This pattern aligns with the findings of Sparks et al. and Hassine et al., who similarly identified the axial skeleton as the most frequently affected site, with less frequent involvement of the long bones and small bones of the hands (6,22). Our observation of fewer cases involving the ribs, scapulae, and sternum, and limited peripheral skeletal involvement, further corroborates existing literature (9). Nevertheless, some discrepancies remain in the reported frequency of skeletal segment involvement, indicating a need for further standardization of imaging-based diagnostics. Exclusive skeletal involvement in sarcoidosis is extremely rare. Consistent with literature, we did not observe any cases of isolated bone sarcoidosis in our cohort. Only

one case of isolated bone sarcoidosis was found in the literature (23), supporting its usual occurrence as part of systemic disease. A particularly noteworthy finding in our study is the statistically significant association between bone involvement and hepatic and splenic localizations. This supports the observations made by Zhou et al. (9) and should be interpreted within the broader framework of sarcoidosis as a systemic inflammatory disorder characterized by clustering of organ involvement rather than as a distinct clinical phenotype. Rather than defining a specific hepatosplenic–osseous phenotype, this association may reflect a shared inflammatory and immunological background predisposing to multisystem granulomatous activity. Several studies have suggested a correlation between splenic and osseous involvement in sarcoidosis, due to an increased systemic propensity for granulomatous inflammation, with preferential involvement of organs rich in reticuloendothelial tissue. In this context, chronic systemic inflammation, immune dysregulation, and immune–metabolic alterations may contribute to the parallel involvement of liver, spleen, and bone. In addition, prolonged corticosteroid exposure may further modulate skeletal involvement, as highlighted by recent literature addressing systemic comorbidities in sarcoidosis (24). Bone involvement in sarcoidosis, although relatively uncommon, typically occurs in the context of a more disseminated and chronic disease, frequently associated with hepatosplenic and extrathoracic lymph node involvement (4,22). Since bone lesions are almost invariably asymptomatic, their detection often relies on imaging rather than clinical presentation. Accordingly, skeletal involvement should be considered part of the overall systemic disease burden, particularly in patients with evidence of extra-pulmonary dissemination (25,26). In line with Baughman's work, our results highlight the importance of further investigating patterns of multisystem involvement to better understand its clinical implications and guide management strategies. Bone mineral density abnormalities were also common, with osteoporosis and osteopenia diagnosed in 15.2% and 13% of patients, respectively. This is consistent with prior studies reporting increased risk of bone fragility in sarcoidosis, likely due to both chronic inflammation and long-term corticosteroid therapy (8,27). From a therapeutic perspective, corticosteroid monotherapy was the most frequently employed first-line treatment (56.5%), in keeping with current clinical practice. Methotrexate was primarily used as a steroid-sparing agent in patients with more extensive disease, in accordance with existing recommendations (28). The observed correlation between the use of combination therapy and the number of organs involved supports the treatment approach advocated by Baughman et al., who recommend more aggressive therapy in cases of multi-organ involvement (4). At one-year follow-up, PET/CT imaging showed an overall reduction in Standard Uptake Value (SUV) at bone sites in only 56.5% of cases, with no significant differences between patients treated with steroid monotherapy and those receiving combination therapy. These findings are consistent with previous reports describing heterogeneity in metabolic response to treatment (11,25). Moreover, changes in SUV did not correlate with the number of affected organs. The absence of a relationship between improvements in pulmonary function and reductions in bone SUV suggests that osseous sarcoidosis may follow a clinical and metabolic course that is at least partially independent from pulmonary disease activity. This highlights the potential value of PET/CT imaging for evaluating extra-pulmonary involvement in patients with mild to moderate pulmonary disease, and for detecting subclinical skeletal involvement that might go unnoticed using standard pulmonary metrics (10,25). Interpretation of treatment effects requires caution. Although all patients received systemic corticosteroids as first-line therapy, with comparable initial doses, a detailed assessment of cumulative corticosteroid exposure and tapering schedules was beyond the scope of this retrospective analysis. Variability in treatment duration and dose reduction reflects routine clinical practice and may have influenced both bone metabolism and metabolic response on PET/CT. In addition, the use of bone-protective agents such as bisphosphonates or denosumab was not systematically collected and could not be reliably analyzed. These therapies may modulate bone turnover and mineral density independently of sarcoid-related inflammation, potentially confounding the relationship between treatment, bone metabolism, and imaging outcomes. Accordingly, the lack of significant differences in metabolic response between corticosteroid monotherapy and

