SCORING RADIOGRAPHIC DAMAGE WITH TWO METHODS IN SOUTH AFRICAN RHEUMATOID ARTHRITIS PATIENTS

Dr Sheetal Daya

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Declaration

I, Sheetal Daya, declare that this research report is my own work. It is being submitted for the degree of MMed (RadD) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

DR Sheetal Daya

On this 6th day of November 2017.

Publications and presentations

Currently working on publications from this MMED research.

Abstract

INTRODUCTION:

The many radiographic damage scoring methods in rheumatoid arthritis (RA) patients such as the Sharp van der Heijde (SHS) method are difficult to implement in a clinical setting. The Simple Erosion and Narrowing Score (SENS) method as well as the Scott modification of the Larsen scoring method are both easier to perform and reliable in early RA.

OBJECTIVES:

To evaluate the level of agreement between two scoring methods, the modified Larsen and SENS, and to correlate these scoring systems between radiographic damage, disease activity and disability in early disease modifying antirheumatic drug (DMARD) naïve RA patients

METHOD:

Baseline digital radiographs of hands and feet of RA patients attending the Arthritis clinic of the Chris Hani Baragwanath Academic Hospital were independently scored by 2 radiologists using the modified Larsen and SENS methods. All patients were DMARD naive with a symptom duration of ≤ 2years. Baseline clinical data, disease activity as calculated by the simplified and the clinical disease activity index and physical disability as measured by the health assessment questionnaire was obtained from the METEOR database. The Spearman covariant assessed the correlation between the two scoring systems, and between radiological scores and disease activity and physical function.

RESULTS:

There is strong correlation (r= 0.892; *p*-value 0.00) between the SENS and the modified Larsen scoring methods in patients with early RA. There is no significant correlation between the modified Larsen score and the SENS and disease activity measures, (CDAI (*p*-value 0.479) and SDAI (*p*-value 0.746)) and (CDAI *p*-value 0.77; SDAI *p*-value 0.86)) respectively. There is no correlation between the modified Larsen score and the SENS with the HAQ, (r = -0.168; *p*-value 0.104) and (r= -0.101; *p*-value 0.332) respectively.

CONCLUSIONS:

Both the SENS and the modified Larsen scoring method are simple to perform and have a high level of agreement in early RA. There is no correlation between either scoring methods with disease activity or physical function.

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Abbreviations

ACCP	Anti-citrullinated protein antibodies
CDAI	Clinical disease activity index
CRP	C-reactive protein
DAS	Disease activity score
DMARD	Disease modifying anti-rheumatic drugs
ESR	Erythrocyte sedimentation rate
HAQ	Health assessment questionnaire
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SDAI	Simple disease activity index
SENS	Simple erosion and narrowing score
SHS	Sharp van der Heijde Score

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1. Introduction

Literature review

Rheumatoid arthritis (RA) is a chronic inflammatory, autoimmune disease of unknown cause which affects synovial joints and results in progressive damage if untreated (Emery, 2006). The estimated prevalence of RA worldwide is 1% (Dowman et al., 2012), which is similar to developing countries (Mody and Cardiel, 2008). However there is paucity of epidemiological data regarding the prevalence of RA in black South Africans (BSA). Females are twice as affected than males, with a peak incidence in the 5th decade of life (Alamanos and Drosos, 2005). The classical feature of RA is symmetrical involvement of the small joints of the hands, namely the metacarpal phalangeal (MCP) and proximal interphalangeal (PIP) joints with sparing of the distal interphalangeal joints (DIP) (da Mota et al., 2012).

Aside from the health burden of the disease, there is significant associated socio-economic impact related to RA (Rat and Boissier, 2004) as the loss of physical function, pain and swelling tends to typically involve the peripheral joints (Dougados et al., 2007).

1.1. Diagnosis of rheumatoid arthritis

The diagnosis of RA is made using the 2010 ACR-EULAR classification (Table 1.1) (Aletaha et al., 2010). The scores are derived from 4 categories, namely: number and site of involved joints (score range 0–5), abnormal serology (score range 0–3), elevated acute-phase reactants (score range 0–1), and symptom duration (2 levels; range 0–1). The presence of synovitis in at least a single joint (provided there is no better alternate diagnosis accounting for the synovitis) and a total score ≥ 6/10 is required to definitively diagnose RA (Aletaha et al., 2010).

Table 1.1. ACR-EULAR diagnostic criteria for Rheumatoid Arthritis

Criteria	**Score†**
A. Joints	
1 large joint	0
2 - 10 large joints‡	1
1 - 3 small joints§	2
4 - 10 small joints	3
>10 joints	5
B. Serology	
Negative RF **and** negative anti-CCP	0
Low-positive RF **or** low-positive ACPA¶	2
High-positive RF **or** high-positive ACPA||	3
C. Acute phase reactants	
Normal CRP and ESR	0
Abnormal CRP or ESR	1
D. Symptom duration	
<6 weeks	0
≥6 weeks	1

ACR = American College of Rheumatology;
EULAR = European League Against Rheumatism; RA = rheumatoid arthritis;
RF = rheumatoid factor; CCP = cyclic citrullinated peptide;
ACPA = anti-citrullinated peptide antibody; CRP = C-reactive protein;
ESR = erythrocyte sedimentation rate.
Patients who (*i*) have at least 1 joint with definite synovitis (swelling), (*ii*) with the synovitis not better explained by another disease.
†Add score of categories A - D; a score of ≥6/10 is needed for classification of a patient as having definite RA.
‡'Large joints' refers to shoulders, elbows, hips, knees, and ankles.
§'Small joints' refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.
¶≤3 times the upper limit of normal.
||>3 times the upper limit of normal.

Aetiology of Rheumatoid Arthritis

The aetiology is not entirely known however it is widely accepted that it occurs in a genetically susceptible host that is exposed to an environmental trigger (Alamanos and Drosos, 2005). Smoking is the only environmental trigger that has conclusively been associated with the risk for RA. Smoking results in the citrullination of amino acids in the lung resulting in the production of anti-citrullinated peptide antibodies (ACPA) (Klareskog et al., 2011). Both ACPA and rheumatoid factor (RF) are the two most commonly tested antibodies and predispose to more severe bony erosive RA (Taylor et al., 2011).

Disease activity and physical function

Disease activity is assessed using the Simplified Disease Activity Index (SDAI) (Aletaha and Smolen, 2005) which is a composite score of the swollen joint count (SJC), tender joint count (TJC), an acute phase reactant, c reactive protein (CRP) as well as patient and physical global assessment. The clinical disease activity score (CDAI) is the SDAI without the CRP. Physical disability is assessed using the modified health assessment questionnaire (mHAQ) (Pincus et al., 1983).

1.2. Imaging of rheumatoid arthritis

1.2.1. Role of imaging

In the clinical setting, imaging aids establishing a diagnosis of RA, monitoring joint damage, and prognosticating long term outcome (Ostergaard et al., 2008). X-rays of the hands and feet guide treatment decisions (van der Heijde, 2000). Interventional management (example sonar or fluoroscopy guidance) of RA patients also relies on imaging for joint aspirations and injections (Balint et al., 2002). In the research setting, imaging is useful to assess inflammation, structural joint damage and to evaluate effectiveness of an intervention (Ory, 2003).

1.2.2. Plain film radiography hands, wrists and feet in RA

Antero-posterior projection plain films of the hands, wrists and feet are used to assess joint damage. A single set of films offers only a static impression of the joints, however, serially assessed films permits the physician to assess progressive joint damage (van der Heijde, 2000). X-ray features in the hands and feet of RA include juxta-articular osteopenia, soft tissue swelling, marginal bone erosions, symmetric joint space narrowing (which is an indirect measure of cartilage thickness), subchondral cysts, joint subluxations, dislocation and ankyloses. In early RA, the joints most commonly involved include MCP, PIP, intercarpal and distal radio-ulnar joints of the hand and wrist, while joints affected in the feet include the metatarsophalangeal and PIP's (Brown et al., 2008).

