Running head: Imaging impact on AxJSpA

Full title: Impact of Characteristic Inflammatory and Structural Pelvic MRI Lesions on Expert Assessment of Axial Juvenile Spondyloarthritis

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Abbreviations:

Akaike Information Criterion (AIC)

Area under the receiver operating characteristic (AUROC)

Assessment of SpondyloArthritis international Society (ASAS)

Bayesian information criterion (BIC)

Confidence interval (CI)

Human leukocyte antigen (HLA)

Inflammatory back pain (IBP)

Inflammatory bowel disease (IBD)

Juvenile Idiopathic Arthritis MRI Score (JAMRIS)

Juvenile spondyloarthritis (JSpA)

Magnetic resonance imaging (MRI)

Non-steroidal anti-inflammatory drugs (NSAIDs)

Outcome Measures in Rheumatology working group (OMERACT)

Relative risk (RR)

Sacroiliac Joint (SIJ)

Spondyloarthritis (SpA)

ABSTRACT

Objective: To evaluate the influence of pelvic MRI findings on axial disease assessment in juvenile spondyloarthritis (JSpA).

Methods: This was a cross-sectional study of JSpA patients with suspected axial disease. Three experts reviewed each case and rated their confidence (-3 to +3) in presence of axial disease, first with clinical data and second with clinical and magnetic resonance imaging (MRI) data. Agreement and high confidence agreement were defined as ≥2/3 clinical experts with a rating of ≤-1 or ≥1 or ≤-2 or ≥2, respectively. The association of clinical features and both global assessments was tested with modified Poisson regression models.

Results: 272 of 303 (89.8%) cases achieved agreement with clinical features alone. Adding imaging data affected agreement in 38.9% (118/303) and directionality of agreement in 23.4% (71/303). Agreement was facilitated in 26 of 31 cases and lost in 21 cases. Of those 71 cases that changed directionality, 33 changed from axial disease absent to present and 38 from present to absent. The final model had an area under the receiver operating characteristic (AUROC) curve of 0.93 and 3 factors were independently associated with expert agreement (HLA-B27: Relative Risk [RR] 1.41, 95% Confidence Interval [CI] 1.14-1.74; pain improvement with activity: RR 1.27, 95% CI 1.05-1.54; bone marrow edema on MRI: RR 4.08, 95% CI 2.91-5.73).

Conclusions: Addition of imaging data changed directionality and improved high confidence agreement of expert assessment of axial disease. These results underscore the integral role of MRI in determination of axial disease in JSpA.

INTRODUCTION

Juvenile spondyloarthritis (JSpA) is a set of conditions characterized by chronic arthritis of the peripheral joints and/or spine, enthesitis, inflammatory bowel disease (IBD), psoriasis, acute anterior uveitis, and HLA-B27 positivity. Axial disease may complicate up to 30% of JSpA cases within 5 years of diagnosis[1–3] and is a major source of morbidity.[4,5] The diagnosis of axial disease in spondyloarthritis (SpA) is based on history, physical exam, laboratory and imaging tests available to the clinician. Algorithms for diagnosis and classification of axial spondyloarthritis in adults[6,7] anchor heavily on "inflammatory back pain" (IBP) features[8] and radiographic sacroiliac joint findings. However, these clinical features are known to be less helpful in JSpA patients, especially in early disease.[9–13] IBP symptoms are uncommon in JSpA patients[14,15] and the overall frequency of lumbar complaints is lower than in adult ankylosing spondylitis cohorts.[10,16,17] Moreover, IBP symptoms and abnormal physical exam findings commonly associated with sacroiliitis have low positive predictive value relative to magnetic resonance imaging (MRI) findings.[2,18]

In recent years, MRI has been increasingly used for diagnostic assessment of axial disease in children and adults. While radiography is commonly used as an initial evaluation of axial disease in adults with spondyloarthritis, this imaging modality only shows structural bony damage and not dynamic inflammatory lesions. In children, radiographs are often used in the initial assessment of back pain if non-inflammatory etiologies of pain are suspected, such as stress fracture, infection, spondylolisthesis. When radiographs are performed as part of the assessment of suspected axial disease they result in a significant amount of both false positive and false negative findings,[13] likely in part to normal maturational findings that can be easily confused for erosion.[19,20] Furthermore, MRI is the imaging modality of choice when inflammatory sacroiliitis is suspected as it can not only visualize damage (which may also be visible on radiographs) but also active inflammation which impacts therapeutic decisions. Further, MRI can

distinguish non-sacroiliitis pathology which may be contributing to axial symptoms, which was reported in over 40% of cases in one large multicenter study.[21]

