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Assessing HandScan's Predictive Value in RA Progression

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Internship

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Abstract

This internship aimed to evaluate the clinical value of the HandScan device in predicting progressive bone damage in rheumatoid arthritis (RA) patients compared to the golden standard for long-term outcomes in RA, i.e. the Sharp van der Heijde score. The study utilized the HandScan registry in Leeuwarden, which monitored daily clinical parameters and blinded HandScan measurements in over 500 RA patients during a two-year follow-up. Baseline data had been previously published, and additional data were being analyzed.

The research question of whether the HandScan could provide a better prediction of progressive bone damage than DAS28 was addressed by applying the Sharp van der Heijde (SvdH) score on X-rays. A total of 728 photographs of hands and feet from 91 patients were scored at baseline and after a two-year from the registry. The patients were grouped based on the degree of joint damage progression, and their characteristics were compared.

The Spearman correlation analysis revealed a positive monotonic relation between SvdH and TOS scores, as well as between DAS28 and TOS scores. These findings suggest that the HandScan (TOS) score may be associated with joint damage progression and disease activity. Subgroup analysis for disease progression showed a high and positive correlation between SvdH and TOS mean scores, while the DAS28 mean scores did not demonstrate the same results. The regression analysis indicated that the mean TOS score at baseline and mean TOS of patients per visit had a stronger relationship with joint damage progression. This suggests that the HandScan has the potential to detect joint damage progression.

Overall, this internship provided valuable insights into the clinical value of the HandScan device in monitoring and predicting progressive bone damage in RA patients, highlighting its potential as a useful tool in daily clinical care.

Introduction

Rheumatoid Arthritis (RA) is a grave and progressive condition that can cause a variety of symptoms. The most common physical symptoms include joint pain, inflammation, and stiffness, which can be debilitating and affect a person's ability to perform everyday tasks. In addition, RA can affect a person's overall quality of life, including their ability to work, participation in leisure activities, and rest or sleep. [1] Recent studies have also shown that RA patients are more prone to depression as well as anxiety.[2] RA is an autoimmune disease characterised by chronic inflammation which can lead to the joint as well as bone destruction and in some situations leads to mortality. While the pathophysiology of RA is not fully understood, genetic and environmental factors can also be an influence. [1]

In the last three decades, much progress has been made in treatment options for RA.
Disease-modifying anti-rheumatic drugs, are abbreviated as DMARD and are divided into synthetic (sDMARDS) and biological (bDMARDS). sDMARDS are further classified as either conventional synthetic (cs) DMARDS or targeted synthetic (ts) DMARDS. csDMARDS includes methotrexate, sulfasalazine, leflunomide or hydroxychloroquine and tsDMARDS have developed to modulate specific targets involved in generating inflammation. bDMARDS are biological agents, which means they are from living organisms or their products and they target specific components of the immune system that are involved in the development of autoimmune disease. Some examples of bDMARDs include adalimumab, etanercept, infliximab, rituximab, and tocilizumab. These medications are typically used when traditional DMARDs have not been effective or well-tolerated, or when a patient has a severe or rapidly progressing disease.[3]

The disease activity of RA is measured by the DAS28, an internationally accepted composite measure. The DAS28 is an overall measure of RA inflammatory disease activity, which combines four discrete components. These components are 28-swollen joint count (SJC), 28-tender joint count (TJC), erythrocyte sedimentation rate (ESR) and general health assessment using a visual analogue score (VAS-GH). When assessing disease activity using DAS28, the assessor observes the SJC and acute-phase response, while the patient reports the TJC and VAS-GH. [4] In the last decades, the principles of 'treat to target' have improved the quality of care and decreased joint destruction[3]. Treat to target means that at regular visits the disease activity is measured (eg by DAS28) and if the RA is not below a certain 'target' eg DAS28 < 2.8, then the medication strategy is adjusted. The more frequently patients are assessed, the better the outcome [5]. Where DAS28 represents the current status of disease activity, a radiographic assessment of joint damage is the golden standard for treatment effect over time e.g. one or two-year treatment.

The Sharp van der Heijde (SvdH) score is the international quantification method for the amount of joint damage. The score is based on the presence and severity of erosions and joint space narrowing in the hands and feet. The scoring system evaluates the joints of the hands and feet using radiographs (X-rays) taken over time. The radiographs are assessed for

erosions and joint space narrowing, which are signs of joint damage (disappearance of cartilage) caused by RA. Erosions are areas of bone loss and destruction around the joint, while joint space narrowing refers to a reduction in the space between the bones of the joint. The Sharp van der Heijde score is calculated by assigning a score to each joint based on the severity of erosions and joint space narrowing. For hands, the erosions are scored on a scale of 0-5, with 0 indicating no erosions and 5 indicating destruction of the joint whereas for the feet, the erosion is scored on a scale of 0-10, with 0 indicating no erosion and 10 indicating destruction of the joint. For both the hands and feet, the joint space narrowing is scored on a scale of 0-4, with 0 indicating no narrowing and 4 indicating complete obliteration of the joint space. The scores for all joints assessed are then added together to give a total score for each patient, ranging from 0 to a maximum of 448. Higher scores indicate more severe joint damage[6].

In clinical practices, the reproducibility of DAS28 tends to vary among rheumatologists [7] and it also has two subjective components (visual analogue scale and tender joint count). In people with RA, tenderness may be linked to increased pain processing and other characteristics of fibromyalgia. As a result, DAS28 scores may overestimate inflammatory disease activity in individuals with a high tender-joint count (TJC) that may further lead to overtreatment [4]. Also, there is a growing shortage of healthcare professionals as well as recently, the Dutch government stated that all growth in healthcare consumption must but handled by the current number of healthcare professionals [8,9]. Therefore, other less time-consuming methods are needed for disease measurement, e.g. an automated and objective method would be perfect.

