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Optical imaging compared to clinical examination in 484 rheumatoid arthritis patients: the Leeuwarden Handscan Registry

Ahmed Al Hasan[1] · Floor Reimann[1] · Nic J. G. M. Veeger[2] · Sytske Anne Bergstra[3] · Dan Zhang[1] · Arno R. Bourgonje[1] · Lidy Hendriks[1] · Titus Beertsen[1] · Liliane Zari Riofrio[1] · Freke Wink[1] · Annemarie Schilder[1] · Tom W. J. Huizinga[3] · Reinhard Bos[1,3]

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Abstract

The Handscan is a novel objective optical imaging device for disease follow-up and management in rheumatoid arthritis patients. We aim to examine the association between the baseline outcomes of the Handscan, disease activity levels and joint swelling. The Handscan measures differences in laser light absorption between joints of fingers and wrists and adjacent reference tissue, indicating the presence or absence of inflammation. The device gives an optical spectral transmission (OST) index per joint. The average of these indices is represented in the total optical score (TOS). Associations between TOS and DAS28 at subject level and OST and swelling at joint level were examined. 484 RA patients were included. Compared to patients with high disease activity (defined by DAS28), TOS was significantly lower in patients with moderate (estimated coefficient B: − 7.09, $P < 0.001$), low disease activity (B: − 6.99, $P < 0.001$) and patients in remission (B: − 7.72, $P < 0.001$) but could not distinguish between the latter three disease states. TOS was significantly lower in females (B: − 3.2, $P < 0.001$). OST was significantly higher in swollen than non-swollen joints (B: 0.28, $P < 0.001$). TOS was significantly higher in patients with high disease activity than in those in remission or with low and moderate disease activity. The difference in TOS between males and females should be accounted for in the interpretation of this outcome. The OST at joint level discriminates swollen from non-swollen joints and could be a more promising tool than the overall optical activity reflected in TOS.

Keywords Rheumatoid arthritis · Optical spectral transmission · Handscan · Treat to target

Introduction

Rheumatoid arthritis (RA) is currently managed according to a treat-to-target strategy (T2T) which aims for remission and prevention of structural joint damage [1]. To achieve this aim, disease activity should be accurately and closely monitored, allowing early treatment initiation. This requires the application of frequent and tight disease control by treating rheumatologists. One burden to this strategy is the predicted shortage of healthcare workers in rheumatology care in Europe and North America. In the US for example, it is shown that this shortage will be more than 4000 rheumatology healthcare workers in 2030 [2]. An automated method (robotic) for measurement of disease activity in RA might reduce the burden on healthcare workers [3].

The DAS28 (we refer to the standard DAS28-ESR in this paper, other types of DAS28 will be mentioned accordingly) is an internationally accepted composite measurement for representing RA disease activity [4]. There are, however, several reasons why a better method for RA disease monitoring should be designed. The reproducibility of DAS28 is for example known to vary in clinical practice between rheumatologists [5]. Furthermore, the DAS28 has two subjective components (visual analogue scale and tender joint count) which may lead to overestimation and thereby overtreatment of patients with chronic pain without inflammation [6, 7].

In recent years, ultrasonography is also increasingly used for the assessment of synovitis but this usage is limited in clinical practice, because it is time-consuming and requires

✉ Reinhard Bos
r.bos@mcl.nl

1 Department of Rheumatology, Medical Center Leeuwarden, Henri Dunantweg 2, 8934 AD Leeuwarden, The Netherlands

2 Department of Epidemiology, Medical Center Leeuwarden, Leeuwarden, The Netherlands

3 Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands

expert hands [8]. Furthermore, adding ultrasound in treatment decision-making and targeting therapy to achieve imaging remission did not previously result in improved outcomes, but instead may lead to overtreatment and inefficient use of healthcare resources [9]. The need for a faster and more practical assessment method for the follow-up of RA is still rising.