MRI is not available in all parts of the world, is expensive, and in younger patients may require sedation. As such, it is not uniformly performed when axial disease is suspected. The objective of this investigation was to evaluate the extent to which MRI influences expert assessment of axial disease when added to existing clinical and radiographic data.

METHODS

Ethics

This study was reviewed by the Children's Hospital of Philadelphia institutional review board (IRB) and the IRB determined the procedures met the exemption criteria per 45 CFR 46.104(d) 4(iii) (IRB 19-016078).

Study Design and Participant Identification

This study is a subanalysis of data used in the development of the classification criteria for axial disease in juvenile spondyloarthritis.[22] All patients had a physician diagnosis of JSpA and suspected axial disease with symptom onset prior to age 18 years and available MR imaging of the sacroiliac (SIJ). The cohort consisted of patients who were clinically diagnosed with juvenile SpA and axial disease, or juvenile SpA and alternative etiologies for axial symptoms who were evaluated in 6 international centers between 2011 and 2021 (North America: Bethesda, MD; Birmingham, AL; Madison, WI; and Philadelphia, PA Europe: Sankt Augustin, Germany; Asia: Istanbul, Turkey). Clinical and imaging data were available from the time axial disease was first suspected. Details of the imaging review are included herein for clarity.

Expert Review of cases

Six imaging experts (WPM, RGL, NC, DB, NH, MF) with expertise in musculoskeletal imaging comprised the central imaging team for the study. All submitted MRIs were dedicated imaging of the pelvis and were required to include T1-weighted and fluid sensitive coronal oblique sequences. Each MRI was reviewed by at least two members of the central imaging team. MRI reviews of de-identified Digital Imaging and Communications in Medicine (DICOM) images were completed using scoring modules on carearthritis.com and included two components: (1) detailed assessment of SIJ inflammatory and structural lesions and (2) an Assessment in SpondyloArthritis International Society (ASAS) eCRF global assessment (MRImagine)[23] that included questions such as "Are there inflammatory and/or structural lesions typical of axial SpA?" Inflammatory and structural lesion definitions were based on the ASAS classification criteria for active sacroiliitis on MRI[24] and the preliminary Juvenile Idiopathic Arthritis Magnetic Resonance Imaging Score - Sacroiliac Joint (JAMRIS-SIJ) from the Outcome Measures in Rheumatology (OMERACT) working group[25] (**Table 1, Supplemental Table 1**). Specifically, bone marrow edema/subchondral inflammation was defined as "an ill-defined area of high bone marrow signal intensity on fluid-sensitive sequences within the subchondral bone of the ilium or sacrum compared to the signal intensity of the iliac crest, edges of the vertebrae, and triradiate cartilage and in comparison, to physiological changes normally seen on MRI examinations of age- and sex-matched children, and visible in 2 planes" (Supplement Table 1). Imaging was rated independently and blind to clinical details by ≥2 central imaging team raters and a 3rd rater adjudicated cases for which there was disagreement on the global assessment of the presence/absence of lesions typical of axial SpA.[26] Interrater agreement of the central imaging team, as measured by Fleiss' kappa for the presence/absence of individual inflammatory and structural lesions was previously reported.[26] Fleiss' kappa was 0.70 for bone marrow edema, 0.72 for erosions, 0.53 for sclerosis, and 0.5 for ankylosis.

14 physicians (AA, RBV, RC, GH, RJ, RML, KM, AR, NR, JS, MS, ST, FVB, PW) with expertise in SpA comprised the clinical expert team. Three clinical experts from this team completed two global assessments for each subject, rating their confidence in the presence of axial disease on an integer scale of -3 (very unlikely) to +3 (very likely). The first assessment was based solely on clinical features and the local radiograph report, if available. The second assessment was performed with access to both clinical features and the central imaging team imaging assessment (MRI +/- radiograph). Raters completed the second assessment over six months after the clinical data only assessment and were blinded to their initial rating. An overview of this process is illustrated in **Figure 1**. Clinical expert agreement in the presence or absence of axial disease was defined as ≥2/3 experts having a rating of ≤-1 or ≥1. Agreement with high confidence, defined as ≥2/3 experts having a rating of ≤-2 or ≥2, was also evaluated in case assessment with and without advanced imaging.