Figure 1.1. Antero-posterior radiograph of the hands demonstrating rheumatoid arthritis

Case courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID: 2741

Advantages of X-rays in Evaluating Rheumatoid arthritis

The advantage of X-rays, compared to ultrasound and MRI, is that they are cheap, readily available, especially in low-income countries with limited resources, and can be blinded for ease of use in clinical trials. They also allow for a permanent recording of joint damage or severity (Ory, 2003, van der Heijde, 2000). It has been shown by Lillegraven that damage in the small joints are a good surrogate for overall joint damage (Lillegraven et al., 2012). An X-ray of the hands and wrists allows a significant amount of small synovial joints to be evaluated using only a single exposure (Drossaers-Bakker et al., 2000). Serial radiographs can be used to quantify, and monitor the amount as well as the distribution of joint disease (Brown et al., 2008).

Limitations of X-rays in Evaluating Rheumatoid arthritis

Though considered an imaging gold standard (van der Heijde, 2000), there are some disadvantages of plain film radiography, which must be taken into consideration. A limitation is that patient’s baseline X-rays may only show non-specific osteopenia, while contemporary treatment strategy results in RA patients being diagnosed and treated before radiographically evident erosive damage has developed, hence radiographs may underdiagnose RA in the early stage of disease (Yazici et al., 2009, Pincus, 2006). This is referred to as the floor effect where pathognomonic findings are only seen later in the course of the disease (Ory, 2003). The ceiling effect describes a limitation whereby radiographic and pathological damage continue despite the maximum score (according to radiographic scoring systems) being attained (Ory, 2003), resulting in an apparent plateau in disease activity despite continued inflammation and destruction. Plain film is not able to assess the disease progression affecting synovium, cartilage and tendons. Other limitations of plain film radiography include limited sensitivity for soft tissue structures such as the synovium, tendons and cartilage, which play an important role in RA diagnosis and disease progression (Tan and Conaghan, 2011). These structures are better evaluated using ultrasound and magnetic resonance imaging (MRI) (Yazici et al., 2009). MRI and ultrasound allow depiction of synovitis, tenosynovitis, bursitis, bone marrow oedema as well as cortical erosions (Boutry et al., 2007, Ostergaard et al., 2008).

Functional status (as measured by the HAQ) is a better predictor of work disability, premature mortality and costs, as compared to plain film joint destruction(Pincus, 2006).

1.2.3. Radiographic follow up and prognostication

Studies have shown a correlation between radiographs and serological tests (CRP, ESR and RF), disease duration and joint deformity, however there is a weak correlation between radiographs and patient pain, joint tenderness, age and functional status (Pincus, 2006, Pincus and Sokka, 2003). In the later stage of RA, there is a significant relationship between disability and joint damage (Lillegraven et al., 2012), which is why radiographic damage has been validated as an outcome measure for RA. An important limitation is that radiographic findings are not able to predict work disability, socio-economic costs nor mortality. This is better assessed using patient tools like the HAQ (Pincus, 2006).

1.3. Radiographic Scoring methods

There are two types of scoring methods: global and detailed. Global methods are easier to perform and involve assigning a single score to each particular joint evaluated, whereas the detailed method allows for two or more variables to be quantified for each joint (Ory, 2003).

The modified Sharp-Van der Heijde (SHS) method is a detailed system that requires two scores for each joint - one for joint space narrowing (scored 0 – 4), the other for erosions (scored 0 – 5) (Table 1.1). Joint space narrowing is assessed in 15 areas in the hands and wrists, and 6 from the feet. For the erosion component, 16 joints in each hand and wrist and 12 joints in each foot are evaluated (Boini and Guillemin, 2001, O'Neill, 2015, Ory, 2003, Sokka, 2008). This results in a maximum erosion score of 280 and a maximum joint space narrowing score of 168, with a total potential score out of 448.

The Scott modification of the Larsen method (modified Larsen's) is a global assessment tool, where joint space narrowing and erosions for each joint are evaluated together against reference radiographs. Joints assessed are the first to fifth proximal interphalangeal joints, first to fifth metacarpophalangeal joints, the wrist (as a single score, multiplied by 5), and the first to fifth metatarsophalangeal joints, thus 15 joints in each hand and 5 joints in each foot are evaluated for a total score out of 200 (Table 1.2) (Ory, 2003, Sokka, 2008, Boini and Guillemin, 2001, O'Neill, 2015).
Multiple studies have demonstrated that the scores from the modified (SHS) and Scott-Larsen methods are significantly correlated, even though the former was demonstrated to be more sensitive (Boini and Guillemin, 2001). The modified Larsen method is less time consuming and easier to apply (Ory, 2003, Finckh et al., 2006, van der Heijde, 2000).

Table 1.2. Sharp – Van der Heijde scoring method per joint

Erosions	Joint space narrowing
0 – Normal	0 – Normal
1 – Discreet erosions	1 – Focal narrowing
2 – 3 – Larger erosions according to surface area affected	2 – Reduction of less than 50% joint space
4 – Erosion extending over middle of bone	3 - Reduction of greater than 50% joint space
5 – Complete collapse	4 – Ankylosis

Table 1.3. Scott Modified Larsen scoring method

Score	Parameter
0	Intact bony outlines and normal joint space
1	Erosion less than 1 mm in diameter or joint space narrowing
2	One or several small erosions, diameter more than 1 mm
3	One or several small erosions, diameter more than 1 mm, on both sides of the joint
4	Severe erosions, where there is usually no joint space left, and the original bony outlines are partly preserved or subluxation
5	Mutilating changes, where the original bony outlines have been destroyed

The (SHS) and modified Larsen methods are used predominantly in research and are difficult to implement in a clinical setting (van der Heijde, 2000, Boini and Guillemin, 2001). A simplified scoring method was therefore developed. The Simple Erosion Narrowing Score (SENS), is based upon the SHS, and assesses the same joints in the hand and foot as the SHS (table 1.3). 16 joints in the hand and 6 joint in the foot are evaluated for erosions while joint space narrowing is considered in 15 joints in the hand and 6 joints in the foot. The positive presence of joint space narrowing is scored as 1 point, as is the presence of any detectable erosion, thus the maximum score per joint is 2 (van der

Heijde, 2000). In the hands, the maximal erosion score is 32, and 30 for narrowing/subluxation. In the feet, the maximal erosion score is 12, and 12 for narrowing/subluxation. As a consequence, the range of the SENS method is from 0 to 86 (van der Heijde et al., 1999).

Table 1.4. SENS scoring method

Erosions	Joint space narrowing
0 – absent	0 - absent
1 - present	1 - present

The SENS method affords similar disease progression rates as the SHS, however it may be limited by the ceiling effect later in the course of the disease by virtue of the smaller score range. This easier method has proven to be reliable in early disease (van der Heijde, 2000, Boini and Guillemin, 2001).

A 2012 study by Barnabe utilized the SENS and SHS methods to assess disease progression and to evaluate if the SENS method is reliable for clinical application. The SHS score was performed by experienced clinicians, and the SENS score was derived from this score. A separate reader with no radiographic scoring training also performed the SENS score. Their study found a strong correlation between the SHS and both the derived SENS as well as the independently scored SENS.

Although less sensitive than both the modified Larsen and the SHS, the SENS method requires less training and is quicker to perform (Barnabe et al., 2012).

