Disease activity in patients with synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome: the utility of the SPARCC MRI scoring system for assessment of axial spine involvement

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Abstract

Objective

The aim of this study is to investigate the relationship between spinal MRI findings with disease activity and other clinical and serological parameters, and to determine the importance of MRI scoring system in evaluating disease activity of SAPHO syndrome.

Methods

Thirty patients with SAPHO syndrome underwent clinical, laboratory and MRI evaluation at baseline, 3 months, 6 months and 1 year. Magnetic resonance images were analysed using modified Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system. Correlations between MRI score and clinical and laboratory parameters were analysed using Spearman's rank correlation test.

Results

Persistent improvement was observed after 12 months in terms of total modified SPARCC scores (37(12,59) vs. 23(5,45) at baseline and 12 months, $p<0.05$). Total modified SPARCC scores showed Spearman correlations with hypersensitive C-reaction protein (hs-CRP), ankylosing spondylitis disease activity score (ASDAS) and bath ankylosing spondylitis metroloty index (BASMI) at baseline, 3 months, 6 months and 12 months (p varied from <0.001 to <0.05, and r varied from 0.418 to 0.601). Modified SPARCC scores of spine joint, as the largest contribution to the total scores with the mean score of 12(5,30) after 12 months vs. 26 (12,40) at baseline.

Conclusion

The modified SPARCC score proposed in this study exhibits promising potential in the evaluation of extensive radiographic damage in SAPHO and the reflection the disease activity. Our study suggests that MRI could be used together with other parameters of disease activity in the assessment of symptomatic SAPHO patients with spine involvement.

Key words

synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome, magnetic resonance imaging, spinal inflammation, disease activity

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Introduction

The association of bone disease and chronic cutaneous pustular lesions has been observed since the 1960s, but it was not identified until Chamot *et al.* (1) in 1987 first used the acronym SAPHO to describe this rare group of chronic, relapsing, and inflammatory osteoarticular disorders which was commonly associated with skin manifestations. To date, SAPHO syndrome is considered a rare disease, but the real prevalence could be underestimated because it is often misdiagnosed due to sharing clinical features with several other disorders, such as infectious discitis, seronegative spondyloarthritis (SpA), and psoriatic arthritis (PsA) (2, 3).

The fundamental osteoarticular manifestations of the SAPHO spectrum include synovitis, hyperostosis, osteitis, arthropathy, and enthesopathy, with or without skin lesions. The main target sites are the anterior chest wall, spine, and peripheral skeleton (4). Abnormalities in spine could be found in all ages, including 32–52% adult patients (5). The pain and stiffness of spine, usually localised and chronic, may result in substantial functional limitations and seriously impair the patients' quality of life. Despite the imperative need for treatment from patients, there is no standard treatment procedures for SAPHO syndrome because of the unknown aetiopathology (6, 7).

It is difficult to evaluate the abnormalities of spine early and accurately on conventional radiographs and CT since they only show the erosions and underlying subchondral sclerosis. However, though magnetic resonance imaging (MRI), doctors could visualise most of the osteoarticular changes especially spinal inflammation of SAPHO, and thus MRI suits for assessing disease activity and therapeutic response even in the early stage of the disease (4). Magnetic resonance imaging scoring systems such as ankylosing spondylitis spine magnetic resonance imagine -activity (ASspiMR-a), the Berlin modification of the ASspiMR-a and the modified Spondyloarthritis Research Consortium of Canada (SPARCC) index have been developed to evaluate inflammatory activity of the spine in patients with ankylosing spondylitis (8). However, a scoring system of MRI used in SAPHO syndrome for better evaluating the lesions in spine is still absent, and it is needed to determine disease activities of SAPHO patients because of the inconsistency between laboratory tests and clinical findings and imaging.

Thus, the aim of this study is to use modified MRI scoring systems assessing the spinal inflammation and explore the relationship between MRI and disease activity and the other outcome parameters.