Statistical Analysis

We examined descriptive statistics of study characteristics and imputed missing data in study covariates using the fully conditional specification method[27] implemented using SAS Proc MI using one imputed dataset. Univariable and multivariable modified Poisson regression models[28] were constructed to assess associations of clinical and imaging factors with clinical expert agreement for both global assessments. The multivariable models for both assessments were built using the best subsets algorithm.[29] The use of best subsets algorithm as a method of variable selection allowed us to examine all possible combinations of predictors and then choose the optimal set of predictors based on statistical criteria (e.g. Area under the receiver operating characteristic (AUROC) curve, Akaike Information Criterion (AIC), Bayesian information criterion (BIC) as well as clinical acumen. This approach for variable selection was chosen over stepwise selection, which can be sensitive to the order of variables in the model and might yield a model that is not generalizable, and regularization, which might not yield an

interpretable model. For each outcome, we identified a few models that performed well and were clinically valuable.

We used bootstrap validation to test the performance of the chosen models in the original data. 500 new samples were created based on the original patient sample with imputation of missing data performed in each new sample before running the multivariable models. The AUROC was calculated in each new sample and then an average AUROC (naïve c-statistic) and optimism-corrected AUROC (optimism-corrected c-statistic) were determined from all 500 models as part of the bootstrap validation. All statistical analyses were conducted using STATA 17 (College Station, TX) and SAS version 9.4 (Cary, NC).

RESULTS

Cohort Characteristics

303 cases of JSpA with suspected axial disease met inclusion criteria for the study. Detailed characteristics of this cohort have been previously published.[22] 63% were male, median age at time of evaluation was 14.8 years (IQR 12.2-16.7), 53% were HLA-B27 positive and 19% had a family history of SpA. The central imaging team reported at least one type of inflammatory or structural lesion in 131 (43.2%) patients. Of those with MRI findings, the most common were subchondral bone marrow edema (90.8%), erosion (69.5%), sclerosis (35.9%), and inflammation at the site of an erosion cavity (36.4%). 29.4% of patients had both inflammatory and structural lesions while 12.2% and 1.7% had inflammatory or structural lesions only, respectively. 34 (11.2%) cases of JSpA with suspected axial disease had enthesitis outside the sacroiliac joint on MRI. 135 patients had pelvic radiographs (X-rays) in addition to MRI available for central imaging assessment. The most common X-ray findings included erosion (10.4%), sclerosis (9.6%) and sacroiliac joint space widening (5.9%).

Impact of Imaging Data on Expert Agreement

Among the 303 cases, expert agreement in the presence/absence of axial disease was reached on 89.8% (272/303) of cases with clinical features only and 91.4% (277/303) of cases with clinical features and imaging data (**Figure 2**). Adding central imaging data affected agreement in 38.9% (118/303) of cases. Agreement was facilitated in 26 of 31 cases without agreement based on clinical data alone; however, agreement was lost in 21 cases for which there was initial agreement on clinical data. Of those 71 cases that changed directionality, agreement was facilitated in 26 cases but lost in 21. Of the 26 cases gaining agreement, 5 and 21 reached agreement that the case was or was not axial disease, respectively. The directionality of agreement changed in 23.4% (71/303) of cases, with 33 cases changing from axial disease absent to present and 38 cases changing from present to absent. **Table 2** details the change in majority assessment and accompanying central imaging team assessment.

Expert agreement with high confidence was achieved on 131 (43.2%) cases with clinical features only and on 214 (70.6%) cases with clinical plus imaging features. Adding central imaging data affected high confidence agreement for 47.5% (144/303) of cases; high confidence agreement was facilitated in 113 cases but lost in 31. Of the 113 cases gaining high confidence agreement, 43 and 70 reached high confidence agreement that the case was or was not axial disease, respectively. For 18 (5.9%) cases, it changed the directionality of agreement; 5 cases from axial disease present to axial disease absent and 13 cases from absent to present.