Recently, the Handscan (developed by Hemics B.V, Eindhoven, The Netherlands) came onto the market as the first non-invasive imaging system for monitoring RA patients [10]. The Handscan is an optical imaging device, designed for the visualization of hemodynamics related to joint inflammation by optical spectral transmission imaging of hands and wrists before, during and after venous occlusion at the lower arm. [11] It is a safe and fast measurement, which takes only 2 min [12]. By using this technique, the Handscan is supposed to be an objective measurement tool of inflammation.

However, clinical data of the Handscan are limited, therefore, we started a registry (the "Leeuwarden Handscan Registry") of double blinded Handscan measurements in established RA patients to investigate the clinical value of the Handscan in daily clinical care. The overall aim was to establish if the Handscan could be used for measurement of disease activity or for specific topics in clinical decision making, such as tapering of medication and prediction of relapse.

The Handscan gives an optical spectral transmission (OST) index per joint and a total optical score (TOS) at subject level, the latter represents the average optical activity of all measured joints. Derived from the data of baseline measurements, this study examined the association between the TOS and DAS28 at the subject level and between OST and joint swelling in individual joints. Furthermore, the theoretically influencing factors on such an optical imaging technique were studied.

Methods

From December 2017 until July 2018, we included patients with established RA in a prospective double-blinded Handscan registry in the Medical Center Leeuwarden, Leeuwarden, the Netherlands. Patients enrolled in a follow-up of 2 years. During this period, the patients underwent a Handscan before each regular visit to their treating rheumatologist. The Medical Ethics Committee of our institution (RTPO Leeuwarden) confirmed the conduct of this study without the need for ethical review and the institutional board approved the execution of the study in accordance with Dutch regulations (nWMO 257, 13 November 2017) and the study was registered in the Dutch trial register (number NL7500, http://www.trialregister.nl). The study was conducted in accordance with the principles of the Declaration of Helsinki (2013). All study subjects gave their informed consent prior to their inclusion in the study.

Study group/patients

The inclusion criteria were:

- A diagnosis of RA existing for at least 2 years, meeting the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria [13].
- The ability to independently provide written informed consent.
- Aged ≥ 18 years.

Patients with photosensitivity and significant deformations of the hands were excluded.

Patients were screened in our outpatient's clinic agenda. Every patient fulfilling the inclusion criteria was asked to contribute to the registry.

Procedures: the Handscan measurement

To start a Handscan measurement, the patient puts his or her hands through a cylindrical opening that holds a pressure cuff. After positioning the hands on the glass plate, the pressure cuffs are slightly inflated to close the gap around the arms before the actual measurement starts. The Handscan measurement itself is simple to perform, painless and non-invasive, it takes 2 min, during which patients can sit comfortably.

During the measurement, the hands and wrists are illuminated sequentially with red and near infrared light (wavelengths 660 and 808 nm). Diffuse transmission images are recorded continuously by a complementary metal-oxide semiconductor (CMOS) camera alternatingly between 660 and 808 nm wavelength.

Main outcome variable: the algorithm of the total optical score

The Handscan measurement will result in an optical spectral transmission (OST) index per joint ranging from 0 to 3. A higher index means less transmission of light, and thus a higher level of inflammation [14]. The total optical score (TOS) of both hands reflects the average of the OST indices of all measured joints. The measured joints are wrists, MCPs and PIPs (22 in total).

Total optical score TOS = Average of OST in the measured joints × 22.

This algorithm is developed in this way to maintain the same range of TOS; regardless of the number of measured

joints or if, for example, only one hand measurement is performed, which is technically possible.

In this registry, Handscan measurements were performed by trained personnel before every regular visit to the rheumatologist. The Handscan measurements are operator independent; the operator (only) ensures proper placement of the hands on the glass plate while the device itself determines the placement of the regions of interest (ROI's). This means OST/TOS scores are not subject to intra- and or interobserver variability.

The frequency of visits was determined by the treating rheumatologist. Both the patient and treating rheumatologist were blinded to the results of the Handscan. The implementation process of this new device was simple. The acceptance of this new technology by patients was broader than initially expected. After connecting the device to the electronic patients' records system, the following results report is displayed after every measurement (Fig. 1).