As a result, the HandScan was developed by Hemics. The HandScan is a safe and fast optical imaging device that can visualise the hemodynamics related to joint inflammation. It works by using optical spectral transmission imaging of the hands and wrists before, during, and after venous occlusion at the lower arm. This is done in one continuous measurement. The measurement only takes two minutes and is non-invasive. By using this technique, the Handscan software can recognise the region of interest (joints) and compare the amount of absorption of laser light with adjacent non-joint tissue and hereby is supposed to be an objective measurement tool for inflammation. The Handscan provides an optical spectral transmission (OST) index per joint and a total optical score (TOS) at the subject level. [10].

The "Leeuwarden Handscan Registry" was established to investigate the clinical value of the Handscan in daily clinical care for established RA patients. The study examined the association between the TOS and DAS28 at the subject level and between OST and joint swelling in individual joints. The factors that influence optical imaging techniques were also investigated. The results showed that in comparison to DAS28, the current algorithms of the Handscan are not sensitive enough to differentiate between different levels of disease activity at baseline. However, the Handscan can accurately detect joint swelling, which holds promise for its use in the follow-up of RA patients. New algorithms can be developed to improve the reflection of joint-level performance, rather than overall optical activity. Longitudinal data

from the ongoing registry will help determine Handscan's performance in predicting flares and detecting subclinical disease activity when compared to DAS28. [10]

Until now, the HandScan has never been validated or compared to the golden standard for long-term outcomes in RA, i.e. the Sharp van der Heijde score. Therefore, the objective of this internship is to score and analyse the clinical data (X-rays) available from the Leeuwarden Handscan Registry to know whether the HandScan has a better predictive value than the DAS28 in the development of erosions/narrowing over time.

Materials and Methods

Study group and inclusion criteria

At the outpatient clinic of the Department of Rheumatology, Medical Centre Leeuwarden (MCL), The Netherlands, a total of 520 patients were invited to participate in the Leeuwarden HandScan registry. During two years of follow-up, patients underwent a blinded HandScan during each visit, also several parameters were monitored such as DAS28, CRP, BSE and medication change. Furthermore, X-rays of both hands and feet were taken at baseline and at the last visit two years later.

The inclusion criteria were:

- RA diagnosis for at least two years.
- Ability to independently provide written consent.
- Should be of age 18 or 18+.

The patients were screened in the MCL outpatient clinic agenda and every patient who fulfilled the inclusion criteria was asked to contribute to the registry.

Sharp van der Heijde scoring of X-rays

For this internship, the scoring of all radiographs was started after intensive training. The Sharp van der Heijde scores were entered in an Excel file. Each joint as mentioned in Figure 1-4 for the right and left hands and legs is labelled with each joint name for score entry. The first row of the Excel sheet contains the joint names for both joint erosions as well as joint narrowing for baseline and last hospital visits. A and B were used to identify the baseline and last hospital visits and the scores were put in accordingly.

The score scale for narrowing for both hands and feet is as given below:
0 → No narrowing
1 → Focal or not important enough to quote 2
2 → Generalize narrowing (> 50% space left)
3 → Generalized narrowing (<50% space left) or subluxation of joint
4 → Complete luxation or ankylosis

The score scale for erosion for both hands and feet is as below:
0 → No erosion
1 → Discreet lesion
2 to 4 → Surafce dependant
5 → Bone collapse

Statistical Analysis

The DAS28 and total optical score (TOS) from the Leeuwarden HandScan Registry were extracted and matched to the Excel file. The last visit X-ray of 9 patients out of the 100 scored was not acquired, hence the DAS28 as well as the TOS of the same 9 patients were excluded for the analysis. Descriptive analysis of baseline and last visit of SvdH, DAS28 and TOS scores were performed. The relation between the baseline and last visit between SvdH and TOS scores, DAS28 and TOS and SvdH and DAS28 scores were analysed with the Spearman correlation coefficient. The patients were categorised based on the SvdH disease progression between the last and baseline visit into high, moderate and low disease progression. This was done to further understand the disease progression in each group. A regression analysis model was performed to predict the radiographic progression with baseline visits of TOS (A) and mean TOS of all patients per visit. All the statistical analysis was performed using RStudio and MS Excel.

