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Increased predictive value of optical spectral transmission in early rheumatoid arthritis through use of patient-adjusted cut-off scores

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Abstract

Objectives The aims of this study were to suggest patient-adjusted optical spectral transmission (OST) cut-off values for the first time and to develop clinical models that predict the probability of an early rheumatoid arthritis (RA) diagnosis based on OST findings and the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria as a reference standard.

Methods OST examinations were performed in newly diagnosed RA patients and healthy controls by the HandScan device. Moreover, RA patients underwent a full clinical [tender/swollen joint counts (TJC/SJC), disease activity score-28 (DAS28)] and laboratory evaluation. OST confounding factors were examined via logistic multivariate regression analyses and patient-adjusted OST-cut-offs were subsequently determined. Furthermore, statistical models to calculate the probability of an RA diagnosis, based on the measured OST values and the presence of OST influencing factors, were developed. Finally, correlations of OST with RA activity parameters were assessed.

Results *1.584* joints of *72* early RA patients were examined via OST and compared to *2.200* joints of *100* healthy controls and *1.166* joints of 53 patients with non-inflammatory arthralgia (NIA), respectively. Overall OST diagnostic performance was excellent in the whole cohort between RA- and healthy control-group [Area-Under-the-Curve (AUC): *0.810* (*95%CI: 0.746–0.873*); $p < 0.0001$], and further improved in RA-patients with ≥ 1 swollen wrist/finger joint(s) [AUC: *0.841 (95%CI: 0.773–0.908*); $p < 0.0001$]. Comparison between RA patients and patients with non-inflammatory arthralgia showed similar results by an AUC of *0.788 (95%-CI: 0.709–0.867*; $p < 0.0001$), and further improved in RA patients with ≥ 1 swollen wrist/finger joint(s) [AUC: *0.822* (95%CI: 0.74–0.90); $p < 0.0001$]. For the assessment of an adjusted RA diagnosis probability, two gender-specific statistical models were developed, based on OST values and patient age. OST cut-off values of *11.2* and *18.21* were calculated for female and male patients with active disease (sensitivity *93%* and *67%;* specificity *71.2%* and *90%)*, respectively. Among RA patients, OST was associated moderately/significantly with DAS28 ($r = 0.42, p < 0.001$) and swollen joint count ($rho = 0.355, p = 0.002$).

Conclusion The development of patient-adjusted OST cut-off values and the suggested statistical models significantly enhance OST's diagnostic performance, supporting its utility in differentiating between RA and non-inflammatory conditions. Future research should include a broader spectrum of arthritis types to validate OST's comprehensive diagnostic utility also across various inflammatory arthritides.

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Introduction

Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease, typically characterized by symmetrical polyarticular swelling, pain, and morning stiffness [1]. Without prompt treatment, RA can result in irreversible joint damage and physical disability [2]. RA is the most prevalent immune-mediated inflammatory arthropathy with an increasing global prevalence and incidence during the last decades [3, 4]. At the same time, many countries worldwide suffer from a lack of rheumatologists and therefore patient care can be suboptimal [5–9]. Failure to initiate therapy within 3 months from the appearance of the first symptoms ("window of opportunity"), associates with a higher risk of radiological progression and a lower probability of achieving long-standing disease remission. Thus, a timely diagnosis is essential to achieve acceptable outcomes and an improved overall prognosis [10].

Next to clinical examination and assessment tools such as the Disease Activity Score 28 (DAS28), several complementary diagnostic tools, like joint ultrasound (US) and magnetic resonance imaging (MRI) are used in everyday practice, to assist rheumatologists to reach an accurate diagnosis promptly. However, the aforementioned diagnostic modalities can be characterized by various limitations. For example, the US can be time-consuming, particularly when thorough multiple joint scoring of both grey scale (GSUS) and power Doppler (PDUS) examinations is performed [11]. Moreover, the US is performed mainly by physicians, and US examinations are examiner-dependent [12]. On the other hand, MRI is associated with high costs and is therefore often performed unilaterally [13].