Statistical analysis

The reports of the Handscan were periodically collected. DAS28, DAS28-CRP, 3 variables DAS28, visual analogue scale (VAS) of the patient, swollen joint count, tender joint count, CRP, ESR, hemoglobin level and medication use were extracted from the electronic health records.

Overall, only 1.4% of the data were missing, with largest missingness in the DAS28 (6.6%) and DAS28-CRP (5%). This missingness was mostly due to lack of one or more components of these composite measurements. The separate components of DAS28 were missing in < 5% of visits, with a range of 0.6% for the swollen joint count to 4.1% for VAS of patients. Due to the low proportion of missing data, we chose to perform a complete case analysis.

At the subject level, the relation of TOS to disease activity scores (particularly DAS28) and other demographic and clinical features was examined with generalized linear models. The differences in TOS between the different DAS28 categories [remission (< 2.6), low (2.6 to ≤ 3.2), moderate (> 3.2 to ≤ 5.1), high disease activity (> 5.1)] was further examined with pairwise comparisons in a post hoc analysis using a Bonferroni correction for multiple comparisons [15].

At joint level, the overall differences in OST indices, as defined per swelling state, were examined using a generalized estimating equation because of clustering of joints within subjects. The same model was used to examine if OST differed significantly per joint between swollen and non-swollen joints.

All analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows, Version 27.0 (IBM Corp., Armonk, New York, USA). *P* values < 0.05 were considered statistically significant.

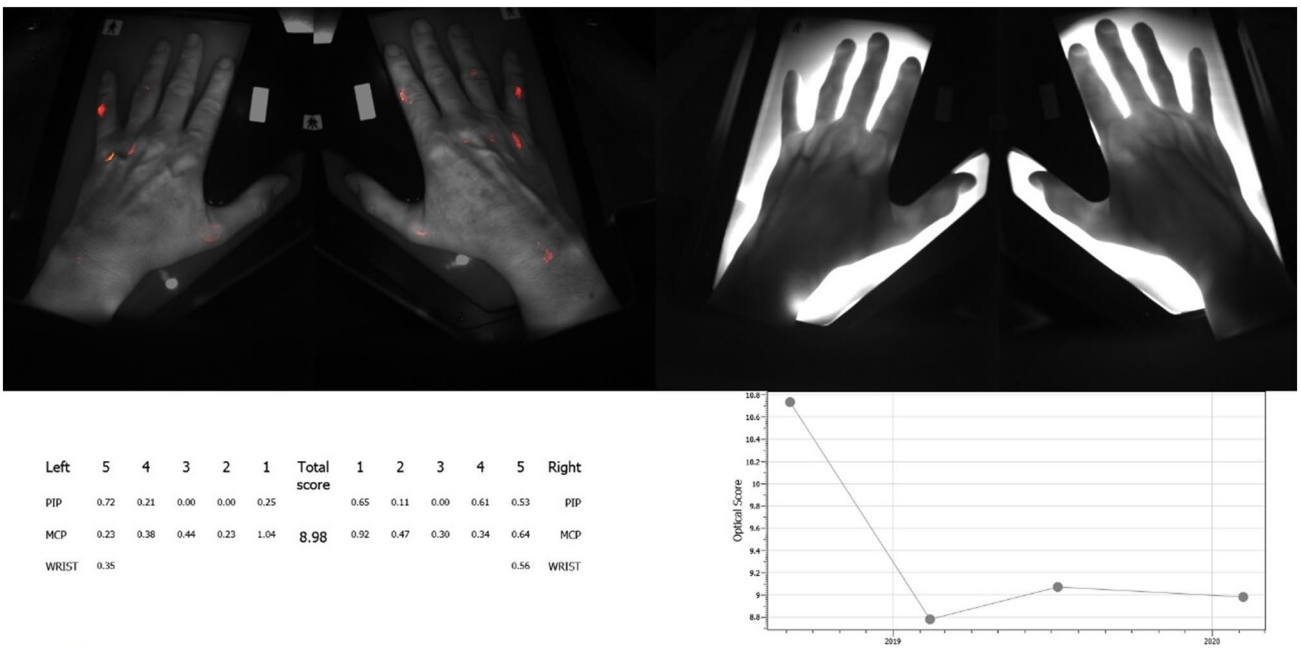

Fig. 1 The report of the Handscan measurement. The optical spectral transmission (OST) indices and the total optical score (TOS) are given in this report. The graph reflects the changes in the TOS value if measurements are repeated over time