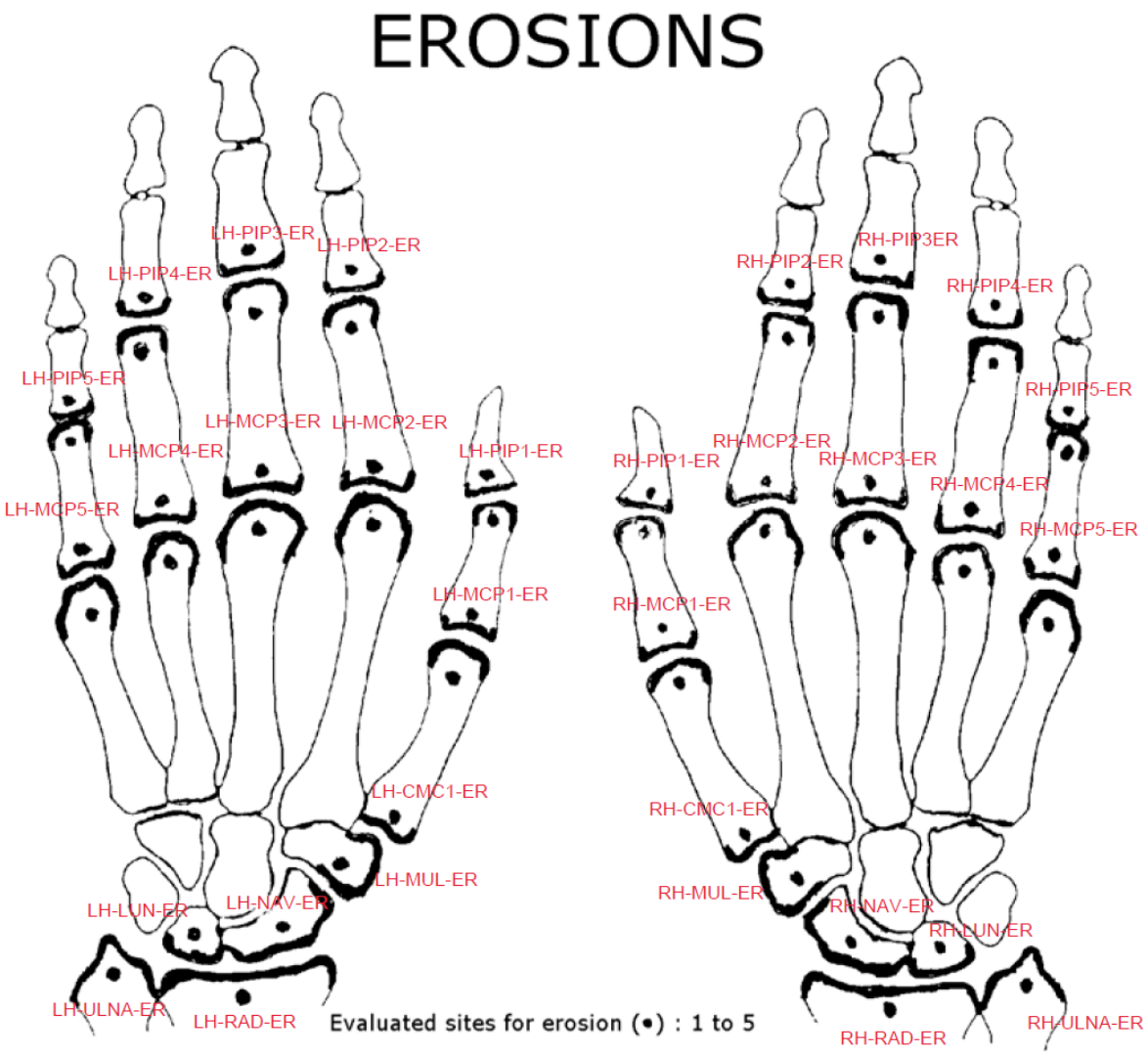

Figure 1: Joint erosion sites labelled with joint names for right and left hands.

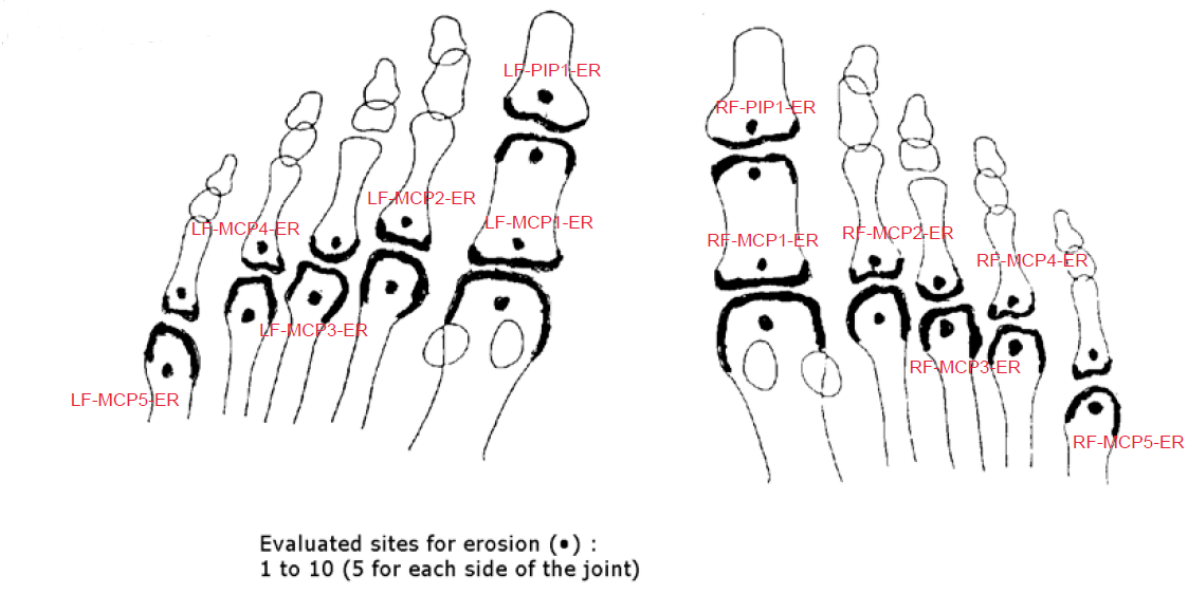

Figure 2: Joint erosion sites labelled with joint names for right and left feet.