A study by Solymossy et al in 1999 demonstrated that the Larsen score calculated from a digitized radiograph is comparable to the original film, even with differing degrees of erosion (Solymossy et al., 1999), thus validating Larsen scores from digital images.

1.4. Predictors of progression of rheumatoid arthritis

Predictors of disease progression and joint damage include positive RF, raised serum inflammatory markers (ESR and CRP), duration of disease and joint swelling, with the most rapid progression occurring in early disease (Ory, 2003). Boers et al found that if a particular joint demonstrated damage, pain or swelling at diagnosis, these factors were predictive of progression of damage within that joint (Boers et al., 2001). This also implies there is a correlation between local inflammation and subsequent joint damage. Another predictor of functional decline is disease activity (Nair et al., 2013).

1.5. Physical disability

The HAQ is a tool used to measure disability. This tool is a patient reported outcome which assesses twenty activities of daily living in eight categories: “dressing and grooming, arising, eating, walking, hygiene, reach, grip and common daily activities” (Pincus and Sokka, 2003). There are four response options to each activity, ranging from ‘without any difficulty’ to ‘unable to do’. According to Pincus et al, patient questionnaires are able to predict functional loss, work disability and death better than radiological and laboratory tests (Pincus and Sokka, 2003)

As the duration of RA increases, so too does the radiographic joint damage and the disability (Scott et al., 2000). Scott et al report that there is a strong relationship between X-ray damage and disability, however they explain that this is only demonstrated in established and late disease (Scott et al., 2000). Lillegraven and colleagues also found no link between the SHS and the HAQ in patients with early RA. This finding is referred to as a 'J-shaped' curve, whereby there is an initial fall in HAQ scores after treatment initiation, with a subsequent increase over time as the disease and joint damage progress (Scott et al., 2003). An explanation for this is that early disease patients have limited joint damage but their disability is attributed to pain and swelling from the acute arthritis.

1.5.1 Non radiological factors affecting disability

There are multiple validated predictors of disability (as measured using the HAQ method) in patients with RA: increasing age, female patients, poor socio-economic status and lower education level (Scott et al., 2003, Scott et al., 2000). Functional state at presentation and level of inflammation are also known to be predictive of poor functional outcome (Emery, 2006). Disability in the early phase of the disease is more likely due to the active inflammatory arthritis causing pain and swelling(Scott et al., 2000).

1.5.2 Radiological factors affecting disability

There is a strong correlation between radiological joint damage and disability later in the course of RA. In early RA, joint damage is not correlated to disability (Lillegraven et al., 2012, Scott et al., 2000). Later in the disease, there is linearity between joint damage and disability (Ory, 2003, Scott et al., 2000, Lillegraven et al., 2012).

1.6. Disease activity

There is a strong correlation between functional disability and disease activity throughout the natural progression of RA (van der Heijde, 2001). It is thus important to measure disease activity to individualize and optimize patient treatment.

There are predefined core sets of disease activity measures as agreed upon by both the European League Against Rheumatism as well as the American College of Rheumatology (Dougados et al., 2007). These variables include tender and swollen joint counts, global assessments of disease activity as determined by both the physician and the patient, acute-phase reactants, pain and assessments of physical disability.

The Simplified Disease Activity Index (SDAI) is simply the sum of tender joint count, swollen joint count (based on a 28 joint assessment), the patient global assessment of disease activity (0-10), the physician global assessment of disease activity (1-10) and the C reactive protein (CRP). A total score is calculated out of 86, with predetermined values for categorizing patients from remission to high disease activity (Smolen, 2003).

The Clinical Disease Activity Index (CDAI) is a similar tool, however acute phase reactants (CRP or ESR) are excluded (Dougados et al., 2007) resulting in an index that does not require blood testing. This means the index can be performed quickly in a clinic setting.

1.7. Rationale for this study

It is well established that serial radiological evaluation and radiographic damage scoring in patients with RA aids disease monitoring and response to therapy. There is however paucity in the South African setting on Rheumatoid arthritis patients ie: assessing radiographic damage, particularly comparing different scoring methods. This study is an attempt to score radiographic damage of the hands and feet in South African rheumatoid arthritis patients using two scoring methods, Scott modification of the Larsen method and the Simple Erosion and Narrowing Score and to evaluate any correlation between these scores and disability as well as disease activity. These scoring methods have been verified for use clinically and in research in early RA, however there is no study to date in South African RA patients assessing the correlation between these two methods, and whether they are interchangeable in the clinical setting.

Study Objectives

1. To score radiographic damage of the hands and feet of DMARD naïve RA patients using two scoring systems (Scott modification of Larsen's score and the Simple erosion and narrowing score (SENS))

2. To test for agreement between the two scoring methods

3. To correlate the two scoring methods with physical disability and disease activity

2.0 Materials and Methods

2. 1 Study type

The research paradigm is a cross-sectional study, nested within the METEOR database, using available radiographs, laboratory data and available clinical information.

2. 2 Study population

The study cohort were early RA patients attending the Arthritis Clinic at the Chris Hani Baragwanath Academic Hospital (CHBAH), Johannesburg, South Africa. The population includes patients from the Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology (METEOR) database from 01 January 2012 – 31 May 2016. The patient's demographic, smoking history and clinical and serological (ACCP and RF) data was obtained from the online international METEOR database which is used to record patient data at each visit (Koevoets et al., 2010). The METEOR database was developed by international rheumatologists as an online, free web-based program. Hospitals and clinics are able to upload and maintain their patient databases within METEOR to allow access to research facilities and other international databases. Rheumatologists are able to document demographic data, disease activity and functional disability. Disease activity is calculated automatically according to the preferred method (CDAI, SDAI, DAS-28 etc.) (Koevoets et al., 2010, van den Berg et al., 2014). Data can be extracted for research from METEOR according to the needs of a particular study.

Inclusion criteria

- Consenting patients over the age of 18
- Fulfilling the ACR/EULAR 2010 criteria for RA (Aletaha et al., 2010)

- Early RA (symptom duration ≤ 2years)
- DMARD naïve at the time radiographs were taken
- Availability of baseline radiographs of the hands and feet on AGFA (Mortsel, Belgium) picture archiving and communication system (PACS), which became active from 1 January 2012 at CHBAH
- Availability of the CDAI, SDAI and HAQ

Exclusion criteria

- Poor quality radiographs as determined by the principal investigator (PI)
    1. Over or under penetrated radiographs
    2. Non inclusion of any joints in the hand or foot
    3. Incorrect radiographic positioning that prevents accurate evaluation of joints
- Factors affecting physical disability such as stroke, congestive cardiac failure, neuropathy and recent surgery

2.3. Methods

X-ray Retrieval Process

Patients fulfilling previously described criteria and whose radiographs were available on the Picture archiving and communication system (PACS) were finally included in the study. This includes radiographs taken from 1 January 2012 to 30 April 2016. PACS, is a computer application for medical imaging, which is designed for radiology departments. It is "an electronic information system" used for acquiring, displaying, storing and transmitting radiological images (Buabbas et al., 2016). The radiographs were extracted to a hard drive to be reviewed by the PI (SD) and a second radiologist (HM) independently, to reduce bias.

X-ray Reading

Limited training of both readers was online, through a teaching website from the University of Sherbrooke, Canada.

(http://rheumatology.usherbrooke.ca/?q=scoresharp#section_3).

Radiographs of the bilateral hands and feet (antero-posterior view) were read using the Apple Mac JGEG viewer, Preview (version 7), by both radiologists. Each set of radiographs were initially read using the modified Larsen method, and then the SENS scoring method. Radiographic scores were entered into a customized report form using an Excel spread sheet (Appendix A). Collated radiographic scores were evaluated and any variation of ≥10% (9 points for Larsen and 20 points for SENS) between the two readers were re-evaluated by both readers together, in order to reach a consensus score.