Materials and methods

Patients

Patients who met the criteria for SAPHO syndrome proposed by Nguyen in 2012 (9) were recruited in Peking Union Medical College Hospital in 2015. Data of the patients presented is that of patients taking part in an open-label clinical trial (Identifier: NCT02544659). Inclusion criteria were as follows: male and female patients between the ages of 18 and 70 years; MRI showed bone marrow edema in affected sites in patients; blood serum tests showed normal white blood cell count, liver and renal function; patients were willing to be followed up for 1 year. The exclusion criteria were as follows: women in pregnancy or lactation; septic osteomyelitis; infectious chest wall arthritis; infections palmoplantar pustolosis (PPP); palmoplantar keratodermia; diffuse idiopathic skeletal hyperostosis (DISH) except for fortuitous association; osteoarticular manifestations of retinoid therapy. The Ethics Committee of Peking Union Medical College Hospital (PUMCH) approved this trial (Identifier: ZS-944). Patients were administered intravenously with pamidronate 1 mg/kg/d, for 3 consecutive days, and treated the same way again three months later.

Clinical evaluation

All patients' medical data were collected including age, gender, onset and course of dermatological and osteoarticular manifestation, age at onset of symptoms and SAPHO diagnosis. For outcome measures, we evaluated Bath

Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Metrology Index (BASMI), VAS (visual analogue scale, 0–10), AS Disease Activity Score (ASDAS). Laboratory evaluation including erythrocyte sedimentation rate (ESR, mm/hour) and hypersensitive C-reactive protein (hs-CRP, mg/dl) were recorded.

MRI evaluation

All patients underwent 4 times MRI scans at baseline, 3 months, 6 months and 12 months separately. MRI examinations of the whole spine and sacroiliac joints were performed using a 3.0T scanner (Skyra, Siemens Healthcare, Erlangen, Germany) with standardised MRI scanning protocol parameters. The whole spine MRI was examined respectively in three different segments, including cervical spine, thoracic spine and lumbosacral spine regions. The following sequences were obtained: T1-weighted imaging (T1WI), T2-weighted imaging (T2WI) and fat-saturation Dixon sequences. MR images of sacroiliac joints were acquired in a coronal oblique plane (parallel to the long axis of the sacrum) with the following sequences: T1WI, T2WI, T2-weighted turbo inversion recovery magnitude (T2-weighted TIRM), T2-weighted two-dimensional fast low angle shot (T2-weighted 2D FlASH). Sequence parameters were (1) T1-weighted spin-echo (time to recovery [TR], 450.0 ms; time to echo [TE], 9.0 ms; field-of-view [FOV], 220 mm; and slice thickness, 3 mm) . (2) TIRM (TR 2, 000 ms; TE, 11.0 ms; [FOV], 260 cm; and slice thickness, 3 mm). (3) 2D-FLASH (TR 501.0 ms; TE, 20.0 ms; [FOV], 260 cm; and slice thickness, 3 mm). MRI images were scored by two radiologists blinded to the patients and reached consensus through discussion when separate results were controversial.

Magnetic resonance images were analysed using the SPARCC scoring system as the entire spine and bilateral sacroiliac joints were evaluated for inflammation. The existing SPARCC scoring system were modified in this study according to the specific clinical feature of SAPHO syndrome.

Modified SPARCC scoring method on spine

The entire spine was evaluated for inflammation. All affected disco-vertebral units (DVU) are scored rather than only the 6 most severely affected DVU. This principle was based on our previous study demonstrating that the median number of affected DVU was 7. For each detected lesion 3 consecutive sagittal slices were assessed in order to evaluate the extent of inflammation in all 3 dimensions. The presence of an increased STIR signal in each of the quadrants was scored on a dichotomous basis (1: presence; 0: absence) and repeated for each of the 3 consecutive sagittal slices. The presence, on each of the sagittal slices, of a lesion exhibiting high signal intensity (comparable to cerebrospinal fluid) in any DVU was given an additional score of 1. A similar additional score is added in case of a lesion with a continuous depth of ≥1 cm extending from the endplate. This brought the maximal score for a single DVU to 18.