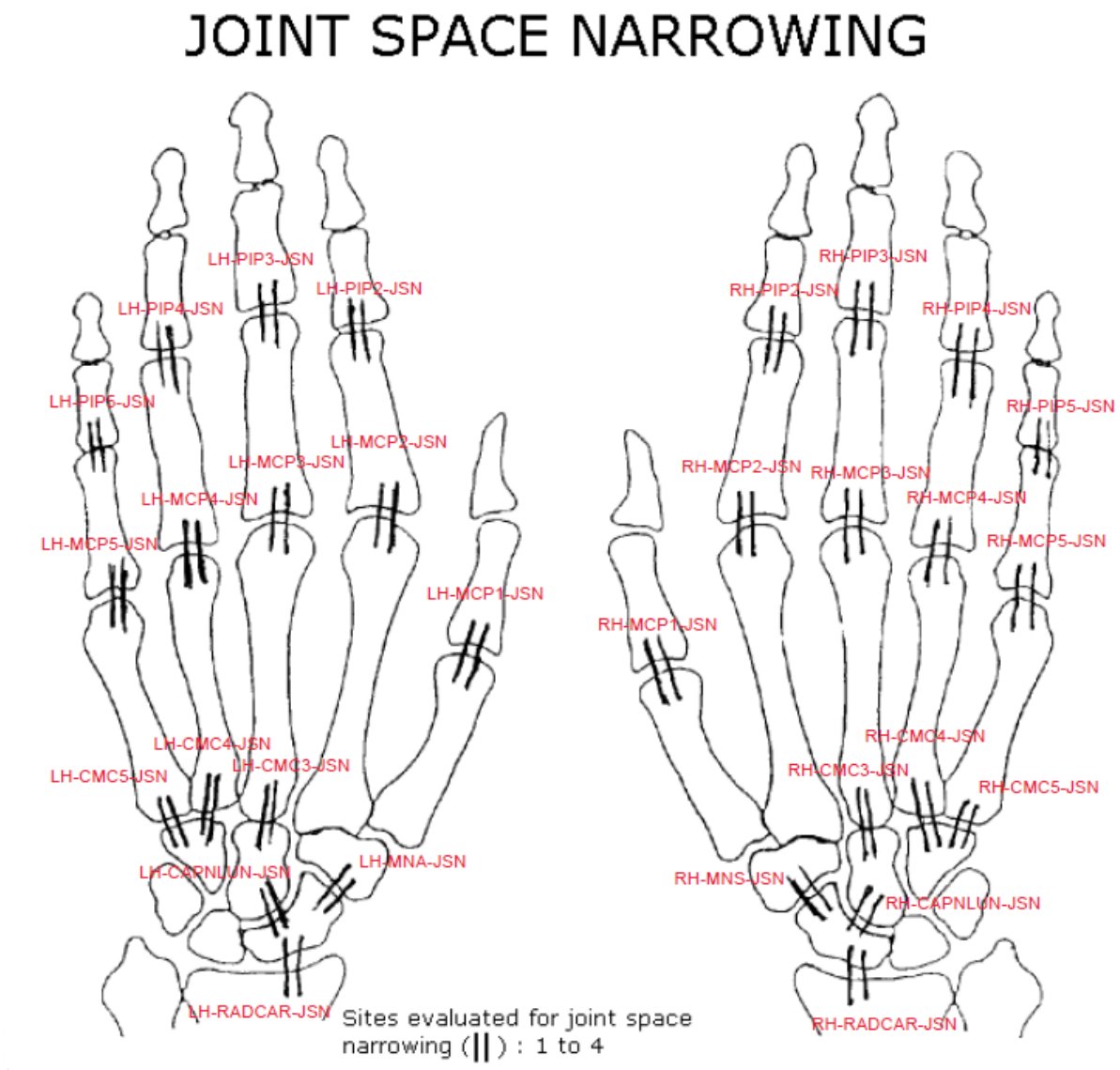

Figure 3: Joint space narrowing sites labelled with joint names for right and left hands.

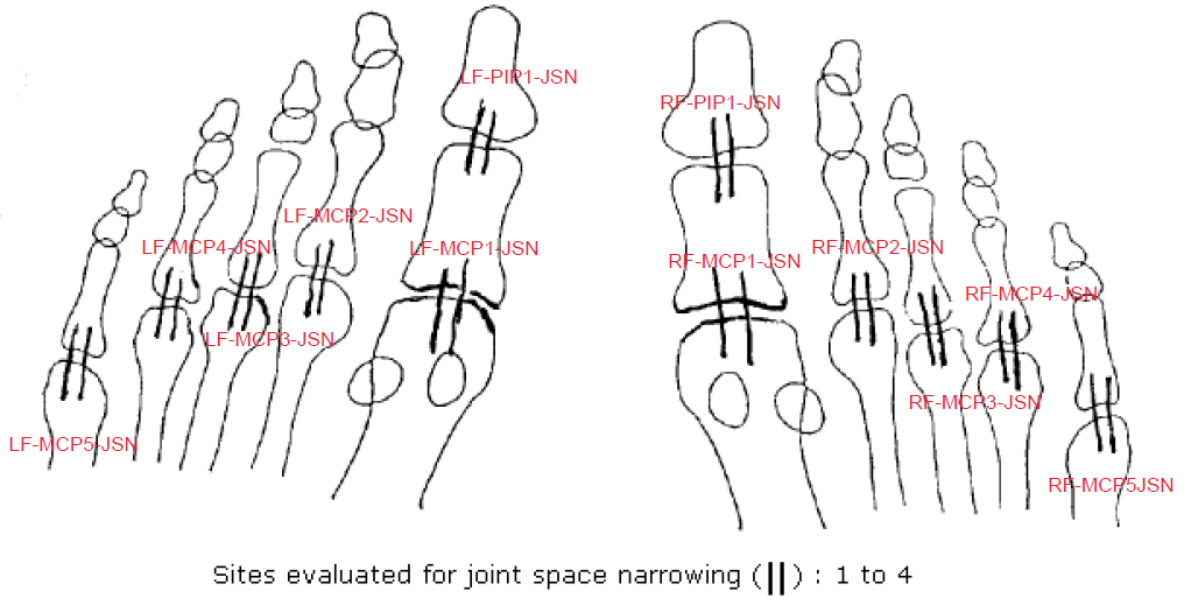

Figure 4: Joint space narrowing sites labelled with joint names for right and left feet.