Both readers were blinded to all clinical information in each patient.

Clinical and demographic data was extracted from METEOR and entered into a second Excel worksheet (Appendix B) after all the radiographs had been evaluated. Thus the PI who was also a reader for this study was blinded to all clinical data during the X-ray reading phase. Radiographic scores were transcribed from Appendix A to Appendix B.

Ethics Approval

Approval was obtained from both the University of the Witwatersrand human research ethics committee (M160553) (Appendix C) and the METEOR executive committee (M146950) (Appendix D).

Study numbers were used in order to maintain confidentiality. METEOR automatically anonymises patients' data by provided a study number. Once radiographs were retrieved from PACS, they were labelled according to study numbers. A key was used to maintain confidentiality. Only the PI and supervisors had access to patients' numbers and study numbers through the METEOR application.

2.4. Statistical analysis

The statistical program "Statistica" version 12.7, as well as STATA version13.0 was used for the analysis.

The Student's T-test was used to compare continuous variables and the Chi-squared test or the two-tailed Fisher's exact test if individual numbers were less than or equal to 5, was used for categorical variables. The correlation between the two readers' radiographic scores was assessed using the Spearman rank correlation test. This is a non-parametric measure of rank correlations between two variables. The Spearman's covariant was also used to assess for correlation between the different scoring methods.

The modified Larsen scores of the two readers were combined and the average was tested for correlation (Spearman covariant) between physical disability as measured by the HAQ, and disease activity as measured by the SDAI and CDAI. The same correlation was performed using the SENS scoring method.

3. Results

3.1. Demographic data

Of the 159 patients on the CHBAH subset from the METEOR database from 1 January 2012 to 30 April 2016, 95 fulfilled the study inclusion and exclusion criteria. Majority of the patients were middle aged females (84%) with a mean disease duration of 9.1 months and moderate disease activity (median CDAI 23.4). Approximately a quarter (24.2%) of patients had smoked at some point and majority (95.5%) were seropositive for RA. (Table 3.1).

Table 3.1. Baseline characteristics of included patients

	n=95 Mean (SD) unless otherwise stated
Female (%)	84.8
Age in years	50.07 (13.8)
Symptom duration (months)	9.17 (5.6)
Ever smoked (%)	24.2
Rheumatoid factor (%)	95.5
[a]CDAI	23.4 (14.1)
Swollen joint count (SJC) (range)	6.03 (0 – 22)
Tender joint count (TJC) (range)	7.68 (0 – 27)
Patient global Visual analogue scale (PG VAS) (range)	6.3 (0 – 10)
Physician global Visual analogue score (PhG VAS) (range)	5.6 (0 – 10)
[b]SDAI	25.7 (15.2)
[c]HAQ DI (0-3)	1.24 (0.8)
[d]CRP(mg/l)	26.8 (34.4)

[e]ESR(mm/h)	33.7 (28.3)

[a]CDAI – Clinical disease activity index; [b]SDAI – Simple disease activity index
[c]HAQ – Health assessment questionnaire ; [d]CRP – C-reactive protein;
[e]ESR – Erythrocyte sedimentation rate

3.2. Radiographic damage scoring using the modified Larsens and SENS scoring methods

Table 3.2. Baseline radiographic scores

	n = 95 median (IQR)
Larsen reader 1	11 (3, 23)
Larsen reader 2	11 (5, 19)
SENS reader 1	7 (3, 11)
SENS reader 2	4 (3, 7.5)
Larsen average (reader 1+2)	11.25 (3.25, 20.5)
SENS average (reader 1 + 2)	5.5 (2.75, 9,25))

All values are median (SD) unless otherwise stated

The modified Larsen and SENS scores showed predominantly early erosive change, with most patients having low scores (Larsen scores <20; SENS scores <10). The distribution of scores was comparable between reader 1 and reader 2, as is demonstrated in figure 3.2. There are some patients who scored higher for both SENS and the modified Larsen, demonstrating more established destructive damage.

To demonstrate an example of the scoring methods, a patient's X-rays are scored in Figure 3.1. Figure 3.1 is an AP of the feet (Figure 3.1.a) and the hands (Figure 3.1.b) of a 29 year old female with RA. Her radiographs demonstrate erosive destruction at the left 1st and right 5th metatarsophalangeal (MTP) joint and the 1st interphalageal (IP) joints of the hallux bilaterally. In addition, there is subluxation of the left 5th MTP. There is an incidental fracture noted of the left 2nd metatarsal.

The hands show erosive change involving both wrists, with the right carpus being more severely affected. There is loss of normal cortical margins as well as indistinct borders of the right distal carpel row. There is also marked joint space narrowing involving all the small joints about the right wrist. This patient's average Larsen score was 54 while her average SENS score was 31.

Figure 3.1.a

Figure 3.1.b AP radiographs of the feet (Fig 3.1.a) and hands (Fig 3.1.b) in a 29 year old female RA patient.

