**The reliability of a novel MRI-based tool for the evaluation of forefoot bursae in patients with rheumatoid arthritis: The ‘*FFB-Score*’**

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 **Short title:** MRI evaluation of bursae in patients with RA

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**Manuscript word count: 1,326ABSTRACT**

**Objective:** To determine the reliability of an MRI-based score that evaluates forefoot bursae (FFB) in patients with RA.

**Methods:** Items for inclusion, grading criteria and MRI sequences were determined iteratively. The score was evaluated in 30 patients with established RA. Reader agreement was evaluated using Percentage Exact/Close Agreement, Bland and Altman plots, kappa, and ICC analyses.

**Results:** The *FFB-Score* assesses 9 forefoot regions and contains 4 items; presence, shape, enhancement, and MR characteristics. The *FFB-Score* showed moderate to good intra/inter-reader agreement (kappa range=0.5-0.9, 0.47-0.87 respectively).

**Conclusion:** The *FFB-Score* is adequately reliable in the evaluation of bursa-like lesions of the forefoot in patients with RA.

**Key words:** Magnetic Resonance Imaging, Rheumatoid Arthritis, Foot, Synovium, Radiology, Outcome measures

**INTRODUCTION**

A high prevalence of bursa-like lesions (FFB) in the forefoot of patients with rheumatoid arthritis (RA) has been reported using ultrasound (US)[[1](#_ENREF_1)]. FFB are associated with increased RA disease activity [[1](#_ENREF_1), [2](#_ENREF_2)], and appear to be a prognostic indicator of foot-related disability [[3](#_ENREF_3)]. Investigations of FFB have not yet characterised the underlying pathophysiology and it is possible that a range of bursa-like lesions have been reported. Accurately characterising FFB would inform future studies of targeted intervention.

Magnetic Resonance Imaging (MRI) allows multi-planar visualisation of the forefoot with differentiation and characterisation of soft tissues structures [[4](#_ENREF_4), [5](#_ENREF_5)]. MRI has greater sensitivity and specificity for RA disease activity within peripheral joints than US or clinical examination which can both be highly operator dependent [[6](#_ENREF_6)], or clinical examination[[7-9](#_ENREF_7)]. MRI is potentially an observer-independent method of characterising FFB in patients with RA. The aim of this study was to determine the reliability of a novel MRI-based score for the evaluation of FFB in patients with RA.

**METHODS**

**Study design**

An iterative process of score design was completed by a team of rheumatologists, radiologists, and podiatrists, in a cross-sectional cohort of patients with RA. Ethical approval was obtained from S.W. Hampshire Ethics Committee. All participants gave written informed consent.

**Study population**

Participants with an ACR diagnosis of RA, aged 18-80 years, were recruited consecutively from a rheumatology clinic. Participants were excluded if they had received forefoot corticosteroid injection within 12-weeks, had concomitant musculoskeletal disease or were unable to provide consent.

**Protocol for score development**

Score development adhered as closely as possible to OMERACT (2009) recommendations for MRI-based quantification of RA. Items included were FFB anatomical location, shape, enhancement, and MR signal characteristics. The categorisation of FFB based upon descriptive characteristics rather than aetiology or clinical importance, was considered the most objective approach and is consistent with principles of radiological investigation.

**Protocol for image acquisition**

A 1.5 Tesla (T) whole body scanner was used for MRI acquisitions and a four channel flex extremity radio frequency (RF) surface coil was used to image the forefoot (Siemens, Germany). Two-dimensional and three-dimensional sequences, of between 29 and 96 slices with 3mm to 0.6mm slice thickness respectively, were completed after orientation with a T1 localiser image. The MRI sequence protocol is included in appendix 1 (web only). Pulse sequence type and timing were selected to visualise a) anatomical structure (coronal T1 SE) b) high contrast between fluid and soft tissue (coronal STIR), and c) synovial inflammation (coronal and sagittal T1w fat suppressed sequences after intravenous contrast administration). The 3D SPACE sequence allowed the three-dimensional reconstruction of identified lesions and orientation with adjacent features. Coronal scans were orientated approximately perpendicular to the metatarsal parabola and sagittal scans were orientated approximately perpendicular to the coronal slice profile and with the shaft of the third metatarsal. The field of view (FoV) in the read direction was determined as the base of 1st metatarsal to the distal aspect of the hallux. The FoV in the phase-encode direction was defined as extending from the medial to the lateral foot borders. The TE/TR ratios were adjusted in an iterative process by the radiologist until appropriate image clarity or contrast was achieved.

**Protocol for image reading**

Images were viewed using Siemens *Syngo©* Fast view software. All images were read by two radiologists, blinded to each other’s scores and clinical data. LK re-read an additional set of 10 image sets, at an interval of 4-6 weeks, for the purposes of intra-rater agreement analysis.