Results

X-ray scoring: training and exam results

To score the X-rays, training is required and this was done at Leiden University Medical Centre (LUMC) under the supervision of Sytske Anne and Isabell Nevins. LUMC has done similar X-ray scoring training, therefore, having a selective number of X-rays to practise and at the end of the training, an exam is conducted. During the training, the instructor taught me the Sharp van der Heijde scoring method with X-rays of normal, mid-severe and severe cases of RA. Since this subject is highly subjective to the scorer, having more practice with the RA X-rays and being observant helps a lot.

The exam consisted of 33 sets of X-rays with a mix of severe cases of RA and normal cases, where each set of X-rays contain a pair of X-rays of hands and legs through 6 years (4*6=24 X-rays in a set). An ICC (intraclass correlation or intraclass correlation coefficient) score for these 33 sets was calculated. ICC is a descriptive statistic used in statistics when quantitative measurements are made on units that are organised into groups. It describes how strongly units in the same group resemble each other. For ICC interpretation, 30 heterogeneous samples should be obtained along with at least 3 rates for reliability study. Under such conditions, ICC values between 0.75 and 0.9 indicate good reliability and values greater than 0.90 indicate excellent reliability.[11] Therefore a score greater than 0.8 was considered as the pass mark for the exam.

Intraclass Correlation Coefficient

	Intraclass Correlation [b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	,840[a]	,701	,918	11,509	32	32	,000
Average Measures	,913[c]	,824	,957	11,509	32	32	,000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition. The between-measure variance is excluded from the denominator variance.

Figure 5: ICC results from the training exam

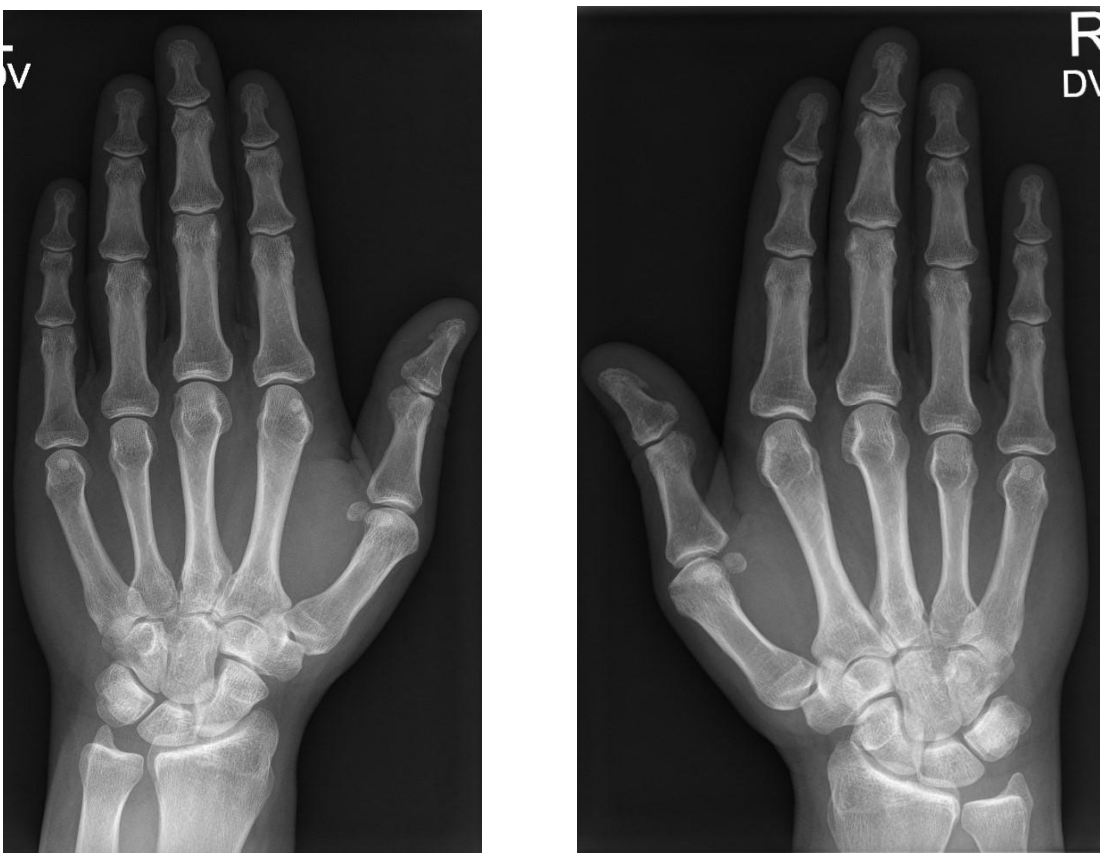

Figure 6: X-rays of hands without erosion or narrowing.