Results

Baseline demographic and clinical characteristics of the Handscan registry

Initially, 821 patients with RA were invited to participate in the registry during the screening process, from which 619 patients agreed to participate. The Handscan was successfully bilaterally completed in 484 patients. From the remaining 135 patients, 72 candidates were excluded, because their hands did not fit on the glass plate due to significant deformities and the other 63 patients either completed the Handscan just unilaterally or did not complete it at all, due to periodic maintenance of the device or technical problems at the time of the study visit. These technical problems were caused by software restrictions in the visualization of anatomically small hands, early in the study, when patients with small hands could not complete the Handscan at their baseline visits. After a software update this was corrected in the follow up visits. In this manuscript about the baseline data, these 63 patients were excluded from the analysis (Fig. 2).

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%). Prevalence of RF and ACPA positivity were 60.5% and 55.3%, respectively. The baseline characteristics of the excluded 135 candidates were almost comparable to this group and are presented in the supplementary data (Table S1).

Associations between total optical score (TOS) and disease activity scores and other demographic and clinical characteristics

The multivariable generalized linear model revealed that TOS is significantly associated with DAS28. Compared to patients with high disease activity, TOS was significantly lower in patients with moderate disease activity (B − 7.09, CI − 10.89 to − 3.29, $P < 0.001$), low disease activity (B − 6.99, CI − 10.75 to − 3.28, $P < 0.001$) and patients in remission (B − 7.72, CI − 11.41 to − 4.03, $P < 0.001$). However, pairwise comparisons using Bonferroni correction for multiple comparisons revealed that TOS did not differ significantly between other group combinations (moderate to remission, moderate to low and low to remission) (Fig. 3). This post hoc analysis showed that Δ mean between moderate to remission, moderate to low and remission to low was 0.63, − 0.1, and 0.73, respectively, with a Bonferroni adjusted p value ($p_{adj} = 1$) for all of them.

A statistically significant association was also evident between TOS and DAS28-CRP (B 0.76, CI 0.22–1.32, $P = 0.006$), DAS with only three variables (B 0.62, CI 0.15–1.1, $P = 0.009$), swollen joint count (B 0.47, CI 0.2–0.75, $P = 0.001$) and tender joint count (B 0.24, CI 0.06–0.43, $P = 0.01$). The association between TOS and ESR (B 0.02, CI − 0.02 to 0.06, $P = 0.271$) and CRP (B 0.03, CI − 0.04 to 0.09, $P = 0.436$) was not statistically significant.

TOS was significantly lower in females than in males (B − 3.2, CI − 4.2 to − 2.2, $P < 0.001$). The association of TOS with hemoglobin (B 1.14, CI 0.48–1.81, $P = 0.001$), disease duration (B 0.07, CI 0.01–0.12, $P = 0.023$) and BMI (B 0.11, CI 0.02–0.2, P: 0.019) was statistically significant. There was no statistically significant association between