SPARCC scoring method on sacroiliac joint

Each sacroiliac (SI) joint was divided into 4 quadrants: upper iliac, lower iliac, upper sacral, and lower sacral. The presence of increased signal on STIR in each of these 4 quadrants was scored on a dichotomous basis, where 1 = increased signal and 0 = normal signal. The maximum score for abnormal signal in the 2 SI joints of 1 coronal slice was therefore 8. Joints that included a lesion exhibiting intense signal were each given an additional score of 1 per slice that demonstrated this feature. Similarly, each joint that included a lesion demonstrating continuous increased signal of depth ≥1 cm from the articular surface was also given an additional score of 1. This brought the maximal score for a single coronal slice to 12. The scoring was repeated in each of the 6 consecutive coronal slices leading to a maximum score of 72. The total SPARCC score is the sum of SPARCC SI and SPARCC spine.

Statistical analysis

Data analysis was performed using SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL, United States). The data were expressed as mean ± SD and (minimum–maximum) for continuous data and medians (interquartile range) for discrete numerical variables. The distributions of continuous variables were determined using Shapiro-Wilk test. Levene test was used for the evaluation of homogeneity of variances. The median differences of variables between groups were compared by Wilcoxon matched-pairs signed-ranks test. Friedman test was applied for independent groups with the number of more than two. Degrees of associations between variables were evaluated by Spearman's rank correlation test. A *p*-value less than 0.05 was considered statistically significant.

Results

Clinical manifestations

Thirty patients (21 women and 9 men) with bone marrow edema fulfilled one-year follow-up were included in the study. The mean age diagnosed and onset of symptoms were 47.71 and 42.37 years old, respectively. There was a delay of 4.62 years between the start of complaints and the diagnosis of SAPHO. Most of the patients (29/30) had skin manifestation of palmoplantar pustolosis. Overall, 96.7% (29/30) of patients were taking non-steroidal anti-inflammatory drugs (NSAIDs). Of these patients, 36.7% (11/30) had previously tried glucocorticoids, 20.0% (6/30) had taken disease-modifying anti-rheumatic drugs (DMARDs). 4 patients (13.3%) had received TNF-α inhibitor before the study. No patient was HLA B27 positive. Details of demographic characteristics of this cohort are shown in Table I.

Disease activities and MRI changes of patients

Table II shows the clinical and biochemical inflammatory markers of the subjects at baseline, 3, 6, 12 months. CRP were 11.8 (SD, 10.19) mg/l, 8.7 (SD, 13.14) mg/l, 5.0 (SD, 5.20) mg/l, and 5.8 (SD, 5.88) mg/l, respectively and ESR were 29.8 (SD, 26.59) mm/hour,

Table I. Demographic and clinical properties of the patients.

Variables	n=30
Demographic characteristics	
Gender (female/male) n (%)	21 (70)/9 (30)
Age (year) (mean±SD, min-max)	47.17 ± 8.79 (28-62)
Age at onset of symptoms, mean (SD), years	42.37 (10.20)
Duration of diagnosis, mean (SD), years	4.62 (6.12)
Clinical characteristics	
Skin manifestations	
PPP	29/30 (96.7%)
SA	1/30 (3.3%)
PV	4/30 (13.3%)
Previous treatment	
NSAIDs	29/30 (96.7%)
Glucocorticoids	11/30 (36.7%)
DMARDs	6/30 (20.0%)
TNF-α inhibitor	4/30 (13.3%)
Diphosphonate	3/30 (10.0%)
Antibiotics	4/30 (13.3%)
None	1/30 (3.3%)
HLA-B27	**0/30 (0)**

PPP: palmoplantar pustolosis; PV: psoriasis vulgaris; SA: severe acne; NSAID: non-steroidal anti-inflammatory drug; DMARDs: disease-modifying anti-rheumatic drugs.

20.5 (SD, 16.81) mm/hour, 18.5 (SD, 14.32) mm/hour, and 18.0 (SD, 18.65) mm/hour. Other laboratory assessment of inflammation as determined by alkaline phosphatase, immunoglobulin A, ferritin, gamma GT, aspartate aminotransferase (AST) and platelets were all within the normal range.