For these reasons, there is a need for new diagnostic tools that can support everyday Rheumatology practice, free from these restrictions. Moreover, new assessment methods that can be also used by non-Rheumatology specialists (i.e. general practitioners) are needed to improve health care status and shorten the time-to-diagnosis of patients with joint inflammatory conditions. One of these modern modalities (HandScan®, Dem-con-Hemics, the Netherlands) is based on a diagnostic methodology called optical spectral transmission (OST) and can assess changes in vascularity using a red- and infrared-light-associated technology. When a joint is inflamed, increased speed and magnitude of blood pooling occur, due to inflammation-associated changes of vascularity [14, 15]. For the same reason, transmission of light through the inflamed joint decreases, and OST can quantify these blood flow changes in a non-invasive manner [16–20].

Early data on OST revealed a moderate-good diagnostic performance in assessing inflammatory changes in patients with RA, compared to healthy controls. Moreover, OST showed moderate-to-strong correlations with clinical and joint-US activity markers of RA and a high diagnostic value during disease follow-up in cohorts examined by our and other research groups [16, 18, 21, 22]. On the other hand, our working group was able to show that OST results can be confounded by various patient-associated characteristics, such as gender and age, which can complicate the establishment of universal cut-off values and decrease the diagnostic performance of OST [21]. Interestingly, Verhoeven et al. came to similar conclusions finding that gender can influence OST values and that male patients may have intrinsically higher OST scores compared to females [23, 24]. It is paramount for every diagnostic method to have well-established cut-off values that allow a clear statement regarding the presence or absence of the examined abnormality. However, clear OST-cut-off values have not been proposed in the literature until today. Moreover, in the clinical routine, there have been cases of observed overlapping OST values in RA patients with similar grades of disease activity. A possible reason for that could be the fact that patient-associated influencing factors (i.e. gender, age, hand size) may have an effect on OST that would not allow the suggestion of valid cut-off values [21].

Therefore, this study aimed to examine the associations of OST with patient-associated influencing factors in a cohort of early RA patients and to suggest OST-cut-off values after adjustment for the effect of these factors. Moreover, we sought to describe a clinical model that would represent the probability of a positive RA diagnosis based on OST values and the presence of confounders in every individual patient. The primary focus of this work was on differentiating RA patients from those with other non-inflammatory conditions.

Methods

For this exploration, we screened consecutive patients admitted to our inpatient and outpatient clinics with arthralgias of the wrist and/or finger and a suspected diagnosis of RA with a symptom duration of less than 6 months. Therefore, in case of a positive RA diagnosis, the term "early RA" is used. RA diagnosis was made by the 2010 American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) classification criteria [25]. Healthy hospital co-workers who responded to an open call for study participation, without underlying inflammatory disease or arthralgias, were

included as a control group and were examined via OST. Moreover, a further group of patients that were diagnosed with non-inflammatory arthralgia (mostly fibromyalgia and/or osteoarthritis) during the screening and diagnostic process was used as a second (intrinsic) control group.

Exclusion criteria for all groups were age < 18 years, joint prostheses/implants, recent trauma or surgery, and known photosensitivity. Additionally, we excluded all patients under immunosuppressive/glucocorticoid medication.

Data collection

We documented gender, age, measured weight, and height for calculation of BMI (kg/m^2), cigarette smoking, history of known arterial hypertension (HTN), diabetes mellitus, and size of both hands (mean surface covered by 2 hands in cm^2) in all groups. Additionally, tender (TJC) and swollen joint count (SJC), were examined on admission day and documented by a trained person who also documented patient-reported disease activity on a visual analogue scale (VAS). Inflammation markers [C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)] were routinely tested and used for the calculation of DAS28 values. ELISA was used to assess rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP).

All subjects gave their written informed consent, and the assessment was reviewed and approved by the Standing Committee for Clinical Studies of Rhineland-Palatinate, Germany, in adherence to the Declaration of Helsinki.

