ORIGINAL ARTICLE

Rheumatology Quarterly

DOI: 10.4274/qrheumatol.galenos.2025.36035
Rheumatol Q 2025;3(4):119-24

INVESTIGATION OF THE ROLE OF HISTOGRAM ANALYSIS IN THE DIFFERENTIAL DIAGNOSIS OF INFECTIOUS AND AXIAL SPONDYLOARTHRITIS-RELATED SACROILIITIS

Emine Yıldırım Uslu[1], Mustafa Yıldırım[2], Şafak Özer Balin[3], Gökhan Alkan[4], Arif Gülkesen[4], Gürkan Akgöl[4], Muhammed Fuad Uslu[5]

[1]University of Health Sciences Türkiye, Elazığ Fethi Sekin City Hospital, Clinic of Physical Medicine and Rehabilitation, Elazığ, Türkiye
[2]Fırat University Hospital, Department of Radiology, Elazığ, Türkiye
[3]Fırat University Hospital, Department of Infectious Diseases and Clinical Microbiology, Elazığ, Türkiye
[4]Fırat University Hospital, Department of Physical Medicine and Rehabilitation, Elazığ, Türkiye
[5]University of Health Sciences Türkiye, Elazığ Fethi Sekin City Hospital, Clinic of Internal Medicine, Elazığ, Türkiye

Abstract

Aim: It is not easy to differentiate *Brucella* sacroiliitis from axial spondyloarthritis (axSpA)-related sacroiliitis using conventional magnetic resonance imaging (MRI). Histogram analysis, a new technique, is considered useful for differential diagnosis. This study aimed to investigate the role of MRI histogram analysis in the differential diagnosis of *Brucella* sacroiliitis and axSpA-related sacroiliitis.

Material and Methods: This study included 25 patients with axSpA-related sacroiliitis and 25 patients with sacroiliitis secondary to brucellosis. Histogram analysis of the sacroiliac MRI images of the patients was performed on inflammatory areas detected on the T2 fat-suppressed sequence. Ten percent, 90 percent, entropy, kurtosis, maximum, mean, median, minimum, skewness uniformity, and variance values were measured. The values obtained were compared between the groups.

Results: There was a statistically significant difference between the 10 percent, median, and minimum values ($p=0.018$, $p=0.029$, $p=0.002$, respectively) and no difference between the other values ($p>0.05$ for all).

Conclusion: MRI histogram analysis appears promising as a potential complementary tool for differentiating *Brucella* sacroiliitis from sacroiliitis associated with axSpA; however, these findings are preliminary and require confirmation in larger studies.

Keywords: *Brucella* sacroiliitis, axial spondyloarthritis, sacroiliitis, histogram analysis

Address for Correspondence: Emine Yıldırım Uslu, MD, University of Health Sciences Türkiye, Elazığ Fethi Sekin City Hospital, Clinic of Physical Medicine and Rehabilitation, Elazığ, Türkiye
E-mail: e.yildirim9346@gmail.com **ORCID ID:** orcid.org/0000-0003-2613-8385
Received: 22.08.2025 **Accepted:** 20.10.2025 **Epub:** 27.10.2025 **Publication Date:** 26.11.2025

Cite this article as: Yıldırım Uslu E, Yıldırım M, Özer Balin Ş, et al. Investigation of the role of histogram analysis in the differential diagnosis of infectious and axial spondyloarthritis-related sacroiliitis. Rheumatol Q. 2025;3(4):119-24

INTRODUCTION

The sacroiliac joint (SIJ) is the largest joint of the axial skeleton and plays a key role in transferring loads between the lumbar spine and lower extremities (1). Sacroiliitis, defined as inflammation of the SIJ, may result from infectious, rheumatic, neoplastic, or metabolic causes (2). Acute sacroiliitis is most often infectious, whereas chronic sacroiliitis is usually associated with spondyloarthropathies, in which it represents an early and characteristic feature (3,4). Infectious sacroiliitis is uncommon, accounting for 1-4% of all bone and joint infections (5). While *Staphylococcus aureus* is the predominant pathogen, other agents such as *Salmonella, Brucella, Streptococcus pyogenes*, and *Mycobacterium tuberculosis* may also be responsible (6-10). *Brucellosis*, in particular, frequently involves the SIJ (11).