The median total modified SPARCC scores at baseline, 3, 6, 12 months were 37(12,59), 33(10,61), 24(6,52), and 23(5,45), with spine joint showing the highest mean modified SPARCC level rather than sacroiliac joint. At baseline, 53.3% (16/30) patients got zero points at SPARCC sacroiliac joint. The median changes in scores between baseline and 3-, 6-, 12-month follow-ups of all patients were -5, -7, -14 in the spine score, and -4, -13, -14 in total score; changes between baseline and 12 months, 3 months and 12 months were significant. (p<0.05). Reduction in total score was seen in 24 (80%) patients (Fig. 1).

Correlation between disease activities and MRI

BASMI, which includes the chest expansion, occiput-wall distance, cervical anteflexion, cervical retroflextion, cervical rotation, cervical lateral flexion, lumbar flexion index, and lumbar lateral flexion, showed spearman's correlations with modified SPARCC-spine joint scores and modified SPARCC-total scores at 3-, 6-, 12 months (p-value <0.01) (Table III).

Total modified SPARCC score shows Spearman correlations with hs-CRP (all p<0.05), ASDAS (p<0.001, p<0.05, p<0.01 and p<0.005, respectively) at baseline, 3 months, 6 months and 12 months. Modified SPARCC spine joint were correlated with hs-CRP (p<0.001, p<0.05, p<0.01 and p<0.05, respectively), ASDAS (p<0.001, p<0.05, p<0.01 and p<0.01 respectively) at base line, 3-, 6-, 12 months. The correlations between modified SPARCC scores and clinical parameters are shown in Table III.

Discussion

SAPHO syndrome is a rare disease usually involving abnormalities of anterior chest wall, spine and sacroiliac joints, which bring great heavy economic pressure and care burden to the patients (10). At the meantime, because of the small size of SAPHO syndrome cohort and the lack of comprehensive understandings of relations among laboratory, imaging and clinical findings, there is no standard method to evaluate the disease activity and it is hard difficult to assess the effectiveness of drugs in abnormalities of spine and sacroiliac joints systematically (11-14).

Table II. Laboratory and clinical parameters and modified SPARCC score.

	Baseline	3 months	6 months	12 months
ESR (mm/hour), mean (SD)	29.8 ± 26.59	20.5 ± 16.81	18.5 ± 14.32	18.0 ± 18.65
hs-CRP (mg/dl), mean (SD)	11.8 ± 10.19	8.7 ± 13.14	5.0 ± 5.20	5.8 ± 5.88
VAS	6 (5,7)	3 (3,6)	3 (2,3)	2 (2,3)
BASDAI	3.92 (2.69,5.54)	2.73 (1.80,4.90)	1.90 (1.28,2.93)	2.05 (1.38,2.8.0)
BASFI	3.4 (1.3,4.9)	1.6 (1.1,3.0)	1.0 (0.4,2.1)	1.0 (0.3,1.9)
BASMI	2 (1,3)	1 (0,2)	0 (0,1)	0 (0,1)
ASDAS	2.65 (2.38,3.4.0)	2.15 (1.40,2.80)	1.60 (1.20,1.98)	1.70 (1.13,2.13)
modified SPARCC-spine joint	26 (12,40)	21 (10,42)	19 (6,39)	12 (5,30)
SPARCC-sacroiliac joint	0 (0,20)	0 (0,15)	0 (0,17)	0 (0,12)
modified SPARCC-total	37 (12,59)	33 (10,61)	24 (6,52)	23 (5,45)

The data (ESR, hs-CRP) was shown as median± SD. The discrete data (VAS, BASDAI, BASFI, BASMI, ASDAS, SPARCC) was shown as median (interquartile).

ESR: erythrocyte sedimentation rate (normal range: 0-10 mm/hour); hs-CRP: hypersensitive-C-reactive protein (normal range: 0-3 mg/dl); VAS: visual analogue scale; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; ASDAS Ankylosing Spondylitis Disease Activity Score; modified SPARCC: modified Spondyloarthritis Research Consortium of Canada.