OST examinations

OST examinations were performed by trained study nurse staff blinded to the results of clinical and laboratory examinations, and to patient diagnosis. OST measurements were performed as previously described [21]. Shortly, during an OST measurement, the subjects slide their both forearms into the HandScan through 2-cylinder openings which hold pressure cuffs, similar to blood pressure cuffs and which are located on the front of the device. Patient hands are then placed on a glass handrest and subsequently, red and near-infrared laser light at wavelengths of 660 nm and 808 nm illuminate the palmar side of the distal forearms (both wrists, MCP, PIP, and reference areas for every joint) (Fig. 1). A metal oxide semiconductor (CMOS) camera which is placed at the upper side of the device records the light transmitted through the hands at a rate of four frames/second. A complete measurement lasts about 100 s and consists of 3 phases: During the first phase (10 s), pressure cuffs are filled with air until a pressure value of 5 mmHg. During the second phase (60 s) pressure rises to 55 mmHg causing blood pooling in the examined areas and during the final phase (30 s), pressure falls back to 5 mmHg resulting in inversion of venous occlusion and blood pooling.

A special built-in software automatically identifies the regions of interest (ROI: wrists, MCP I-V, and PIP I-V) and their respective reference areas. A comparison between the blood flow in the ROIs and in the reference areas serves as a control mechanism for the presence of impaired or increased peripheral blood flow, due to systemic factors such as body temperature, diabetes mellitus, nicotine use, or vasoactive medication. OST assesses joint hypervascularity according to known semiquantitative power Doppler US (PDUS) scores and translates it to a grade between 0 and 3 (meaning: 0 = missing hypervascularity and 3 = highest possible grade of hypervascularity [26]. All OST scores were generated automatically by the HandScan software.

Statistical analysis

Continuous variables were tested for normal distribution by the Shapiro-Wilk-Test and quantile-quantile-plots [27]. For comparisons between the RA and the control group, we used Fisher's exact test for categorical variables and the Mann-Whitney-U-test or t-test for continuous variables. Correlation analysis was performed for the association between OST and all continuous variables using Spearman's rank correlation coefficient in both groups.

To assess the OST diagnostic performance, receiver-operating characteristics (ROC) were calculated for the whole group [RA vs. control group], for an RA-subgroup (≥1 swollen hand- or finger-joint), and by stratification for both genders. Furthermore, additional ROC analyses were performed comparing the RA group with the non-inflammatory arthralgia group. To choose the best cut-off values of OST, we used Youden's index [28] out of the coordination of the ROC curve.

Logistic regression was performed to predict the risk of having RA based on selected risk factors. The goal was to select the optimal model for the prediction of RA based on the maximum likelihood method. The global goodness-of-fit of the regression models was evaluated by a chi-square test. Additionally, the sum of the percentage of overall correct predictions was assessed. Model selection was conducted by using the likelihood ratio test (LR test). Effect size estimation is presented as an odds ratio (OR) with 95% confidence intervals. Results were assessed as statistically significant with an alpha-error level of 5%. The selected variables of the final logistic models were then presented as a formula for the prediction of risk for RA. The goal was to estimate an equation, which can be used to accurately predict the risk for the presence of RA in new patients. Total OST values, and not single joint values, were used as statistical units.