Magnetic resonance imaging (MRI) is the gold standard for diagnosing sacroiliitis, as it can detect early inflammatory changes in the SIJ (12). However, findings such as bone marrow edema (BME), enthesitis, capsulitis, and synovitis are not specific to axial spondyloarthritis (axSpA) and may also occur in infectious sacroiliitis (13). Distinguishing between infectious and axSpA-related sacroiliitis is crucial because their treatment approaches differ, and delayed diagnosis of infection may lead to morbidity (14). MRI characteristics, including extensive bone erosions, pronounced capsulitis, extracapsular fluid accumulation, and periarticular muscle edema are typically suggestive of infectious processes, while iliac-sided BME and enhancement of the joint space are more commonly associated with axSpA (15).

Digital images are employed in clinical practice for diagnostic purposes. Pixels make up a two-dimensional digital image, and each pixel's gray-level intensity is represented by a value (16). By assessing signal heterogeneity that is invisible to the human eye, histogram analysis of pictures can provide quantitative information about texture-based tissue features (17). The gray-level intensity histogram offers a straightforward and compact representation of the statistical characteristics within an image. It is derived from individual pixel values, which reflect first-order statistical properties of the image (15). Parameters such as the 10^{th} and 90^{th} percentiles, entropy, kurtosis, maximum, mean, median, minimum, skewness, uniformity, and variance are included in this analysis (17,18). This method enables a more objective evaluation and provides dependable data for distinguishing and classifying benign and malignant tumors (19).

Conventional MRI sequences provide important anatomical and structural information, but their interpretation often relies on subjective assessment and visual identification of inflammatory changes. This can make it challenging to differentiate between infectious and axSpA-related causes of sacroiliitis, particularly in early or ambiguous cases. Histogram analysis is a novel, quantitative imaging method that evaluates signal heterogeneity within a region of interest (ROI) by analyzing pixel intensity distribution. Unlike conventional interpretation, this method provides objective numerical values that may reflect underlying tissue characteristics not readily visible to the human eye. While histogram analysis has been explored in other musculoskeletal and oncologic conditions, to our knowledge, it has not yet been applied to the evaluation of sacroiliitis. In this study, we aimed to investigate whether histogram-based MRI analysis can contribute to the differential diagnosis of *Brucella* and axSpA-related sacroiliitis.

MATERIAL AND METHODS

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki after obtaining approval from the Fırat University Non-Interventional Research Ethics Committee (approval no: 17285, date: 20.07.2023). Informed consent was obtained from all participants.

Patient Selection

Medical records from January 2021 to January 2023 were reviewed. Twenty-five patients diagnosed with axSpA according to the Assessment of SpondyloArthritis International Society criteria, and 25 patients diagnosed with *Brucella* sacroiliitis based on positive serology (standard tube agglutination ≥1:160 or enzyme-linked immunosorbent assay positivity) and compatible clinical findings, were included. The inclusion was irrespective of whether *Brucella* species were isolated from blood culture.

Inclusion criteria were: age >18 years, Presence of sacroiliitis confirmed on MRI, diagnosis of axSpA or brucellosis according to the above criteria.

Exclusion criteria were: history of pelvic or spinal trauma, other causes of sacroiliitis (e.g., neoplasm, tuberculosis), inadequate image quality precluding histogram analysis.

To minimize bias related to inactive disease, only patients with active BME on T2 fat-suppressed (T2-FatSat) images were included. Patients with axSpA who had only chronic structural changes without active BME were excluded.

MRI Acquisition Protocol

All MRI scans were conducted on a 1.5 Tesla system using a dedicated pelvic phased-array coil (Philips Achieva, Philips Healthcare, Best, the Netherlands). The SIJ imaging protocol consisted of semi-oblique coronal T1-weighted sequences (TR/TE: 500/12 ms), semi-oblique coronal T2-weighted fat-suppressed

sequences (TR/TE: 3500/60 ms), and axial T2-FatSat sequences (TR/TE: 3500/60 ms). Images were obtained with a slice thickness of 4-mm, an interslice gap of 0.4-mm, a field of view of 320×320 mm, and a matrix of 320×256.