combination therapy should be interpreted with caution, particularly given the limited sample size of the follow-up cohort and the descriptive nature of the analysis. Larger prospective studies with standardized treatment protocols and comprehensive assessment of bone-directed therapies are warranted to better clarify treatment effects on osseous sarcoidosis. The strengths of this study include being the largest multicenter Italian study—and one of the largest internationally—specifically focusing on bone involvement in sarcoidosis, providing valuable insights into disease behavior, localization patterns, and treatment response within the context of a multisystem disorder. However, several limitations must be acknowledged. The retrospective design introduces potential selection bias and limits the ability to infer causal relationships. Incomplete or missing clinical data may also have influenced the analysis of associations between clinical features, metabolic findings, and therapeutic outcomes. As the study was conducted at tertiary referral centers, a referral bias toward patients with more complex or multisystem disease cannot be excluded. In addition, imaging interpretation was performed locally as part of routine clinical practice and was not centralized, and PET/CT assessment was qualitative, without standardized SUV cut-off values or formal inter-reader concordance assessment. In conclusion, our findings confirm that osseous sarcoidosis, though relatively uncommon, is a clinically significant manifestation frequently associated with multi-organ involvement—particularly in the liver, spleen, and extra-thoracic lymph nodes—and a clear predilection for the axial skeleton. These results further support the concept of sarcoidosis as a multisystem inflammatory disorder characterized by clustering of organ involvement rather than isolated phenotypes. Given its potential for underdiagnosis, especially in asymptomatic patients, bone sarcoidosis requires comprehensive clinical, laboratory, and imaging assessment. Accordingly, optimal diagnostic and therapeutic management should rely on a multidisciplinary approach involving pulmonology, internal medicine, radiology, nuclear medicine, and metabolic expertise, in line with emerging models that frame sarcoidosis as a complex multisystem disorder requiring integrated and patient-centered care rather than an organ-specific approach (29). Personalized treatment strategies and close radiological monitoring are essential for effective management and follow-up. Continued efforts to collect and characterize this patient population will be crucial in refining diagnostic pathways and optimizing therapeutic approaches. Ultimately, a better understanding of this disease pattern will support the development of more tailored, evidence-based care strategies and improve clinical outcomes for patients with systemic sarcoidosis.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Annex

Table S1. Demographic and clinic characteristics of the Bone Sarcoidosis Cohort at the baseline

	N (%) or mean (SD)
Demographics	
Gender F/M	27 (58,7%) / 19 (41,3%)
Age, years	49,7 (12,2)
BMI, kg/m2	26,5 (4,78)
Smoking habit	
Current smoker	3 (6,7%)
Ex smoker	17 (37,8%)
Not smoker	26 (56,5%)
Ethnicity	
Caucasian	41 (89.1%)
North African *Central African* *South American*	3 (6,5%) 1 (2.2%) 1 (2.2%)
Scadding radiographic scale	
Stage 0	1 (2.2%)
Stage 1	3 (6.5%)
Stage 2	34 (73.9%)
Stage 3	5 (10.9%)
Stage 4	3 (6.5%)
mMRC	
Stage 0	14 (38.9%)
Stage 1	15 (41.7%)
Stage 2	4 (11.1%)
Stage 3	3 (8.3%)
Stage 4	0
PFTs	
FEV1%	90.3 (17)
FVC %	99 (16.4)
DLCO %	83.22 (17.19)
Vitamin D and Calcium metabolism (n = 23)	
25OH-Vitamin D, ng/ml	20,2 (11,9)
1-25OH-Vitamin D, pg/ml	42.4 (25.6)
Serum calcium levels, mg/dl	8.4 (1.9)
24h urinary calcium, mg/24h	155 (142)
Comorbidities	
Cardiovascular disease	12 (26%)
Arterial Hypertension	12 (26%)

	N (%) or mean (SD)
Autoimmune thyroiditis	4 (8.7%)
Diabetes	8 (17.4%)
Cancer (in the last 10 years)	3 (6.5%)
Bone disorders	
No	33 (71.7%)
Osteoporosis	7 (15,2%)
Osteopenia	6 (13,0%)