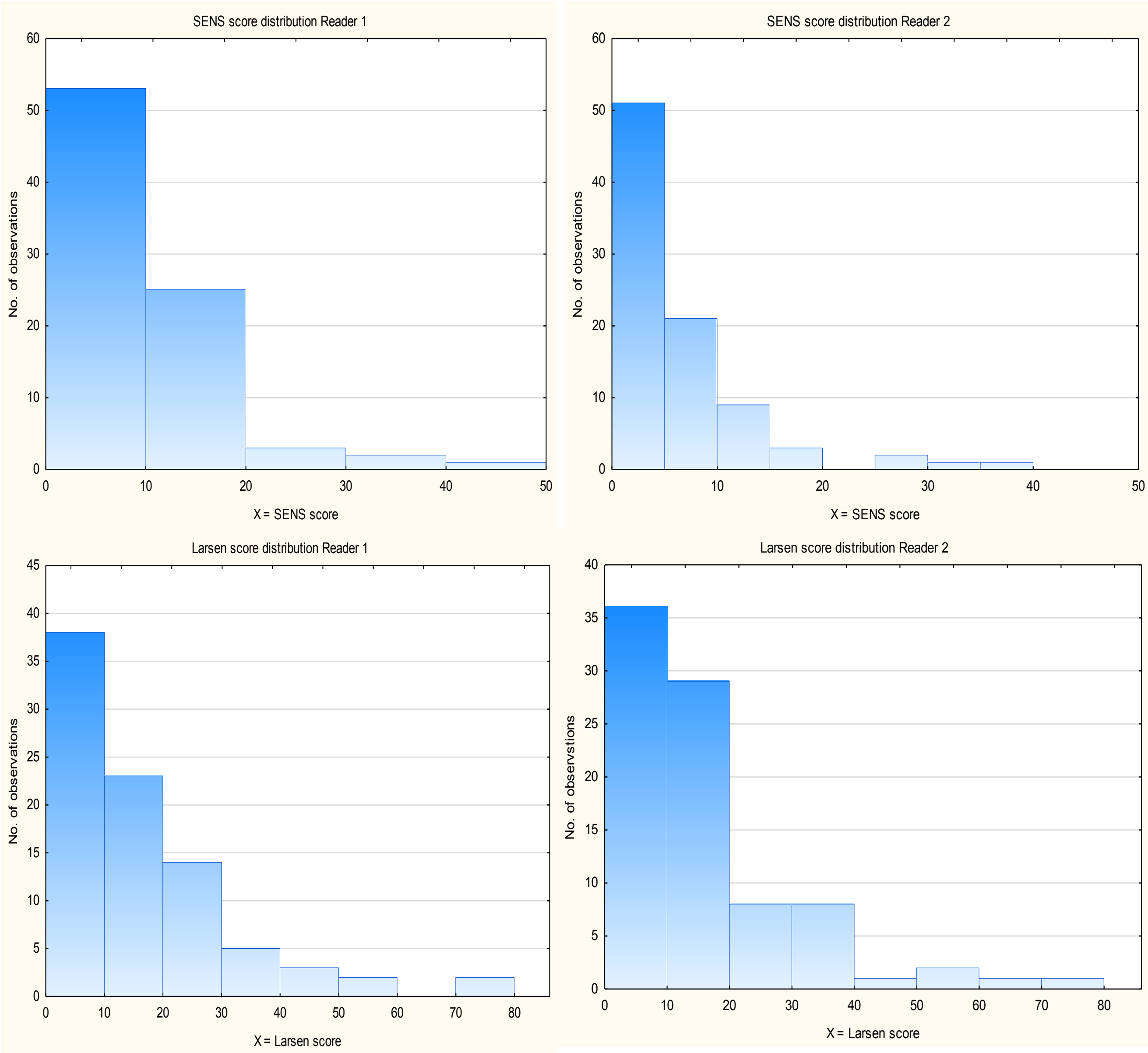

Figure 3.2. Distribution of radiographic scores for reader 1 and 2

The Spearman rank correlation for Larsen score between reader 1 and 2 (figure 3.3) was significant (0.914; *p*-value <0.00). The data points are clustered around the 100% correlation mark (diagonal red line), with no outliers.

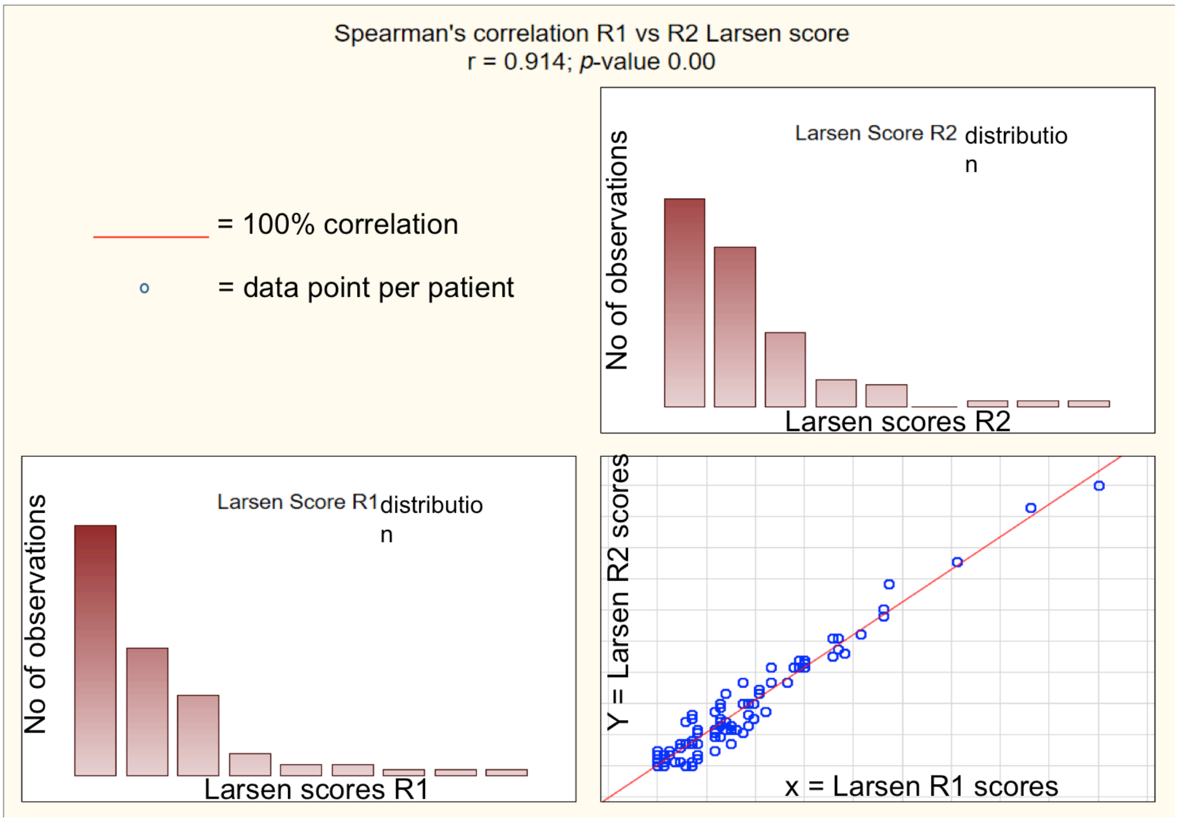

Figure 3.3. Scatterplot of Larsen scores for reader 1 vs reader 2

Likewise, for SENS (figure 3.4), the Spearman rank correlation between reader 1 and 2 is 0.709 (*p*-value <0.001). Despite the data points being less tightly concentrated around the 100% correlation line than the modified Larsen scores, they are still within close proximity to it, and there are no outliers. Thus the radiographic scores between the two readers was better correlated for the modified Larsen than the SENS.

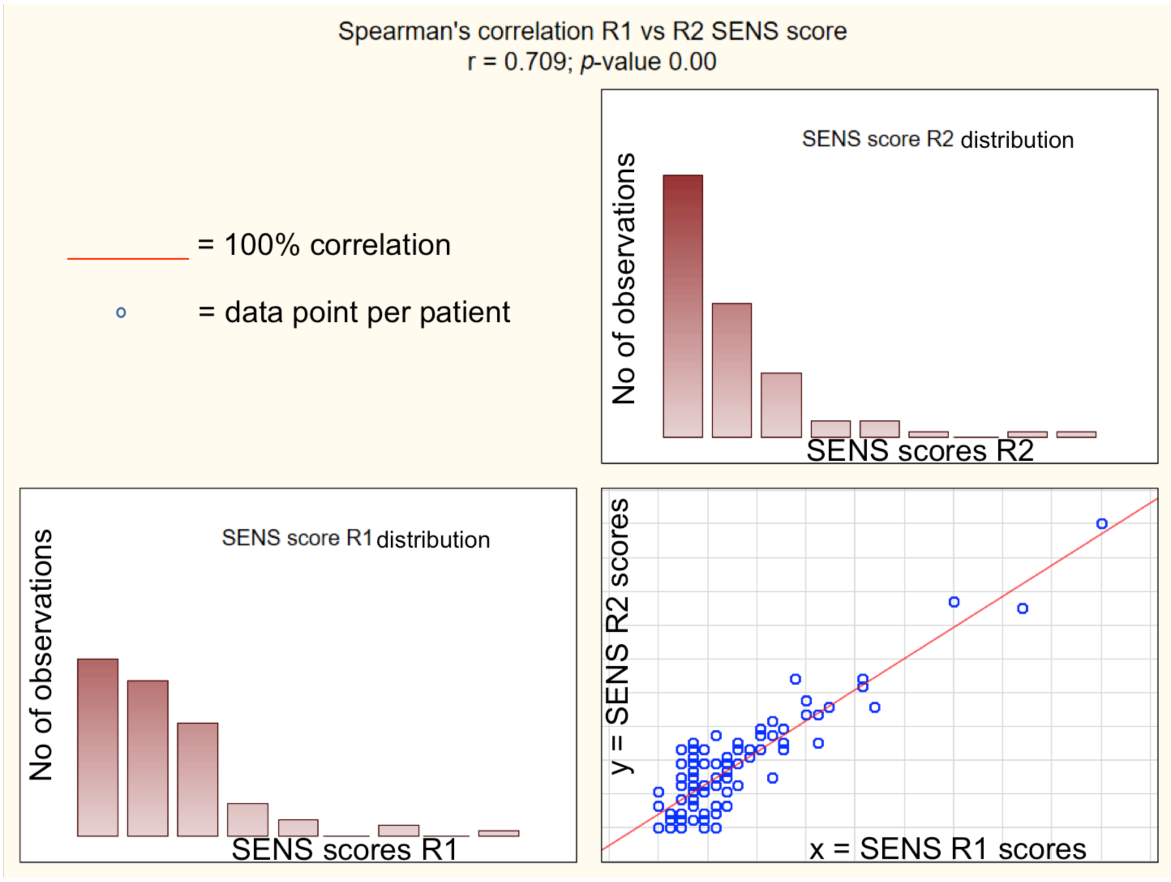

Figure 3.4. Scatterplot of SENS scores for reader 1 vs reader 2

When comparing the average modified Larsen to the average SENS score (figure 3.5), there is a very strong correlation of 0.892 (*p*-value 0.00). The data points are located within close proximity to the diagonal line, which depicts perfect correlation between the two methods, meaning that either of the two methods can be used interchangeably in early RA.