ROI Placement and Histogram Analysis

A musculoskeletal radiologist with five years of experience, musculoskeletal radiologist blind to the clinical diagnosis, performed histogram analysis on the semi-oblique coronal T2-FatSat images.

Anatomical boundaries: The ROI, was drawn freehand within the BME area for each patient, eliminating cortical bone, joint space, and periarticular soft tissue, and was rigidly limited to the subchondral bone marrow space. To preserve comparability with axSpA patients, the ROI was nevertheless limited to the subchondral region in *Brucella* sacroiliitis, even if edema occasionally went beyond the usual anatomical boundaries.

Changes in axSpA structure: The ROI was positioned to cover only the edematous bone marrow and to avoid chronic lesions while taking into account the presence of erosions, fat metaplasia, or bony buds next to BME.

Participation of multiple quadrants: The ROI was positioned on the slice displaying the largest confluent BME region, if BME was found in more than one quadrant of the SIJ. To prevent intra-patient duplication bias, only one ROI per subject was examined. OsiriX V.4.9 (Pixmeo, Switzerland) was used to extract the following histogram parameters: variance, skewness uniformity, entropy, kurtosis, maximum, mean, median, minimum, and the 10th and 90th percentiles. An internal MATLAB script (version R2017a, MathWorks, Natick, MA, USA) was used to process the ROI data.

Statistical Analysis

The study data were analyzed using SPSS version 21.0 (IBM Corporation, Armonk, NY, USA). The Kolmogorov-Smirnov and Shapiro-Wilk tests were applied to assess the normality of continuous variables. Parametric numerical data with a normal distribution were expressed as mean ± standard deviation, while qualitative variables were presented as percentages. Independent group comparisons were performed using the Student's t-test, and categorical variables were compared using the chi-square test. A p-value of <0.005 was considered statistically significant in all analyses.

RESULTS

The mean age of the axSpA-related sacroiliitis group was 34.24±12.66 years, and the mean age of the *Brucella* sacroiliitis group was 41.00±14.77 years (p=0.088). The male-to-female ratios were similar between the two groups (p=0.777).

Histogram analysis parameters, including the 10th percentile, 90th percentile, entropy, kurtosis, maximum, mean, median, minimum, skewness uniformity, and variance, were compared between groups (Table 1).

A statistically significant difference was observed in the 10th percentile, median, and minimum values between the groups:

- **10th percentile:** The mean 10th percentile value was significantly lower in the *Brucella* sacroiliitis group compared with the axSpA group (p=0.018), indicating reduced signal intensity in the lowest-intensity voxels within the ROI.
- **Median:** The median gray level measurement also decreased in the *Brucella* sacroiliitis group (p=0.029), reflecting an overall shift of the intensity distribution toward lower values in infection-related sacroiliitis.
- **Minimum:** The lowest gray-level value was markedly reduced in the *Brucella* group (p=0.002), suggesting the presence of very low-intensity voxels, potentially corresponding to areas of necrosis or pronounced BME.

No statistically significant differences were found for the 90th percentile, entropy, kurtosis, maximum, mean, skewness uniformity, or variance (p>0.05 for all). The large numerical values observed for skewness and kurtosis reflect the non-normal, highly heterogeneous intensity distribution of bone marrow signal on MRI, rather than unit or calculation errors.

Although formal box-plot visualizations were not available, descriptive analysis showed that the *Brucella* sacroiliitis group consistently demonstrated a narrower range of high-intensity values and a downward shift in central tendency measures (median and 10th percentile), while the axSpA group displayed a relatively balanced distribution with higher central intensity values.

DISCUSSION

Our study showed a statistically significant difference between the two groups in the median, minimum, and 10th percentile values. According to our study, MRI histogram analysis may be promising for use in the differential diagnosis of axSpA-related sacroiliitis and *Brucella* sacroiliitis.