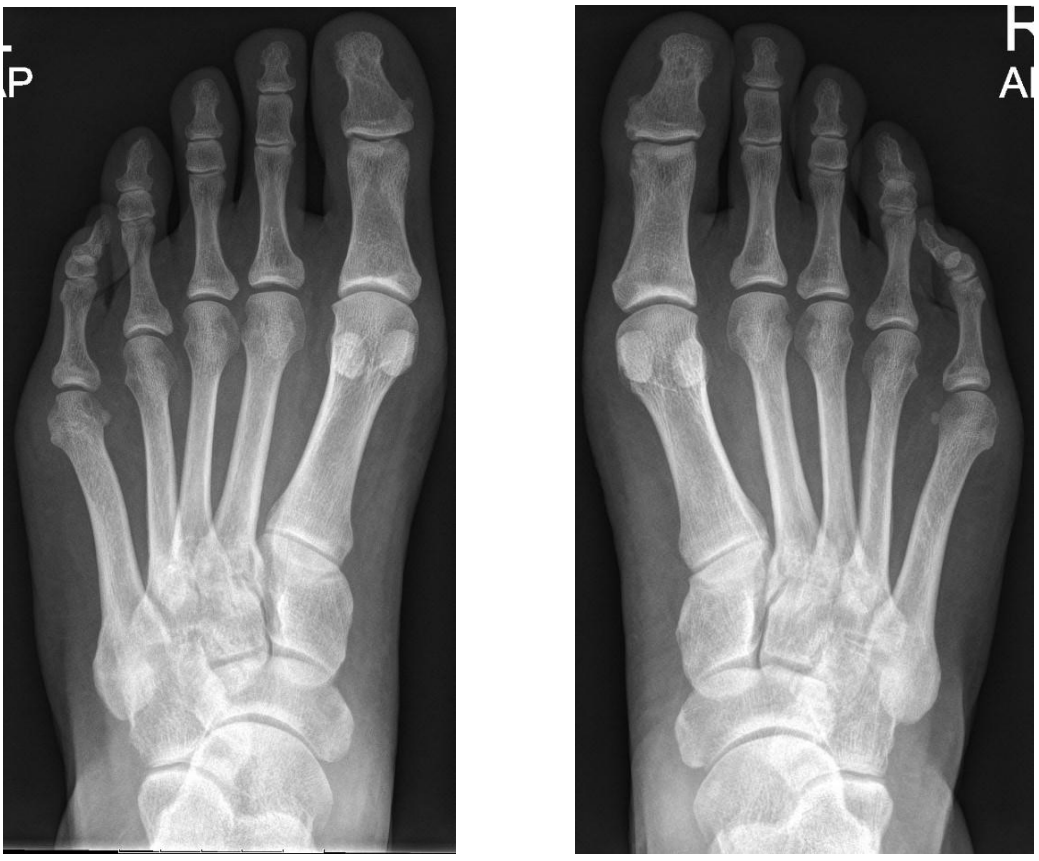

Figure 7: X-rays of feet without erosion or narrowing.

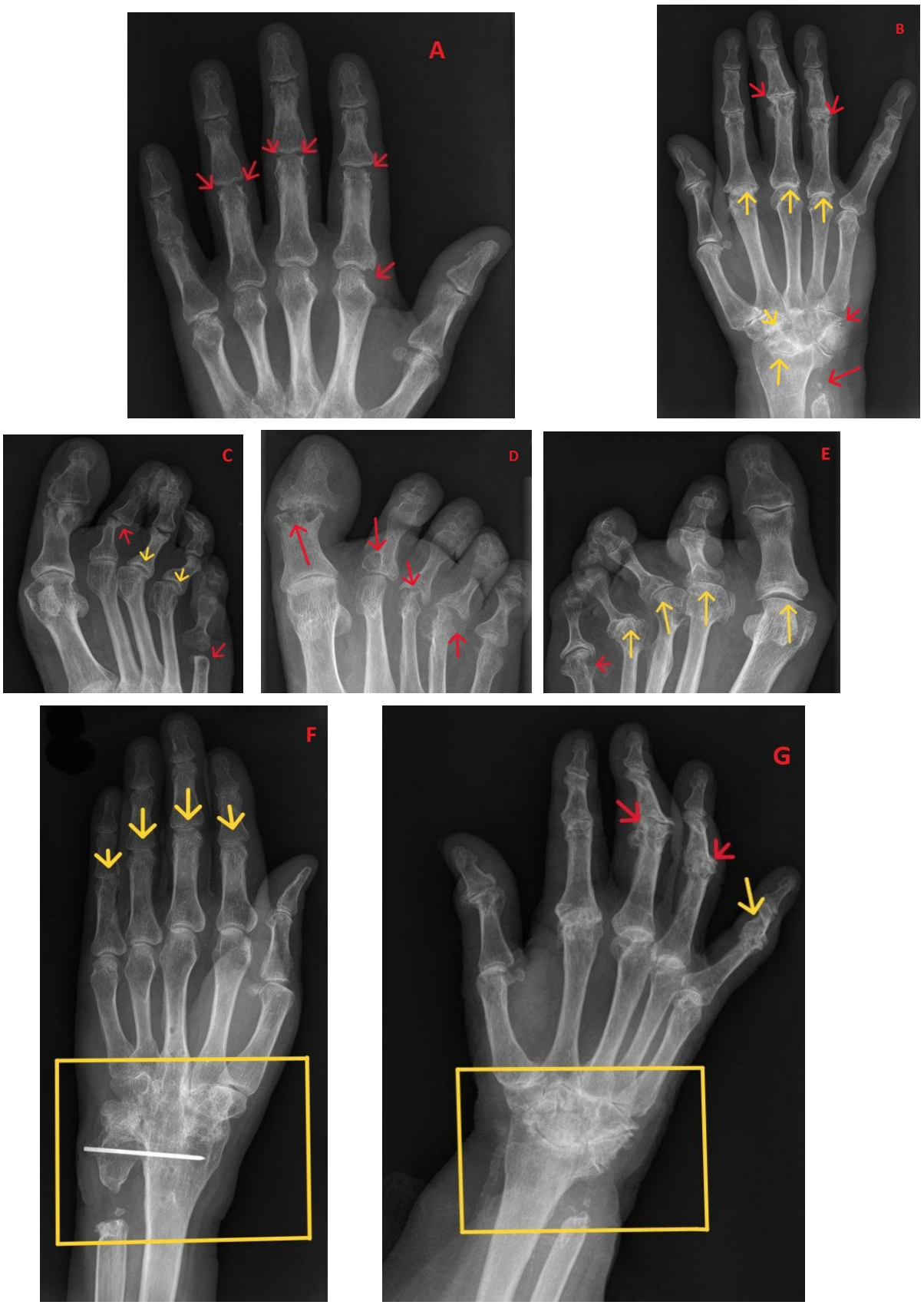

Figure 8: Examples of RA patients with narrowing and erosion of joints in hands and feet. The red arrows indicate the erosion and the yellow arrows and boxes indicate the narrowing.