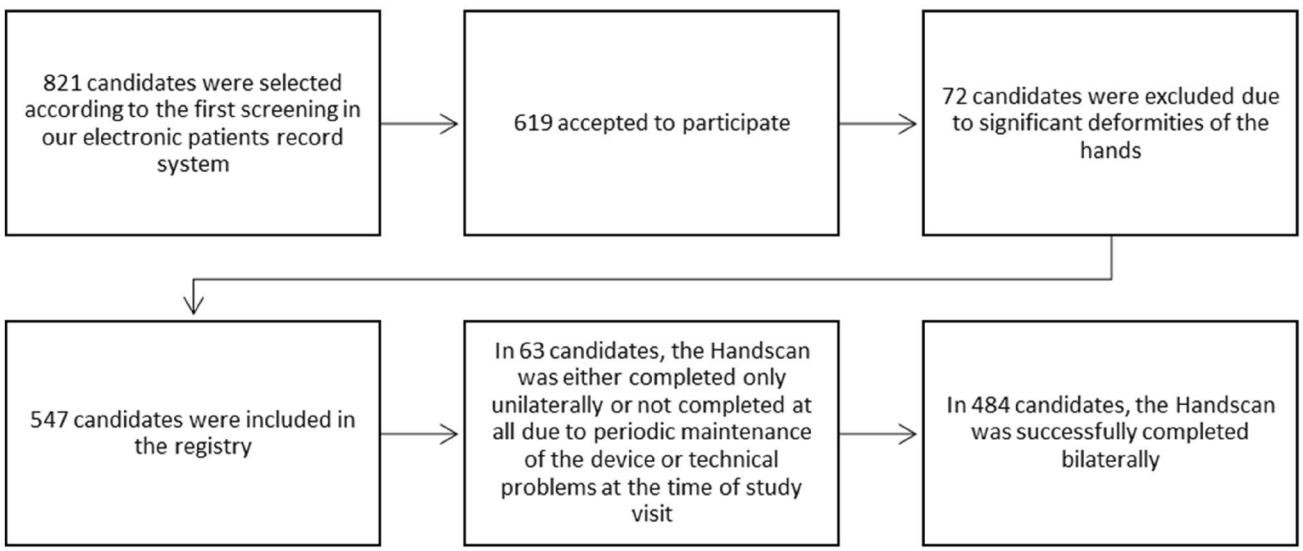

Fig. 2 Flowchart of the inclusion process

Table 1 Baseline characteristics of study population

Variables	Total cohort ($n=484$)
Age (years)	61.4 (11.4)
Female, *n* (%)	313 (64.7)
BMI (kg/m^2)[a]	27.2 (4.9)
Systolic blood pressure (mmHg)	136 (20)
Diastolic blood pressure (mmHg)	81 (10)
Disease duration (years)[a]	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[a]	1 [0–1]
28 swollen joint count[a]	0 [0–0]
VAS patient global[a]	30 [20–40]
DAS28 (3VAR)	2.41 (0.95)
DAS28-CRP[a]	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	
Hemoglobin (g/dl)	8.6 (0.8)
CRP (mg/l)[a]	2.0 [1–5]
ESR (mm/h)[a]	12 [6–23]

Data are presented as mean (SD) or proportions (*n*, %)

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

[a]Skewed data are presented as median (interquartile range)

TOS and systolic blood pressure (*B* 0.01, CI − 0.02 to 0.04, $P=0.361$), diastolic blood pressure (*B* − 0.01, CI − 0.07 to 0.05, $P=0.765$), smoking behavior (*B* 0.23, CI − 0.94 to 1.34, $P=0.705$), Raynaud disease (*B* − 1.3, CI − 2.77 to 0.16, $P=0.08$), erosive lesions (*B* 0.12, CI − 0.83 to 1.07, $P=0.8$), and carpal tunnel syndrome (*B* − 0.56, CI − 2.92 to 1.8, $P=0.641$).

Associations between optical scores and physician's assessment of individual joint inflammation

Physical examination revealed 10,253 non-swollen joints and 274 swollen joints. Generalized estimating equation with joints clustered within patients were performed to assess the difference in OST index as defined by swelling. For all patients together, OST was significantly higher in swollen than non-swollen joints (*B* 0.28, CI 0.12–0.33, $P<0.001$). Per individual joint, the OST values were always higher in swollen than non-swollen joints (Fig. 4). The differences were statistically significant in MCP2 (*B* 0.41, CI 0.18–0.64, $P=0.001$), MCP3 (*B* 0.35, CI 0.11–0.59, $P=0.004$), MCP4 (*B* 0.33, CI 0.18–0.47, $P<0.001$), MCP5 (*B* 0.57, CI 0.23–0.92, $P=0.001$), PIP1 (*B* 0.3, CI 0.21–0.39, $P<0.001$), PIP3 (*B* 0.16, CI 0.03–0.28, $P=0.013$), PIP4 (*B* 0.41, CI 0.21–0.62, $P<0.001$), and PIP5 (*B* 0.25, CI 0.05–0.45, $P=0.014$). The differences in OST values were not statistically significant in MCP1 (*B* 0.14, CI − 0.07 to 0.36, $P=0.205$), PIP2 (*B* 0.17, CI − 0.02 to 0.37, $P=0.091$) and wrist (*B* 0.1, CI − 0.06 to 0.26, $P=0.204$). MCP2, PIP2 and PIP3 joints were the joints that were most often swollen during clinical examination (42 each), followed by the wrists (38) and MCP3 joints (24). The difference in OST in swollen versus non-swollen joints was statistically significant in MCP2, PIP3 and MCP3. Arthritis of the wrist is more difficult for the Handscan to detect than arthritis of the small finger joints.