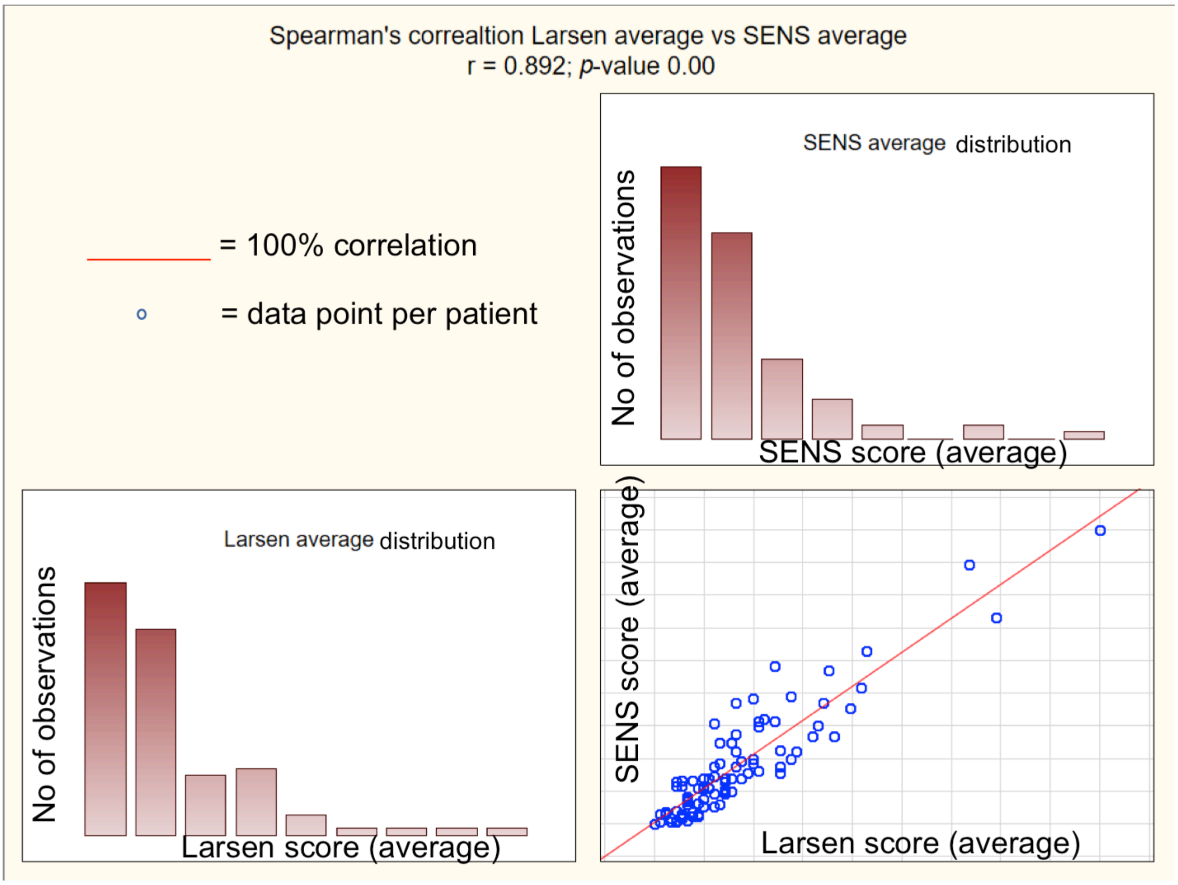

Figure 3.5. Scatterplot of Larsen average vs SENS average and correlation of methods

3.3. Radiographic damage and disease activity

There is direct correlation between modified Larsen score and inflammatory markers ESR (0.24; *p*-value 0.023) and CRP (0.255; *p*-value 0.013) when the Spearman rank correlation test is applied. Similarly, SENS score is also significantly correlated with ESR (0.312; *p*-value 0.006) and CRP (0.312; *p*-value 0.004).

Despite the inflammatory markers correlating with radiographic damage, there is no relation between the modified Larsen and disease activity measures: CDAI (*p*-value 0.479) and SDAI (*p*-value 0.746) (Table 3.3). Similarly, SENS score showed no correlation to either disease activity marker (CDAI *p*-value 0.77; SDAI *p*-value 0.86) (Table 3.5). The individual components making up the SDAI (TJC, SJC, PGA, PhGA) also showed no correlation with either the modified Larsen or SENS scores. (Table 3.3 and 3.4)

There is no significant correlation between disease duration and radiographic damage as assessed using either SENS (0.09, *p*-value 0.34) (Table 3.5) or the modified Larsen (0.13; *p*-value 0.20) (Table 3.3).

There is no significant correlation between the modified Larsen score and ACCP (0.00; *p*-value 0.511) or RF seropositivity (-0.46; *p*-value 0.668) (Table3.3), despite the majority of our patients being seropositive. Similarly for SENS, there is no significant correlation with ACCP (0.00; *p*-value 0.670) and RF seropositivity (-0.40; *p*-value 0.551) (Table 3.4)

Table 3.3. Square root of the average Larsen score and disease activity

Variable	Coefficient	95% CI	P-value
Disease duration	0.04	-0.022 – 0.109	0.190
Smoking	0.21	-0.663 – 1.086	0.633
[a]RF (>14)	-0.46	-2.58 – 1.66	0.668
[b]ACCP	0.00	-0.001 – 0.002	0.511
[c]CDAI	-0.01	-0.037 – 0.016	0.440
[d]TJC	-0.05	-.0114 – 0.010	0.102
[e]SJC	-0.06	-.0137 – 0.021	0.147
[f]PGA	-0.01	-0.029 – 0.003	0.100
[g]PhGA	0.00	-0.019 – 0.016	0.888

[h]SDAI	-0.01	-0.032 – 0.018	0.597
[i]CRP	0.0113	0.010 – 0.022	0.032
[j]ESR	0.01	-.0004 – 0.024	0.176
[k]HAQ DI	-0.35	-0.805 – 0.115	0.140

[a]RF – Rheumatoid factor; [b]ACCP - Anti-citrullinated protein antibodies
[c]CDAI – Clinical disease activity index; [d]TJC – Tender joint count
[e]SJC – Swollen joint count; [f]PGA – Patient global assessment
[g]PhGA – Physician global assessment; [h]SDAI – Simple disease activity index
[i]CRP – C-reactive protein; [j]ESR – Erythrocyte sedimentation rate
[k]HAQ DI – Health assessment questionnaire disability index