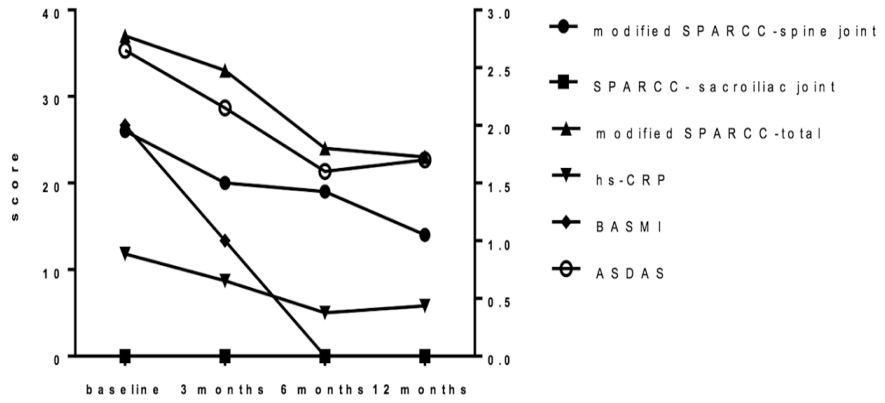

Fig. 1. Radiographic and clinical changes from weeks 0 to 12 months for all patients.

Therefore, the clinical and laboratory examination scores, such as VAS, BASDAI, BASFI and acute-phase reactants as well as ASDAS and MRI used in the similar disease studies like ankylosing spondylitis, are applied in the evaluation of patients with SAPHO syndrome with spine and/or sacroiliac joint involvement (6, 7). However, there are also some researches showing that BASDAI score does not represent the level of inflammatory activity in AS patients, proposing that the role of the therapeutic effects of monitoring drugs is questionable for clinical trials (12). In our cohort, patients whose BASDAI score more than four performed better on MRI than the remaining patients who had BASDAI less than four. This inconsistent relationship between MRI findings and BASDAI could be related to the inability of BASDAI to discriminate between inflammatory and mechanical low back pain (15). Therefore, recent studies attempted to use MRI semi-quantitative scores instead of those subjective clinical scores for disease assessment (13, 16, 17).

There are three different methods for scoring spinal inflammatory lesions of AS patients detected by MRI: Ankylosing spondylitis spine MRI-active (ASspiMRI-a) method, the Berlin method (modified ASspiMRI-a) and the SPARCC method. According to test results on different aspects of discrimination and feasibility, SPARCC method consistently showed higher intraclass correlation coefficient (ICC) and increased consistency in ICC values between different reader pairs than ASspiMRI-a method and Berlin method, confirming previous proposals that the SPARCC is the most reliable method to evaluate the spine lesion in MRI (8, 18). We modified the method and changed the amount of scored DVU to all affected DVU rather than the 6 most severely affected DVU according our observation of the 30 patients. This report presents the first systematic analysis of inflammatory and structural spinal changes as assessed by MRI in patients with SAPHO using a scoring system developed with the MRI technique.

Acute-phase reactants like ESR and CRP are valuable in diagnosis and follow-up, so they are widely used in clinical work. However, in our former cohort study of 164 patients with SAPHO, almost half of the patients who complained of an obvious progression of symptoms did not have elevated ESR and CRP (6, 19, 20). In contrast, 70.8% of patients had an increased hs-CRP level, suggesting that hs-CRP may be a better parameter to monitor the disease activity than ESP or CRP (6) In this study, modified SPARCC-spine joint scores and modified SPARCC-total scores showed positive correlations with hs-CRP, with correlation coefficients varying from 0.42 to 0.57 which indicated the MRI lesion may be associated with systematic inflammation.

The modified SPARCC-total scores also showed positive correlations with ASDAS, and correlation coefficients varied from 0.39 to 0.64. As an analogue of DAS 28 in RA, ASDAS is the first confirmed disease activity index that combines patients' response with the acute-phase reaction (21, 22). The present study, the first time, utilised ASDAS to evaluate the disease activity in SAPHO and observed a favorable correlation between ASDAS and modified SPARCC total score. Furthermore, the spine-scores and sacroiliac joint-scores were analysed separately, and the final

Table III. The correlation between modified SPARCC scores and clinical parameters.