Discussion

Objective disease monitoring of RA with laser light by usage of non-invasive and fast Handscan measurements seems a promising innovation. However, clinical validation of the Handscan with systemic parameters of inflammation such as ESR, CRP and arthritis activity is limited. This registry is the largest study until date, studying the value and the implementation of this device in daily care. This first report revealed that TOS is associated with DAS28, DAS28-CRP, 3 variables DAS28, swollen joint count and tender joint count. There was no association between TOS and the inflammatory markers ESR and CRP. TOS was significantly higher in patients with high disease activity compared to those in remission or with low-to-moderate disease activity. The

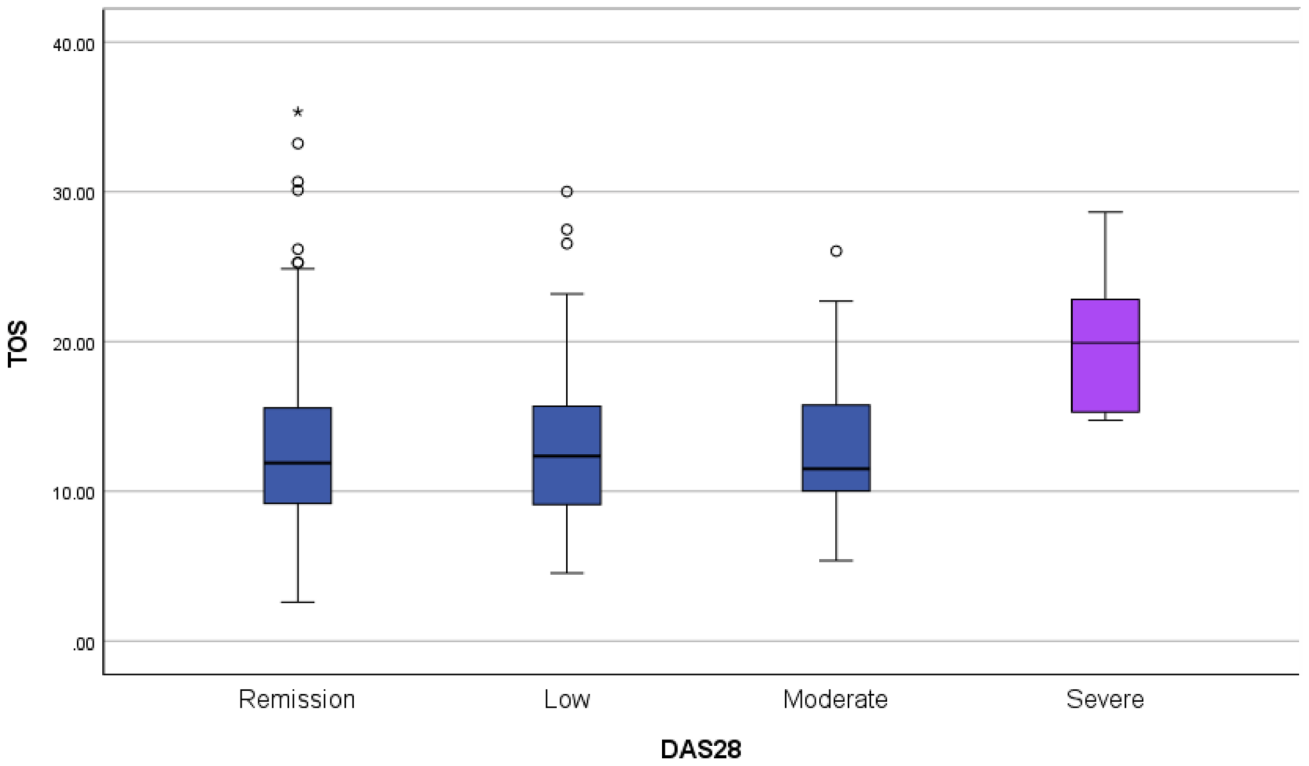

Fig. 3 Boxplot of total optical score (TOS) differences as defined by DAS28 categories. TOS was higher in patients with high disease activity compared to other groups (moderate, low, remission). However, TOS did not differ significantly between other disease activity group combinations (moderate to remission, moderate to low, low to remission)

number of patients with high disease activity was very small ($n=6$). Based on this small number, we cannot conclude that TOS really differentiates high disease activity from remission or low-to-moderate disease activity in clinical practice. Furthermore, TOS did not differ significantly between other disease activity groups. Two previous studies also investigated the relationship between TOS and DAS28. Onna et al. observed that TOS associated better with US than DAS28, but they did not study the association between TOS and the components of DAS28 [16]. Triantafyllias et al. also described an association between TOS and DAS28. They also observed that TOS was only able to distinguish high disease activity from moderate and low disease activity and remission [17]. A possible explanation is that TOS is a reflection of the overall optical activity of all the