Table 3.4. Square root of the average SENS score and disease activity

Variable	Coefficient	95% CI	P-value
Disease duration	0.02	-0.020 – 0.063	0.304
Smoking	0.20	-0.349 – 0.748	0.473
[a]RF (>14)	-0.40	-1.728 – 0.928	0.551
[b]ACCP	0.00	-0.001 – 0.001	0.670
[c]CDAI	0.00	-0.019 – 0.015	0.810
[d]TJC	-0.02	-0.062 – 0.017	0.261
[e]SJC	-0.02	-0.068 – 0.032	0.479
[f]PGA	0.00	-0.008 – 0.014	0.627
[g]PhGA	-0.01	-0.017 – 0.002	0.134
[h]SDAI	0.00	-0.016 – 0.015	0.978
[i]CRP	0.008	0.002 – 0.149	0.007
[j]ESR	0.01	-0.001 – 0.016	0.071
[k]HAQ DI	-0.87	-2.595 – 0.860	0.321

[a]RF – Rheumatoid factor; [b]ACCP - Anti-citrullinated protein antibodies
[c]CDAI – Clinical disease activity index; [d]TJC – Tender joint count

[e]SJC – Swollen joint count; [f]PGA – Patient global assessment
[g]PhGA – Physician global assessment; [h]SDAI – Simple disease activity index
[i]CRP – C-reactive protein; [j]ESR – Erythrocyte sedimentation rate
[k]HAQ DI – Health assessment questionnaire disability index

There is no significant correlation between the average modified Larsen score and the HAQ score (r = -0.168; *p*-value 0.105) as well as between the average SENS and HAQ (r= -0.101; *p*-value 0.333) using the Spearman's covariant (Table 3.5)

Table 3.5. Spearman rank correlation between radiographic damage scores and HAQ

	Spearman R	*P* - value
Average Larsen score & HAQ	-0.168	0.105
Average SENS score & HAQ	-0.101	0.333

4. Discussion

4.1. Results in context

A radiographic score is a quick, cheap and easily accessible means of assessing joint damage in RA patients. Adopting a simple and sensitive scoring method may be beneficial to the clinician. This study demonstrates a strong correlation between the Scott modification of the Larsen scoring system and the SENS score, when assessing radiographic damage in early RA on X-rays of the hands and feet. Our results in a South African context are similar to the study by Guillemin et al (Norway, France), who compared five different scoring methods (Guillemin et al., 2005). In addition the scoring methods, including Larsen and SENS, had good inter- and intraobserver reliability. Lastly, as disease severity increased, the interobserver reproducibility worsened.

Multiple studies showed that the SENS method is more sensitive in early disease (Boini and Guillemin, 2001, van der Heijde, 2000). A recent study (Barnabe et al., 2012) found the SENS performed well in cross sectional studies, with good interobserver reliability, however it was noted to be significantly less sensitive to change in joint destruction over time. Thus the SENS was recommended for use in clinical practice or observational studies. The poor sensitivity of SENS with progressive disease is attributed to the narrow range of scores, resulting in the ceiling effect, therefore for monitoring disease progression or radiographic damage in established disease, an alternate radiographic scoring systems (such as the Sharp, Sharp/van der Heijde or the Larsen modification) is recommended.

The interobserver reliability of the Scott modification of the Larsen system demonstrated in this study (r = 0.892) is similar to a previous study in 2001 (r = 0.92) (Boini and Guillemin, 2001). These results are promising considering that there was no formal training of the radiologists in either of the radiographic scoring systems by an experienced rheumatologist nor musculoskeletal radiologist prior to the study. There was limited online, web-based training for both readers through the University of Sherbrooke, Canada. (http://rheumatology.usherbrooke.ca/?q=scoresharp#section_3). Guillemin et al recommend that trained readers be used, as they perform more accurately in the method for which they were trained. However, in a study conducted in the Netherlands, there was no significant interobserver variability difference between the scores of trained and untrained readers (Zijlstra et al., 2002)

The time to score seven sets of hand and feet radiographs is 3.9 minutes for the Larsen method and 7 minutes for the SENS method (van der Heijde et al., 1999, Wassenberg S, 1998). Given that there is good correlation between the SENS score and the Larsen score in early RA, it is recommended to utilize the Larsen method in a busy clinical setting.

In this study, there was no correlation between radiographic damage and functional disability. These results are similar with a study performed in 2005 (Plant et al., 2005) that assessed the HAQ score in relation to the modified Larsen score (r = -0.06). They found that in early disease, disability was more strongly correlated with CRP (r= 0,24) and other markers of active inflammation. This study goes on to show a significant correlation at 5-year follow up between radiographic damage and HAQ score. As previously shown the correlation between joint damage and functional disability increases with disease duration while functional disability and radiographically evident damage are often not correlated early in RA (Scott et al., 2000, Scott et al., 2003).

Table 4.1. Summary of studies that estimate correlation between functional disability and radiographic joint damage at baseline

Study	**Variable**	**Statistical test**	**Correlation (*p* value)**
Eberhardt (1995)	[a]HAQ vs modified Larsen	Spearman's correlation	0.008 (>0.05)
Fex (1996)	HAQ vs Larsen	Spearman's correlation	0.11 (>0.005)
Mottonen (1998)	HAQ vs Larsen	Spearman's correlation	-0.03 (>0.05)
Gordon (2001)	HAQ vs Larsen	Spearman's correlation	0.465 (0.001)
Plant (2005)	HAQ vs modified Larsen	Spearman's correlation	-0.06 (>0.05)
Daya 2016	HAQ vs modified Larsen HAQ vs SENS	Spearman's correlation	-0.168 (>0.05) -0.101 (>0.05)

[a]HAQ – Health assessment questionnaire;

Table 4.1. adapted from Bombardier et al (Bombardier et al., 2012)

Scott et al (Scott et al., 2003) explain that there is either a weak or no correlation between radiographic damage and disability in early RA. This is explained by the J-shaped curve of disease duration and functional disability. High levels of disability in early disease tend to improve on treatment and when inflammation is decreased. As disease progresses, the HAQ increases as irreversible joint damage results in permanent disability (Bombardier et al., 2012). Multiple previous studies showed that radiographic damage exerts a significant effect on functional disability but only after 6 to 12 years (Scott et al., 2000) (Welsing et al., 2001) (Ory, 2003). Another explanation for the disconcordance between the HAQ score and radiographic damage may be that HAQ may cause large joint dysfunction, while both the Larsen and SENS scores evaluate only small joints. In this study, only small joints were evaluated.

Disease activity has long been known to be an important outcome and therapeutic target in RA trials as well as in clinical practice. This is because it plays a central role in the relationship between disease activity, joint damage and functional impairment (Aletaha and Smolen, 2009) by virtue of the fact that it causes joint damage which eventually results in loss of function. This study was cross-sectional at the time of diagnosis, prior to any therapy being instituted. The correlation between disease activity (as measured by CDAI and SDAI) and radiographic damage was not significant, however there was a significant correlation between acute phase reactants (CRP and ESR) with radiographic scores. Previous studies have demonstrated that there is a positive correlation ($r = 0.59$ for CDAI, p-value <0.0001) (Anderson et al., 2011), (CDAI $r=0.59$ and SDAI $r=0.54$) (Aletaha et al., 2005) however these studies were longitudinal, assessing the relationship between change in disease activity relative to change in radiographic score, thus using time averaged values. It has been previously demonstrated that the radiographic progression in patients with early RA is not linear, and that fluctuation in disease activity were associated with joint damage, but that this is a longitudinal relationship (Welsing et al., 2004). This highlights the need to monitor disease activity closely in patients with RA to guide therapy options, with the end goal of achieving remission.

Earlier studies found that radiographic damage is a result of the additive effects of the disease prior to the current measure of disease activity. This study (van Leeuwen et al., 1997) showed that inflammatory markers CRP and ESR are closely correlated with radiographic damage. Subsequent work (Aletaha et al., 2005) has shown that acute phase reactants are not significantly contributory to disease activity scores.