It is very difficult to diagnose infectious sacroiliitis because it presents similar findings as other lumbar and hip pathologies (20). Blood culture is positive in approximately 40-50% of cases, and SIJ biopsy may be required to identify the causative agent (21). It is known that 24% of patients with *Brucella* sacroiliitis are clinically asymptomatic (22). In the absence of other signs

Table 1. Comparison of histogram analysis results of groups

	Brucella sacroiliitis (mean ± standard deviation)	Inflammatory sacroiliitis (mean ± standard deviation)	p-value
10 percent	87.19±27.82	109.01±31.07	**0.018**
90 percent	154.84±43.12	179.12±49.83	0.132
Entropy	13.836±97.031	12.407±10.374	0.854
Kurtosis	17.518±16.145	16.776±13.145	0.528
Maximum	184.64±44.27	204.36±45.85	0.096
Mean	13.335±11.354	12.000±66.954	0.691
Median	115.14±31.89	143.32±45.62	**0.029**
Minimum	37.32±29.40	65.92±30.42	**0.002**
Skewness	97.688±35.708	-713.121±35.656	0.455
Uniformity	0.29343±0.07733	0.27320±0.08811	0.282
Variance	10.186±10.362	12.866±13.157	0.516

of infection, it may be difficult to differentiate between *Brucella* sacroiliitis and axSpA-related sacroiliitis. Clinical findings and laboratory tests are usually non-specific and provide limited diagnostic information. The causative bacteria may not be easily detected in blood tests and patients may be misdiagnosed with axSpA-related sacroiliitis, leading to inappropriate treatment. While early stage, changes on MRI can be important for diagnosis, they may not always provide enough information to make a definitive distinction between these conditions. Therefore, additional diagnostic tools are required for differentiation. Karayol and Karayol (23) investigated the role of diffusion-weighted MRI in the differential diagnosis of *Brucella* sacroiliitis and seronegative spondyloarthropathy but found no statistically significant difference between the measurements. In contrast to diffusion-weighted MRI, histogram analysis offers voxel-based quantification of intensity distributions and may detect subtle signal differences invisible to the naked eye, which may explain the significant findings in our study.

Histogram analysis has been applied in various radiologic contexts to quantify tissue characteristics and improve diagnostic accuracy. For instance, Ağlamış and Baykara (24) demonstrated its utility in differentiating malignant from benign breast lesions, showing significantly lower minimum and low-percentile values, along with higher skewness and lower uniformity in malignant cases. Similarly, Baykara et al. (25) found that histogram-derived parameters such as entropy, variance, and skewness were significantly lower in the affected median nerves of patients with carpal tunnel syndrome, despite normal-appearing signal intensity. Colombi et al. (26) used histogram-based quantitative computed tomography assessments to monitor disease progression in idiopathic pulmonary fibrosis. In another study, Yildirim and Baykara (18) observed significantly higher minimum, median, and maximum values in lytic bone metastases compared to multiple myeloma. These studies collectively show that histogram parameters can reveal microstructural alterations and tissue heterogeneity not visible on conventional MRI. Similarly, in sacroiliitis, the distribution of voxel intensities may correspond to variations in marrow perfusion, inflammatory infiltration, and edema. Such pathophysiological changes differ between infection-related and axSpA-related sacroiliitis, explaining the distinct histogram profiles observed in our study.

Our findings align with recent quantitative imaging studies in axSpA. Xie et al. (27) performed whole-joint histogram analysis using mono- and bi-exponential diffusion-weighted imaging (DWI) and diffusion kurtosis imaging in 82 patients with axSpA and 17 with non-specific low back pain. Parameters such as perfusion fraction, mean kurtosis, and mean diffusivity were analyzed. While these metrics showed limited ability to distinguish active from inactive axSpA, they successfully differentiated both groups from controls. Mean diffusivity correlated with high-sensitivity C-reactive protein, and most parameters correlated with bath ankylosing spondylitis disease activity index, whereas the Spondyloarthritis Research Consortium of Canada score did not differentiate disease activity. Although our study differed by using T2-FatSat sequences and lacking a control group, both studies support the idea that quantitative histogram-derived parameters can provide diagnostic information beyond conventional MRI.