measured joints and not only the inflamed joints and substantial RA activity is needed to influence it. Another explanation is that TOS could be more sensitive to subclinical disease activity which is not yet measured by DAS28. This baseline analysis is, however, not suitable to confirm this hypothesis. Due to the low swollen joint count it was neither suitable to establish sensitivity to change.

The performance of the Handscan at joint level was more promising. The OST values were in general always significantly higher in swollen joints than non-swollen joints. For most individual joints, this difference was statistically significant. Using the clinical evaluation of the rheumatologist as a reference, the performance of the OST at MCPs and PIPs was better than the wrists. Our results are in agreement with a previous study comparing the Handscan with ultrasound [16]. However, another study concluded that the diagnostic performance of OST was good for MCPs, PIPs as well as for wrist joints [17]. A difference in the absolute values of OST has been observed between joints (Fig. 4) which should be studied in the validation studies of this device.

Potential difference in outcome of this optical imaging technique due to baseline characteristics were tested. From the studied factors, only gender, BMI, disease duration and hemoglobin were found to be associated with TOS. The positive association between TOS and hemoglobin was already expected for this optical technique. An additional sensibility analysis correcting for individual abnormal Hemoglobin values (anemia) needs to be performed. The increase in TOS values with higher BMI could be explained by the obstruction of light transmission through fatty tissue. The high TOS values in males could be due to larger hand surface area, as described by previous studies [17, 18].

The Handscan would be very valuable for clinical use if it could help either to distinguish those patients with subclinical disease activity or to compensate for the shortage