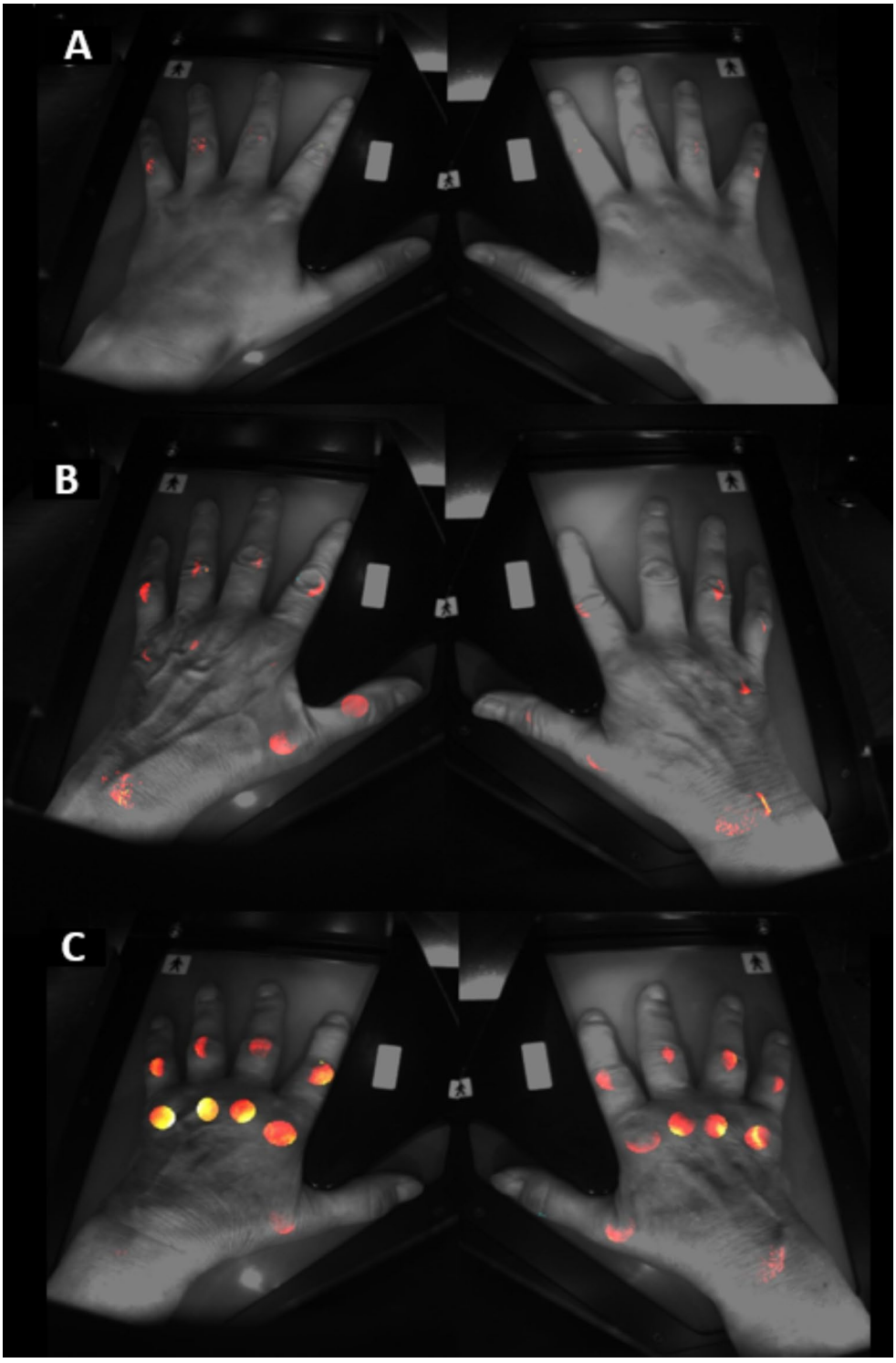

Fig. 1 Optical spectral transmission findings in: **A**. a healthy subject (OST-Score: 8.06) **B**. an RA-patient with low diseaseactivity (OST-Score: 14.32, DAS28: 3.1), **C.** an RA-patient with high disease activity (OST-score: 27.16, DAS28: 5.5). OST: optical spectral transmission; DAS28: disease activity score; RA: rheumatoid arthritis

Table 1 Descriptive characteristics by group

Variable	RA-patients (*n = 72*)	Healthy (*n = 100*)	NIA[b] (*n = 53*)	*p*-value (RA vs. Healthy)	*p*-value (NIA[b] vs. RA)
OST°	16.8 ± 5.5	10.8 ± 4.0	11.4 ± 4.4	< 0.001***	< 0.001***
OST female°	15.5 ± 4.7	9.6 ± 3.4	10.6 ± 3.6	< 0.001***	< 0.001***
OST male°	19.3 ± 6.0	15.3 ± 3.0	16.3 ± 6.1	0.009**	0.241
Sex (female), %[a]	63.9	80.0	86.8	0.036*	0.004**
Age, yrs‡	56.5 (17)	50.0 (23)	51.0 (10)	< 0.001***	< 0.001***
BMI, kg/m^2‡	27 (7.8)	25.5 (6.7)	28.0 (8.5)	0.011*	0.366
Arterial HTN, % [a]	33.3	19.0	32.1	0.025*	1.000
Diabetes, % [a]	12.5	2.0	15.1	0.009**	0.793
Raynaud, % [a]	16.7	0	17	< 0.001****	1.000
Nicotine use, % [a]	22.2	19	30.2	0.847	0.407
Hand size, cm^2‡	189.3 (38.8)	173.0 (23.7)	-	< 0.001****	-
RF % [a]	62,3	-	-	-	-
Anti-CCP % [a]	56,2	-	-	-	-
ESR, mm/h‡	27.0 (31.0)	-	12 (14)	-	< 0.001***
CRP, mg/l‡	5.4 (15.8)	-	2.21 (4.7)	-	< 0.001***
Tender joint count‡	3.5 (8.0)	-	6 (15)	-	0.041***
Swollen joint count‡	2.0 (6.0)	-	-	-	-
VAS, mm‡	50.0 (34.0)	-	60.0 (40)	-	0.253
DAS28-ESR°	4.5 ± 1.4	-	-	-	-