4.2. Limitations of the current study

A limitation of our study is that neither of the readers are experienced nor formally trained musculoskeletal radiologists. There was also no formal training of the readers by a musculoskeletal radiologist. The limited training was online, through a teaching website from the University of Sherbrooke, Canada (http://rheumatology.usherbrooke.ca/?q=scoresharp#section_3).

There was an agreed acceptable variance (<10%) between the readers for each patients' Larsen and SENS scores, as a result, second read consensus agreements for 32 (33,7%) patients was performed. The importance of a limited variance is that the statistical analysis between radiographic scores and secondary variables assessed in the study (HAQ, CDAI, SDAI, CRP & ESR) is more reliable and not swayed by incorrect radiographic scores. The limitation of this decision is that the agreement between scores of reader 1 and 2 are skewed.

The cross sectional nature of this study also limits the conclusions that one can extrapolate between radiographic damage, disease activity and functional disability. Future prospective studies, also evaluating patients on treatment for RA can follow this South African cohort of patients to see if the relationship between radiographic damage is similar to study populations globally.

4.3. Future applications

The current study utilised two radiologists to score the radiographs. A potential future application would be to perform a similar study using a rheumatologist and a radiologist. The rheumatologist would benefit in every day practice, by using radiographic scores to have an immediate idea of patients' disease progression, thus guiding treatment. The rheumatologist also has a good understanding of each particular patient's background as well as clinical examination findings. This may result in him focusing on particular joints when assessing radiographs. Radiographic damage scoring can be performed by either the rheumatologists or the radiologists. The marked staff shortage at CHBAH means that plain film radiographs of patients attending the arthritis clinics are not reported, let alone scored for radiographic damage. These X-rays are interpreted by the attending physician or rheumatologist in the clinics. Ideally, collaboration between the radiology and rheumatology department should be set up to facilitate training for radiographic scoring for both specialities. The benefits of this would be twofold: patient management would be improved and teaching of trainee rheumatology and radiology doctors to enhance their skills.

4.4. Conclusion

This aim of this study was to score radiographic damage in early rheumatoid arthritis using two scoring systems. We have demonstrated that there is strong agreement between the Larsen and SENS methods, and that these systems are useful in early RA disease. The relatively simple nature of performing these scores means that they can be performed in everyday clinical practice with minimal formal training, as a means to gauge disease severity and to guide future management.

There is no significant correlation between the radiographic scores and disease activity scores, however the inflammatory markers (which make up a part of the disease activity scores) are statistically correlated to both the SENS and modified Larsen scores.

There is no correlation between functional disability and radiographic damage scores of patients with early RA. Continued longitudinal radiographic monitoring is of more value than a single evaluation of joint damage at initial presentation to the health care provider.

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Appendix A: Radiographic scores

		PATIENT IDENTIFIER								
		Larson	0	0	0	0	0	0	0	0
		SENS	0	0	0	0	0	0	0	0
LARSON										
	LEFT	MCP (1)								
		MCP (2)								
		MCP (3)								
		MCP (4)								
		MCP (5)								
		PIP (1)								
		PIP (2)								
		PIP (3)								
		PIP (4)								
		PIP (5)								
		Wrist (x 5)								
		MTP (1)								
		MTP (2)								
		MTP (3)								
		MTP (4)								
		MTP (5)								
EROSIONS		SENS								
	LEFT	MCP (1)								
		MCP (2)								
		MCP (3)								
		MCP (4)								
		MCP (5)								
		PIP (1)								
		PIP (2)								
		PIP (3)								
		PIP (4)								
		PIP (5)								
		Scapho-radial								
		Lunate-radial								
		Distal Ulna								
		Trapeziometacarpal								
		Scapho-tripezial								
		MTP (1)								
		MTP (2)								
		MTP (3)								
		MTP (4)								
		MTP (5)								
		IPJ (1)								
JSN		SENS								
	LEFT	MCP (1)								
		MCP (2)								
		MCP (3)								
		MCP (4)								
		MCP (5)								
		PIP (2)								
		PIP (3)								
		PIP (4)								
		PIP (5)								
		Base of 3rd MC								
		Base of 4th MC								
		Base of 5th MC								
		Scapho-tripezial								
		Scapho-capitate								
		Scapho-radial								
		MTP (1)								
		MTP (2)								
		MTP (3)								
		MTP (4)								
		MTP (5)								
		IPJ (1)								

LARSON									
RIGHT	MCP (1)								
	MCP (2)								
	MCP (3)								
	MCP (4)								
	MCP (5)								
	PIP (1)								
	PIP (2)								
	PIP (3)								
	PIP (4)								
	PIP (5)								
	Wrist (x 5)								
	MTP (1)								
	MTP (2)								
	MTP (3)								
	MTP (4)								
	MTP (5)								
EROSIONS									
RIGHT	MCP (1)								
	MCP (2)								
	MCP (3)								
	MCP (4)								
	MCP (5)								
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	Scapho-radial								
	Lunate-radial								
	Distal Ulna								
	Trapeziometacarpal								
	Scapho-tripezial								
	MTP (1)								
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	MTP (4)								
	MTP (5)								
	IPJ (1)								
JSN	JSN								
RIGHT	MCP (1)								
	MCP (2)								
	MCP (3)								
	MCP (4)								
	MCP (5)								
	PIP (2)								
	PIP (3)								
	PIP (4)								
	PIP (5)								
	Base of 3rd MC								
	Base of 4th MC								
	Base of 5th MC								
	Scapho-tripezial								
	Scapho-capitate								
	Scapho-radial								
	MTP (1)								
	MTP (2)								
	MTP (3)								
	MTP (4)								
	MTP (5)								
	IPJ (1)								

Appendix B: Data collection sheet

Identifier	Sex	Marital Status	Smoking	Larsen Score (SD)	SENS score (SD)	Larsen Score (HM)	SENS score (HM)	RF status	RF value	antiCCP status	ACCP value	Age	Debut of Symptoms

Date of Diagnosis	Symptom duration (Months)	Visit Date	TJC	SJC	ESR	CRP	CDAI	VAS	SDAI	PHYSCIAN_GLBL_ASSMT	HAQ_SCORE	PATIENT_GLBL_ASS	PAIN_SCORE

Appendix C: Ethics clearance certificate

R14/49 Dr Sheetal Daya

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160554

NAME: **(Principal Investigator)**	Dr Sheetal Daya
DEPARTMENT:	Diagnostic Radiology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Scoring Radiographic Damage with Two Methods in South African Rheumatoid Arthritis Patients
DATE CONSIDERED:	27/05/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Nimmisha Govind
APPROVED BY:	Professor P Cleaton-Jones,Chairperson, HREC (Medical)
DATE OF APPROVAL:	22/07/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/2nd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in May and will therefore be due in the month of May each year.

Principal Investigator Signature ____________ Date ____________

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix D: METEOR database ethics clearance certificate

R14/49 Dr Li Ling Winchow

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140950

NAME: (Principal Investigator) Dr Li Ling Winchow

DEPARTMENT: Internal Medicine
Rheumatology
CHBAH

PROJECT TITLE: A Comparison of Convergent Validity and Sensivity to Change of the Conventional Scoring Method to Alternative Scoring Methods of the Health Assessment Questionnaire in Rheumatoid Arthritis

DATE CONSIDERED: 03/10/2014

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Mohammed Tickly

APPROVED BY: Professor P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 20/02/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature   Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix E – Turn it in report

SheetalMMED2016.docx

ORIGINALITY REPORT

%28	%18	%23	%9
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.sancda.org.za Internet Source	%3
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