The X-Rays of hands and feet with no erosion and narrowing are shown in Fig 6 and Fig 7 respectively. Figure 8 (A-G) are examples of joint erosion and narrowing. The joint erosions are indicated with red arrows and the joint narrowing is in yellow arrows and yellow boxes. In Fig 8A, the slight erosions at the PIP joints and MCP2 joints can be clearly seen and a score of 2 or 3 can be given out of 5. The worst erosions can be seen in Fig 8B, 8F and 8G, where the ulna head is completely or partially eroded. In this case, a score of 5 is given. Fig 8B, 8F and 8G are examples of extreme joint narrowing for CMC3, CMC4, CMC5, MNS, CAPNLUN and RADCAR joints. In Fig 8C, 8D, 8E and 8G luxation of joints can also be seen.

Baseline characteristics of the study population from the Leeuwarden Handscan Registry

The baseline characteristics of the study population are presented in Table 1. Patients had a mean age of 61.4 ± 11.4 years and consisted of 171 males (35.3%) and 313 females (64.7%). The prevalence of RF- and ACPA-positivity were 60.5% and 55.3%, respectively.

Variables	Total Cohort (n=520)
Age (years)	61.4 (11.4)
Female	313 (64.7)
BMI (kg/m^2)	27.2 (4.9)
Systolic blood pressure (mmHg)	136 (20)
Diastolic blood pressure (mmHg)	81 (10)
Disease duration (years)*	8.6 [4.9 – 15.1]
Current smoking, n (%)	89 (18.5)
Erosive lesions, n (%)	151 (31.2)
RF positivity, n (%)	293 (60.5)
ACPA positivity, n (%)	268 (55.3)
HandScan Outcomes	
TOS	12.88 (5.07)
OST	0.6 (0.46)
DAS28	
DAS28 (total)	2.48 (0.99)

DAS28 (categorical)	
Remission (< 2.6), n (%)	258 (57.1)
Low (2.6 to ≤3.2), n (%)	98 (21.7)
Moderate (>3.2 to ≤5.1), n (%)	90 (19.9)
High (> 5.1), n (%)	6 (1.2)
28 tender joint count*	1 [0 -1]
28 swollen joint count*	0 [0 - 0]
VAS patient global*	30 [20 – 40]
DAS28 (3VAR)	2.41 (0.95)
DAS28-CRP*	2.07 [1.63 – 2.73]
Comorbidities	
Diabetes mellitus, n (%)	10 (4.1)
Hypertension, n (%)	101 (20.9)
Cardiovascular disease, n (%)	47 (9.7)
Thyroid disease, n (%)	39 (8.1)
Raynaud's phenomenon, n (%)	46 (9.5)
Carpal tunnel syndrome, n (%)	16 (3.3)
Medication, n (%)	
Glucocorticoids, n (%)	11 (2.3)
Methotrexate, n (%)	385 (79.5)
Sulfasalazine, n (%)	78 (16.1)
Hydroxychloroquine, n (%)	125 (25.8)
Leflunomide, n (%)	15 (3.1)
Adalimumab, n (%)	49 (10.1)
Etanercept, n (%)	51 (10.5)
Tocilizumab, n (%)	16 (3.3)
Rituximab, n (%)	13 (2.7)

Infliximab, n (%)	8 (1.6)
Laboratory measurements	
Haemoglobin (g/dl)	8.6 (0.8)
CRP (mg/l)*	2.0 [1 - 5]
ESR (mm/h)*	12 [6 - 23]

Table 1: Baseline characteristics of the study population from the Leeuwarden HandScan Registry

Data are presented as mean (SD) or proportions (n, %). *Skewed data are presented as median (interquartile range). Abbreviations: BMI, body mass index; RF, rheumatoid factor; ACPA, anti–citrullinated protein antibody; DAS, disease activity score; VAS, visual analogue scale; TOS, total optical score; OST, optical spectral index; 3VAR, 3-variables DAS score; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Statistical Analysis

Out of these 520 patients, I scored 100 patients (both hand and feet at baseline and after two years) during this internship period and out of these 100, 9 patients' X-rays weren't acquired during the last hospital visit. Therefore, 91 patients' X-rays were used for analysis.

Descriptive Analysis	**Baseline**			**Last visit**		
	DAS28	**SvdH**	**TOS**	**DAS28**	**SvdH**	**TOS**
Mean	2.69	9.00	12.62	2.91	11.73	13.75
Standard Error	0.13	1.93	0.52	0.32	2.32	0.61
Median	2.62	1.00	11.85	2.26	2.00	12.38
Mode	0.00	0.00	6.01	0.00	0.00	11.75
Standard Deviation	1.23	18.43	4.96	3.06	22.11	5.84
Sample Variance	1.52	339.56	24.58	9.34	488.97	34.07
Kurtosis	0.87	10.45	1.46	11.14	8.73	1.10
Skewness	0.12	3.15	0.93	3.02	2.84	1.00
Range	6.46	94.00	27.45	17.00	120.00	30.22

Table 2: Descriptive Analysis of DAS28, SvdH and TOS at baseline and last hospital visit.