Association of Clinical Features with Axial Disease Assessment

Strengths of association between clinical features and expert agreement of axial disease are shown in **Table 3.** In the assessment of clinical features alone, several features had strong univariable associations with agreement including lumbar spinal pain, insidious-onset pain, pain improvement with activity, stiffness duration ≥15 minutes, and HLA-B27 positivity. Using the best subsets algorithm and clinical acumen, the multivariable model that performed best

(AUROC 0.90) included the following clinical factors: patient-reported lumbar pain, sacroiliac pain elicited on exam with deep palpation or by FABER/Mennell/Gaenslen's maneuvers, pain most days, moderate to total pain relief with NSAIDs, improvement of pain with activity, stiffness duration ≥15 minutes, and HLA-B27 status. All parameters were significant in this model and the factors with the highest relative risk were pain improvement with activity (RR 2.02), patient-reported lumbar spinal pain (RR 1.59), and HLA-B27 positivity (RR 1.56). The bootstrap validation model had a consistent average AUROC of 0.9 and optimism-corrected AUROC of 0.89.

Association of Clinical and Imaging Features with Axial Disease Assessment

In the assessment inclusive of clinical and imaging features, variables with a significant univariable association with expert agreement of axial disease included pain present most days, HLA-B27 positivity, pain duration between 6-12 weeks and ≥12 weeks, and structural and inflammatory MRI lesions. Using the best subsets algorithm, the multivariable model including stiffness duration ≥15 minutes, any structural MRI lesion(s), pain improvement with activity, HLA-B27 status, and bone marrow edema on MRI performed best (AUROC 0.93) with the latter three factors having a significant and independent association with expert agreement (HLA-B27: RR 1.41, 95% confidence interval [CI] 1.14-1.74; pain improvement with activity: RR 1.27, 95% CI 1.05-1.54; bone marrow edema on MRI: RR 4.08, 95% CI 2.91-5.73). Models including additional clinical factors that were significant in univariable analysis added little to no incremental value. The bootstrap validation model had a consistent average AUROC of 0.93 with an optimism-corrected AUROC of 0.92.

DISCUSSION

This study examines how advanced imaging data impacts expert evaluation of axial disease in patients with JSpA. Leveraging a large multicenter, international cross-sectional cohort of JSpA patients with suspected axial disease, we found that imaging data altered expert agreement on

axial disease in over one-third of cases, with nearly a quarter of cases changing the directionality of agreement. Furthermore, rates of high confidence agreement in the presence or absence of axial disease were enhanced by the addition of imaging data. Several clinical features had a significant and independent association with expert agreement in the absence of imaging data other than pelvic radiograph results but most clinical features did not independently contribute to the expert assessment of axial disease once the MRI data was included other than HLA-B27 status and pain improvement with activity. Bone marrow edema on MRI had the strongest independent association with expert agreement of axial disease, suggesting that experts relied heavily on imaging results in their global assessment of axial disease presence or absence.

Several key findings warrant additional discussion. First, the addition of advanced imaging data caused the directionality of expert agreement of axial disease to change in nearly a quarter of cases, arguing for the integral role of MRI in the evaluation of axial disease. Back pain and the presence of IBP symptoms have historically been important in the evaluation of axial disease in adult patients with spondyloarthritis, but our findings reinforce the notion that they are less helpful in pediatric cohorts,[2,14–18] particularly when advanced pelvic imaging is available. The heavy reliance on imaging data is reflected in the recently published axJSpA classification criteria in which imaging evidence of axial disease is necessary however not sufficient in the absence of clinical features, to surpass the threshold for classification.[22] However, advanced imaging is not readily available in all parts of the world. The axial disease classification criteria for JSpA were not intended to determine clinical care or to guide therapeutic decisions in patients diagnosed with axial disease, but rather to help identify youth with unequivocal disease that would be appropriate for clinical study participation. As such while imaging may be paramount to determination of classification of axial disease and may facilitate the accuracy of

diagnostic evaluation, its role in the decision of whether or not to treat axial symptoms is likely different.