Identified FFB were categorised to one of nine sites (Appendix 1). In the event of an FFB extending across anatomical boundaries, the site in which contained the majority of the FFB was recorded. Fluid and soft tissue lesions were differentiated using STIR sequence. Fluid collections were defined as homogeneous hyperintense structures, with fluid-equivalent signal on STIR sequence and homogenous intermediate signal on non-contrast T1-weighted images. Soft tissue lesions were defined as non-fluid equivalent/intermediate signal on STIR, relative to skeletal muscle.

**Statistical analysis**

Analysis was completed using Stata version 11.0, (Stata Corp, USA) or SPSS version 18.0 (Chicago, USA). The study sample size (n=30) was pragmatically determined based upon estimates of presence/absence identified in previous our previous work [[10](#_ENREF_10)]. An additional cohort of 10 patients was recruited to complete preliminary intra-rater agreement analysis. Participant demographic and clinical characteristics are reported as means, standard deviations (SD) and ranges.

A radiologist combined mean score for each item was calculated. Agreement was evaluated using estimations of percentage exact agreement (PEA), percentage close agreement (PCA; within ± 2 scores) for all items and Kappa agreement for determination of presence or absence. Weighted kappas were used to determine inter-rater agreement for fluid and soft tissue lesion shape and enhancement scores where both readers identified a lesion as being present.

**RESULTS**

**Study population**

The score was evaluated in 30 RA patients (n=23 female, n=7 male), with mean (±SD) age 61.7 (±4.1) years, disease duration 15.3 (±10.3) years, and DAS28 (crp) 3.4 (±4.5).. A total of 300 joints and 540 possible FFB sites per reader were reviewed.

**The *FFB-Score***

The *FFB-Score* items, definitions and grading criteria are presented in Appendix file 2. The *FFB-Score* image atlas and user guide can be found in Appendix 3 (web only).

***FFB-Score* reader reliability**

A range of lesion characteristics was observed. The FFB score was demonstrated to have moderate to substantial intra-reader agreement in the additional set of 10 scans that were re-read (table 1). Weighted kappa analysis demonstrated that, where both readers identified a lesion as being present, there was moderate to substantial agreement in shape and enhancement grading. ICC analysis demonstrated low to moderate agreement; with greater agreement regarding intermetatarsal lesions than plantar lesions demonstrated. As illustrated in the Bland Altman plots, (figure 2), the standard error mean difference between reader scores was 0.69 (95% CI -8.9 – 6.72). The majority of scores were bounded between the upper and lower limits of two standard deviations from the mean.

**DISCUSSION**

This study is the first to propose a systematic method, for the semi-quantitative characterisation of bursa-like lesions of the forefoot in patients with RA. In this preliminary analysis, the *FFB-Score* was demonstrated to have moderate to substantial reliability.

The evaluation of forefoot bursae (FFB), completed as part of the *FFB-Score* development, identified differences in the tissue characteristics of observed lesions. Previous authors have suggested that such differences are related to the FFB aetiology [2, 11], although characterisation by pathological or aetiological means has arguably contributed to confusion within the literature. It is proposed that the *FFB-Score* can be utilised to characterise a range of forefoot bursa-like lesions without bias towards their potential aetiology or clinical importance. It should be noted however that despite all identified lesions meeting our study definition of bursa (fluid filled cavity), a range of bursa-like lesions were observed and the clinical significance of this remains unclear. Further evaluation of the clinical importance of MRI-detected FFB in patients with RA is warranted.

This study has strengths and potential limitations. Bland and Altman plots, Kappa values and ICC analyses were used to determine the agreement between readers for the presence of lesions and the characteristics thereof. These analyses consistently demonstrated moderate to substantial agreement between readers, across all items. These methods do not account however, for instances where the same lesion may be observed by each reader but scored as occurring in neighbouring locations. The studied population is a cross-sectional consecutive sample of well phenotyped patients with established RA. Thus, the generalisability of the study findings to those patients with early or high disease activity should be explored. Similarly, the studied population were recruited from a single site and therefore external validation of the *FFB-Score* is required. In addition, the measures of MRI-determined localised disease activity used within this study have not been validated, although they are reproducible [[12](#_ENREF_12)]. Development of a tool for the evaluation of RA disease activity in the forefoot would significantly enhance work in this area.