From a methodological perspective, *Brucella* sacroiliitis often presents with edema extending beyond typical anatomical boundaries and may occasionally form abscesses. In our study,

ROIs were restricted to the subchondral bone marrow to maintain comparability with axSpA cases, potentially excluding some peripheral infection-related changes. This restriction may have also led to the omission of perilesional edema or small abscess formations, commonly seen in *Brucella* sacroiliitis, which could have resulted in underestimation of signal heterogeneity in these cases. The lower minimum and median histogram values observed in the *Brucella* group likely reflect the underlying pathophysiology of infection, characterized by diffuse marrow edema, inflammatory infiltration, and micro-necrotic changes that reduce signal homogeneity. In contrast, sacroiliitis associated with axSpA tends to show localized inflammation with relatively preserved marrow architecture, resulting in higher median intensity values. Conversely, axSpA often presents with coexisting structural changes (erosions, fat metaplasia) near active lesions, although these were avoided during ROI placement, subtle overlap could still influence histogram values. Furthermore, the radiologist performing ROI placement was blinded to diagnosis, but could not be entirely unaware of certain typical patterns, introducing potential observer bias.

Compared with other advanced quantitative MRI techniques such as DWI and radiomics, histogram analysis provides a simpler and sequence-independent method that can be implemented on standard MRI data without additional scanning time. While DWI and radiomics yield more complex diffusion or texture-based metrics, they often require specialized acquisition protocols and post-processing software. In contrast, histogram analysis allows rapid voxel-based quantification of tissue heterogeneity using routinely acquired images. Therefore, it may serve as a practical complementary technique, and its integration with diffusion or radiomic parameters could further enhance diagnostic accuracy in distinguishing infectious and inflammatory sacroiliitis.

To our knowledge, this is the first study to evaluate histogram analysis in the differential diagnosis of sacroiliitis. The significant differences in median, minimum, and 10th percentile values between groups indicate that histogram parameters can quantitatively reflect disease etiology and assist in diagnosis. Larger multicenter, prospective studies with control groups and blinded multi-reader analysis are required to validate these preliminary findings. Integrating histogram analysis with other advanced imaging techniques, such as radiomics or diffusion metrics, may further improve diagnostic accuracy.

Study Limitations

This study has several limitations that should be acknowledged. First, the retrospective and single-center design may introduce selection bias and limit the generalizability of the findings. Second, the relatively small sample size (25 patients per group) reduces statistical power and precludes robust subgroup analyses. Third, the absence of a healthy control or non-specific low back pain group prevented the assessment of diagnostic accuracy parameters such as sensitivity, specificity, and ROC analysis. Fourth, although the radiologist performing the ROI analysis was blinded to the clinical diagnosis, subtle imaging patterns could still have introduced observer bias. In addition, the restriction of the ROI to subchondral bone areas in *Brucella* cases may have excluded peripheral edema or abscess formations, potentially influencing the histogram parameters. Because multiple histogram variables were analyzed, the possibility of type I error due to multiple comparisons cannot be excluded. Furthermore, the relatively large numerical values observed for skewness and kurtosis reflect non-normal intensity distributions rather than calculation errors; however, this heterogeneity may complicate direct comparison across cases. Finally, the results should be interpreted as preliminary and exploratory; larger, multicenter, prospective studies incorporating control groups and advanced quantitative MRI techniques are needed to validate and expand upon these findings.

CONCLUSION

MRI histogram analysis of T2-FatSat images provides objective and quantitative information that may potentially assist in differentiating *Brucella* sacroiliitis from sacroiliitis associated with axSpA. The lower minimum, median, and 10th percentile values observed in the *Brucella* group suggest characteristic signal intensity patterns related to infection. However, these findings should be regarded as preliminary and exploratory. Histogram-derived parameters may serve as supportive tools in differential diagnosis, but larger, multicenter, prospective studies are required to validate their diagnostic value.

Ethics

Ethics Committee Approval: This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki after obtaining approval from the Fırat University Non-Interventional Research Ethics Committee (approval no: 17285, date: 20.07.2023).

Informed Consent: Informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.Y.U., Concept: E.Y.U., G.A., M.F.U., Design: E.Y.U., A.G., M.F.U., Data Collection or Processing:

E.Y.U., M.Y., Ş.Ö.B., Gü.A., Analysis or Interpretation: E.Y.U., M.Y., Ş.Ö.B., A.G., Gü.A., Literature Search: E.Y.U., M.Y., Gü.A., Writing: E.Y.U., M.F.U.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study received no financial support.

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