Second, interestingly, structural MRI lesions did not have a significant association with expert global impression of axial disease in the multivariable model. This is likely multifactorial. The presence of structural lesions is associated with the assessment of axial disease, as reflected in the strong univariate analysis, but in the presence of inflammatory lesions it adds little incremental or independent value. In this cohort, only 5 (1.7%) patients with structural lesions had these changes in the absence of concurrent inflammatory lesions. This low percentage of isolated structural lesions reflects the fact that the imaging data was obtained at the time of initial suspicion of axial disease, likely early in the disease process when inflammation was present and resulting in clinical symptoms. Furthermore, there is a lower prevalence of structural abnormalities in children who generally have a shorter duration of disease at the time of imaging relative to adults. This is supported by recent prospectively collected data that ongoing sacroiliac joint inflammation likely leads to the eventual development of structural lesions in the same quadrant over the course of several years.[30] Another possibility is that awareness of structural lesions, their interpretation on MRI scans, and understanding of their significance may be less evident among pediatricians.

There are several notable strengths to our study including the generalizability of our data. This analysis leveraged data from 6 international centers with JSpA patients and suspected axial disease and all data was collected using a standardize electronic case form. Imaging protocol variability across the 6 centers existed and was expected. However, all submitted MRIs were dedicated imaging of the pelvis and were required to include T1-weighted and fluid sensitive coronal oblique sequences. This lack of standardization further increases the real-world generalizability of the findings as it highlights the importance of inflammatory axial lesions irrespective of specific imaging protocols used at different clinical sites. Additional strengths

included the central imaging team, international clinical SpA expert panel, and standardized imaging evaluations. Radiology experts were blinded to relevant clinical data for patients other than age and sex which reduced the risk of detection bias in their interpretation of the imaging. In addition, the evaluation of each imaging study by two radiologists and the use of standardized assessment criteria helped ensure internal consistency for MRI reads of all subjects. Similarly, the risk of both recency and anchoring bias was minimized during the JSpA expert assessment by having raters perform the two global assessments for a given case at different times, in randomized order, and blinded to their prior assessment.

There are several limitations to this study. The cohort was intentionally limited to those with a diagnosis of JSpA and thus is not applicable to patients with other types of autoimmune disease and suspected axial arthritis or non-JSpA patients with back pain. Second, misclassification of patients as JSpA was possible if local physician diagnosis was inaccurate. However, all submitted cases were from centers with expertise in juvenile arthritis and all submitted cases underwent quality checks to verify the diagnostic criteria based on submitted clinical information. Third, as with all retrospective studies there was a degree of missing data in the electronic case report forms, but this was minimal and rigorously addressed with single imputation and bootstrap validation. Fourth, since scans were obtained per standard clinical care practice and local institution imaging protocols and not as part of a specified prospective study protocol, there was imaging acquisition variability. However, included images all had the sequences necessary to perform SIJ quadrant-based scoring for inflammatory and structural lesions; as such, there was no variability in the sequences used to assess for quadrant-based scoring. Additionally, the clinical experts who reviewed each case did not review the actual scans, but instead were given the central imaging team's assessment of the imaging as part of the standard case report form. The variability in the imaging protocols (other than the sequences used for scoring) did not impact the clinical expert's assessment of the reported imaging findings and clinical features.

Lastly, bootstrap validation was used to test the performance of the chosen models using resamples of the original data, so we do not know truly how these models would perform with independent data; however, the use of best subsets algorithm enabled examination all possible combinations of predictors and then selection of the optimal set of predictors in a data driven manner.

In summary, we systematically evaluated expert consideration of clinical features and MRI findings in their assessment of axial disease in patients with established JSpA. The addition of imaging data changed the directionality and improved high confidence agreement of expert assessment of axial disease. These results underscore the integral role of MRI in the determination of axial disease in JSpA.

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FIGURE LEGENDS

Figure 1. Overview of study design. JSpA: juvenile spondyloarthritis

Figure 2. Agreement (≥2/3 clinical experts having a rating of ≤-1 or ≥1) and high confidence agreement (≥2/3 experts having a rating of ≤-2 or ≥2) on axial disease presence based on assessment of clinical features alone or clinical features plus MRI data.