Variables	modified SPARCC-total				modified SPARCC-spine joint				SPARCC-sacroiliac joint			
	Base line	3 months	6 months	12 months	Base line	3 months	6 months	12 months	Base line	3 months	6 months	12 months
ESR	0.328	0.256	0.303	0.476**	0.357	0.279	0.287	0.510**	0.218	0.128	0.269	0.3
hs-CRP	0.476**	0.418*	0.468**	0.443*	0.567***	0.444*	0.518**	0.421*	0.033	0.093	0.141	0.152
VAS	0.305	0.308	0.345	0.471**	0.251	0.208	0.325	0.418*	0.249	0.304	0.168	0.175
BASDAI	0.206	0.36	0.249	0.416*	0.217	0.232	0.219	0.396*	0.094	0.354	0.218	0.117
BASFI	0.073	0.419*	0.196	0.315	0.063	0.277	0.141	0.27	0.172	0.483**	0.392*	0.274
BASMI	0.115	0.583***	0.495**	0.527**	0.253	0.530**	0.537**	0.556**	0.111	0.441*	0.209	0.089
ASDAS	0.601***	0.457*	0.509**	0.447*	0.641***	0.387*	0.519**	0.406*	0.199	0.277	0.253	0.14

***p<0.001 **p<0.01 *p<0.05.

ESR: erythrocyte sedimentation rate; hs-CRP: hypersensitive - C-reactive protein; VAS: visual analogue scale, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; modified SPARCC: modified Spondyloarthritis Research Consortium of Canada.

results indicated that the clinical outcome measures had little effect on the sacroiliac joints but had significant influence on the spines, and the mean value of the score of spine was higher than the sacroiliac joints along the whole observed year. But in patients with other axial spondyloarthritis diseases, active inflammatory changes and structural damage generally arise in the sacroiliac joints first, so the MRI of the spine is not usually required for early diagnosis (23, 24). This may indicate that the MRI of spine might be considered as a useful tool to differentiate SAPHO patients and axial spondyloarthritis patients.

This group of patients with SAPHO syndrome shows that the modified SPARCC score have no obvious correlation with the following clinical scores, such as VAS, BASDAI, BASFI except BASMI. The possible reasons are as follows: 1) VAS, BASDAI and BASFI, which are based on the subjectivity of patients/doctors rather than laboratory results, are easily influenced by personal factors, and thus only roughly reflect the disease activities of patients. In this respect, VAS, BASDAI and BASFI were less accurate in the patients' evaluation compared with ASDAS, MRI semiquantitative scores, and the BASMI. 2) This study adopts the SPARCC semiquantitative MRI rating score of only bone marrow oedema. Other lesions such as bone destruction, bone bridge, toughening with osteophyte are not included, which are more likely to associate with the evaluation of spinal movement such as BASFI score. 3) The MRI only evaluates the spine and sacroiliac joints, while those clinical scores are used to assess the systemic lesions, such as the anterior chest wall.

As a result, in our study, the spine was the region most related to disease activity parameters and clinical outcome measures. Consequently, the current evaluation methods where sacroiliac joint and total MRI scores are taken into account might be inadequate for patients with SAPHO. We suggest using MRI evaluation of spine for patients with spine involvement to determine disease activity. The modified SPARCC score should be used in the evaluation of treatments such as bisphosphonate and anti-tumour necrosis factor agents. There are some limitations of this study. 1) The low number of patients examined is one of the limitations of the present research. 2) There is no suitable scoring system for anterior chest wall, though the anterior chest wall is the most typical and frequent axial involvement in in SAPHO.

For further study, there is a need to expand the sample size. The evaluation of spine could be separated into different segments such as cervical spine, thoracic spine and lumbar spine and at the same time involving the anterior chest wall. A cross-sectional study which compared histopathological findings with active lesions on MRI concluded that a substantial degree of bone marrow oedema was necessary for the detection by MRI (25). This indicates that MRI may not have 100% sensitivity in detecting all spinal inflammatory lesions. The modified SPARCC score should be validated further in long-term studies, with particular attention to other aspects of validity such as predictive validity and validation in respect of clinical variables.

Conclusion

The modified SPARCC score proposed in this study exhibits promising potential in the evaluation of extensive radiographic damage in SAPHO and the reflection of the disease activity. MRI could be used together with other parameters of disease activity in the assessment of symptomatic SAPHO patients with spine involvement.

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