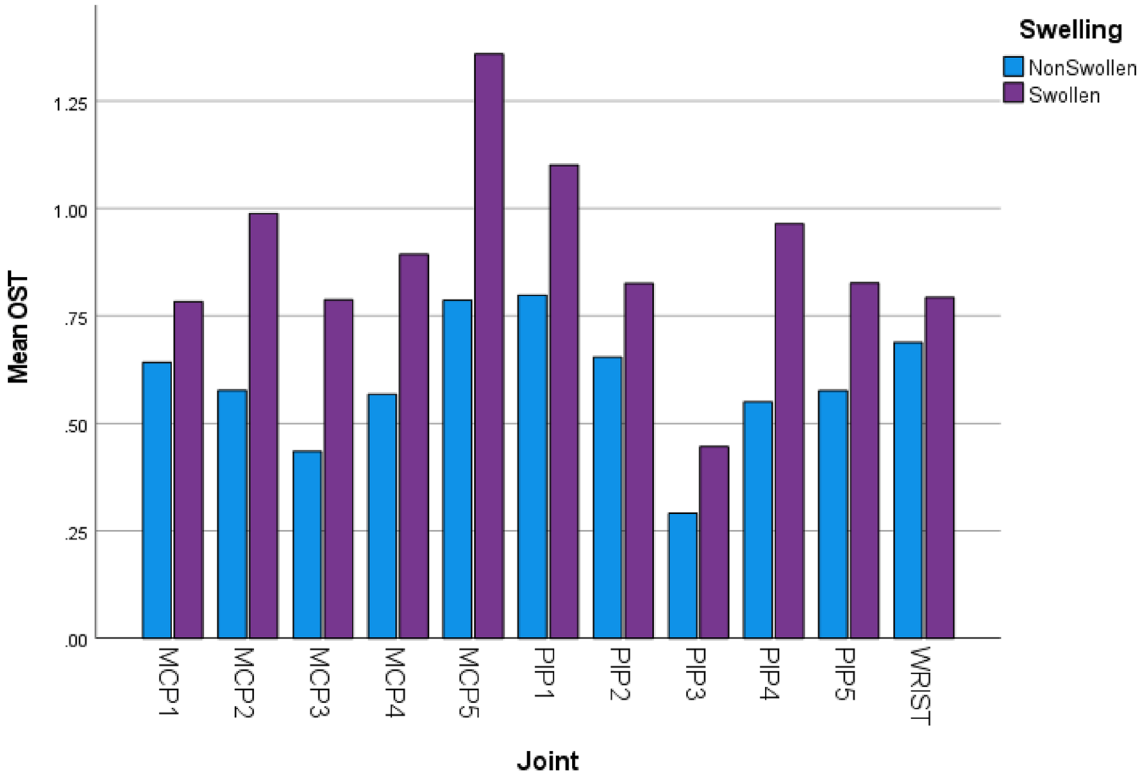

Fig. 4 Difference in optical transmission index (OST) value as defined by swelling. OST was always higher in swollen than non-swollen joints. Except of wrist, PIP2 and MCP1; this difference was significant per individual joint

of healthcare employees by correct assessment of disease activity state. Our study population includes a large number of patients, who were mostly in remission or had low-to-moderate disease activity. This reflects the daily practice in western countries and the cohort is large enough to answer the two aforementioned questions after a follow up period of 2 years. With the current presented data of the baseline visits we are able to verify the association of the current algorithm of the TOS versus the DAS28 and OST per joint with clinical joint swelling.

Study limitations

Despite the large number of the included patients in this analysis, 63 patients were excluded because of not completing the first measurement. The baseline characteristics between the included and the excluded group were however quite similar (Table S1). Technical problems in the startup phase accounted for a large portion of these exclusions. These patients were asked to continue in the registry and during follow-up visits most of these patients underwent successful Handscans. However, the necessary ability to place both hands flat on a glass plate does exclude a substantial proportion of established RA patients, which limits the usage of the Handscan for all RA patients.

We use the clinical joint assessment of the rheumatologist and the DAS28 as comparator for the performance of the Handscan. Usage of ultrasound or MRI would be another objective comparator; however, this was not feasible in this large study population.

Furthermore, multiple experienced assessors performed joint scoring instead of one dedicated study assessor. This is in line with the primary goal of the 2-year registry: to establish the potential added value of the Handscan in daily clinical care.

Conclusion

Based on the current algorithms and compared to the DAS28, the Handscan is not sensitive enough to differentiate between different levels of disease activity at baseline. Nevertheless, the accurate detection of swelling at joint level by the Handscan seems more promising for the follow up of RA patients in the near future. With this knowledge, new algorithms can be developed for better reflection of this performance at joint level rather than the overall optical activity. Forthcoming longitudinal data of the here described registry

will help to determine the performance of the Handscan in subclinical disease activity and prediction of flares compared to the DAS28.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00296-021-05060-6.

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Availability of data All data generated or analysed during this study are included in this article.

Code availability Not applicable.

Declarations

Compliance with ethical standards The study was conducted in accordance with the principles of the Declaration of Helsinki (2013).

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

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