**KEY MESSAGES**

* The *FFB-Score* is adequately reliable for the characterisation of bursa-like lesions of the forefoot in patients with RA
* Further validation of the FFB-Score is required.
* Additional validation of MRI-determined disease activity within the joints of the forefoot would be of considerable clinical and research benefit

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**CONFLICT OF INTEREST:** None

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**TABLES**

**Table 1: *FFB-Score* intra & inter-reader agreement**

|  |  |  |
| --- | --- | --- |
|  | Intra-reader agreement | Inter-reader agreement |
| Lesion type | Factor | PEA | PCA | Kappa(Left: right) | PEA | PCA | ICC(SDD) | Kappa(left: right) |
| Intermetatarsal | Fluid | Count | 50 | 100 | 0.55: 0.55 | 50 | 100 | 0.784 (0.60-0.88) | 0.5: 0.5 |
| Shape | 50 | 90 | 0.8: 0.8 | 50 | 90 | 0.816(0.66-0.90) | 0.8: 0.7 |
| Enhancement | 20 | 100 | 0.7: 0.7 | 90 | 100 | 0.950(0.90-0.98) | 0.9: 0.9 |
| MR T1 | 50 | 90 |  | 50 | 100 | 0.792(0.60-0.89) |  |
| MR T2 | 50 | 50 |  | 50 | 50 | 0.783(0.60-0.84( |  |
| Soft tissue | Count | 50 | 100 | 0.75: 0.8 | 100 | 100 | 0.683(0.41-0.83) | 0.8: 0.7 |
| Shape | 40 | 50 | 0.6: 0.6 | 100 | 100 | 0.416(0.10-0.69) | 0.4: N/A |
| Enhancement | 50 | 100 | 0.7: 0.7 | 100 | 100 | 0.716(0.47-0.85) | 0.9: 0.9 |
| MR T1 | 60 | 90 |  | 100 | 100 | 0.698(0.44-0.84) |  |
| MR T2 | 30 | 80 |  | 80 | 100 | 0.687(0.42-0.83) |  |
| Plantar lesion | Fluid | Count | 100 | 100 | 0.9: 0.9 | 100 | 100 | 0.491(0.08-0.72) | 0.9: 0.7 |
| Shape | 100 | 100 | N/A: N/A | 100 | 100 | 0.573(0.19-0.77) | N/A: N/A |
| Enhancement | 100 | 100 | N/A: N/A | 90 | 100 | 0.573(0.19-0.77) | N/A: 0.9 |
| MRI T1 | 100 | 100 |  | 100 | 100 | 0.575(0.23-0.77) |  |
| MRI T2 | 100 | 100 |  | 100 | 100 | 0.491(0.08-0.72) |  |
| Soft tissue | Count | 90 | 100 | 0.8: 0.7 | 70 | 100 | 0.429(0.13-0.71) | 0.6: 0.6 |
| Shape | 90 | 100 | 0.6: 0.6 | 40 | 70 | 0.600(0.002-0.82) | 0.5: 0.6 |
| Enhancement | 90 | 100 | 0.9: 0.8 | 100 | 100 | 0.686(0.27-0.85) | 0.9: 0.9 |
| MRI T1 | 90 | 100 |  | 60 | 100 | 0.098(0.18-0.38) |  |
| MRI T2 | 90 | 100 |  | 40 | 100 | 0.395(0.17-0.69) |  |

**FIGURE LEGENDS**

**Figure 1: Bland & Altman Plots of inter-rater agreement (both feet combined)**

**APPENDICES (Web only):**

**Appendix 1: Lesion site definitions**

Anatomical subdivision into 9 sub-regions using a slice defined bybisection of the midline of the metatarsal head, relative to the short axis of the foot, for medial-lateral boundaries and the base of the lesser metatarsal heads for plantar boundaries. Subdivision of plantar sites is by vertical bisection of the midline of the intermetatarsal space, relative to the short axis of the foot, for medial-lateral boundaries and the base of the lesser metatarsal heads for dorsal boundaries.

1= abductor hallucis tendon, 2 = extensor hallucis longus tendon, 3 = extensor hood, 4 = extensor hallucis brevis tendon, 5 = adductor hallucis tendon, 6 = dorsal interosseous tendon, 7 = extensor digitorum longus tendon, 8 = extensor digitorum brevis tendon, 9 = plantar interosseous tendon, 10 = deep transverse metatarsal ligament, 11 = section of plantar plate, 12 = abductor digiti minimi tendon, 13 = vertical fibres of plantarfascia, 14 = superficial transverse metatarsal ligament, 15 = flexor digitorum brevis tendon, 16 = flexor digitorum longus tendon, 17 = lumbrical tendon, 18 = neurovascular bundle, 19 = sesamoid ligament, 20 = flexor hallucis longus tendon. S = sesamoid bone, M1-5 = head of metatarsal bone 1-5.

**Appendix 2: MRI sequence protocol**

**Appendix 3: *FFB-Score* image atlas, typical score ranges and user guide**