Relation between SvdH and TOS scores, DAS28 and TOS scores and SvdH and DAS28 scores

Using the Spearman correlation coefficient, the relation between SvdH and TOS scores, DAS28 and TOS and DAS28 and SvdH scores was analysed for baseline (A) as well as last visit (B) of the 91 patients. The correlation between SvdH and TOS for both baseline and last visit shows a correlation coefficient of 0.21 and 0.28 respectively, indicating a positive monotonic relationship. For DAS28 and TOS baseline and last visit score, the correlation coefficient is 0.10 and 0.19, also showing a positive monotonic relationship. But the correlation coefficient for DAS28 and SvdH score for the baseline and last visit is -0.03 and 0.05 respectively. This indicates a weak correlation between the DAS28 and SvdH for baseline and last visit scores.

To better understand the disease progression between the baseline and last visit, the patients were divided into subgroups based on the amount of SvdH joint damage in two years. The subgroups were categorised as high disease progression (>6), moderate disease progression (between 2 to 6) and low disease progression (<2).
The mean of these groups was used to investigate the relation between SvdH, DAS28 and TOS scores.
The disease progression is observed with the SvdH and TOS score mean of each group, but the DAS28 score doesn't show the progression.
In all the groups, the mean age of the patients was 54±2. The high disease progression group had more male patients when compared to the other group the female patients were observed to have more.

Mean Score	**SvdH score < 2 [low] (n=68)**	**SvdH score increase between 2-6 [moderate] (n=15)**	**SvdH score increase > 6 [high] (n=8)**
SvdH	0.90	3.73	22.44
DAS28	0.44	-0.52	-1.10
TOS	0.44	2.68	5.57

Table 3: Mean of disease progression of high, moderate and low groups

Regression analysis model to predict the radiographic progression with baseline visit of TOS (A) and mean TOS of all patients per visit

To find out the predictability of radiographic progression with the TOS scores regression analysis model was performed. In the regression analysis with the TOS baseline score as the independent variable, the coefficient of TOS A is 0.3131, indicating that for every unit increase in TOS A, the estimated radiographic progression value increases by 0.3131.

However, the p-value associated with the coefficient is 0.0518, which is slightly above the conventional threshold of 0.05. This suggests that the relationship between TOS A and radiographic progression is marginally statistically significant.

On the other hand, in the regression analysis with the mean TOS of all patients per visit as the independent variable, the coefficient for the mean TOS of all patients per visit is 0.4743. This also suggests that for every one-unit increase of the mean, the estimated radiographic progression value increases by 0.4743. The p-value associated with this coefficient is below 0.05, indicating a statistically significant relationship between the mean TOS of all patients per visit and radiographic progression.

Comparing the two analyses, the relationship between the mean TOS of all the patients per visit and radiographic progression is statistically significant. In contrast, the relationship between TOS A (baseline) and radiographic progression is marginally significant. Additionally, the R-squared values for both models indicate that the variability in joint damage progression explained by the predictors is higher in the mean TOS of all patients per visit model (approximately 8.618%) compared to the TOS A model (approximately 4.185%).

Discussion and Conclusion

The HandScan is a new device developed for monitoring rheumatoid arthritis patients. However, the machine is introduced without a proper, validated guideline on how to use it in daily clinical practice. Several groups studied the association with DAS28, which is limited. However, recent data from Utrecht showed that a composite of TOS with VAS and BSE (the OSDAS) does approach the current DAS28 [12]. Other clinical guidelines are lacking, therefore the machine is not yet used in daily clinical care.

In the HandScan registry Leeuwarden, daily clinical parameters were monitored together with blinded HandScan measurements in > 500 RA patients during the two-year follow-up. Baseline data have been published (ref), and all other data are currently being analysed.

In this internship, we investigated the clinical value of the HandScan when comparing the radiographic outcome over two years in comparison to the current DAS28 disease activity marker and TOS from the HandScan. The main research question ‘Does the HandScan have a better prediction of progressive bone damage than DAS28?’ was investigated by practising and applying the Sharp van der Heijde score on X-rays.

In total photographs (728) of both hands and feet of 91 patients were scored at baseline and after a two-year registry after X-ray training. From these preliminary data, we selected the subgroup of patients with the most progressive joint damage (more than 6 points increase in 2 year time) and compared their characteristics with the group with moderate (between 2 and 6 points) and low progression (less than 2 points progression in two years).

The correlation between SvdH and TOS scores, DAS28 and TOS scores and also DAS28 and SvdH scores were analysed using the Spearman correlation coefficient for baseline and last visit. The correlation results showed a positive relation between both SvdH and TOS scores and DAS28 and TOS scores. This might indicate that the HandScan score is associated with the progression of joint damage and disease activity.

When the patients were subgrouped to further understand the disease progression, based on the joint damage in two years' time, the SvdH and TOS mean scores showed high and positive results with each other. The DAS28 mean score for all the subgroups didn’t show the same results.

The regression analysis performed for predictability of radiographic progression suggests that the mean TOS of all the patients per visit has a more significant and stronger relationship with disease progression compared to TOS A. This shows that the HandScan can pick up the joint damage progression. However, it's important to consider that other factors not included in the models may also influence radiographic progression.

Based on the results from this internship and the previously published articles, it's evident that the HandScan has the potential to be used for daily clinical purposes and could also help compensate for the shortage of healthcare employees by correct assessment of disease activity. But for better improvement of the HandScan, more studies similar to this internship should be done. To improve the long-term predictability and accuracy of the HandScan reading of the x-rays of the other 400 patients in the Leeuwarden HandScan registry is recommended.

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