RA patients and controls are tested for differences, numbers in bold show a significant difference (two-sided, alpha = 0.05)

[b]NIA: Non-inflammatory arthralgia

°continuous data with normal distribution are presented as mean (standard deviation). T-tests have been used for the comparison

‡continuous data without normal distribution are presented as median (interquartile range). Mann-Whitney-U tests have been used for the comparison

[a]categorical data are presented in percentage. Fisher's exact tests have been used for the comparison

OST: optical spectral transmission; BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein;, VAS: visual analog scale; RF: Rheumafacto; Anti-CCP: Anti-Cyclic Citrullinated Peptide Antibody; DAS28-ESR: disease activity score 28-ESR; NIA: Non-inflammatory arthralgia.

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

The statistical analysis was performed via the SPSS software 23.0.

Results

For this study, *309* consecutive patients with arthralgias of the wrist- and/or finger joints were screened for the presence of an RA diagnosis, via clinical, laboratory, OST, and US examinations (examined joints: *n* = 6,*798*). The diagnosis of RA was made in *94* patients, *22* of whom were excluded due to initiated glucocorticoid therapy, previous to study screening. Of the *215* remaining non-RA patients, *53* were diagnosed with non-inflammatory arthralgia (fibromyalgia and/or osteoarthritis) and were used as a second control group (next to the healthy control group). The other *162* patients were diagnosed with further rheumatologic diseases (i.e. various inflammatory arthritides, crystal arthropathies, and connective tissue diseases) and were excluded from the study.

Table 2 Association between patient characteristics and OST in RA group and control group

Variable	RA group		Healthy control group	
	Spearman's (rho)	Significance (*p*)	Spearman's (rho)	Significance (*p*)
Age	0.385	0.001**	0.033	0.742
BMI, kg/m2	0.204	0.086	0.258	0.010*
Arterial HTN	0.169	0.155	-0.057	0.571
Diabetes	0.038	0.749	0.168	0.094
Nicotine use	-0.114	0.339	0.028	0.780
Hand size, cm^2	0.267	0.023*	0.465	< 0.001***
ESR, mm/h	0.124	0.300	-	-
CRP, mg/l	0.093	0.44	-	-
SJC	0.355	0.002**	-	-
TJC	0.198	0.095	-	-
VAS, mm	0.383	0.001**	-	-
DAS28-ESR	0.361	0.002**	-	-

Spearman's rank correlation coefficient was used to investigate the association between OST and quantitative patient characteristics

OST: optical spectral transmission; BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TJC: tender joint count; SJC: swollen joint count; VAS: visual analog scale; DAS28-ESR: Disease Activity Score 28 based on erythrocyte sedimentation rate; CRP: C-reactive protein

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

1,584 joints of *72* RA patients (*65.3%* female), *2,200* joints of *100* healthy control subjects (*80%* females), and *1.166* joints of *53* non-inflammatory arthralgia patients (*86.8%* female) were examined by OST. OST scores of the RA group were statistically significantly higher compared to the healthy control group (*16.8 ± 5.5 vs. 10.8 ± 4.0*) and the non-inflammatory arthralgia group (*16.8 ± 5.5 vs. 11.4 ± 4.4*), respectively (both; $p < 0.001$) (Table 1). Further descriptive characteristics of the 3 groups are presented in Table 1.

Associations of OST score with continuous variables

Except for the OST score and DAS28-ESR, further examined variables were not normally distributed (Shapiro-Wilk-test $p < 0.05$). Thus, we calculated Spearman's rank correlation for all bivariate associations. Among RA patients, Spearman's analyses showed a moderate correlation between OST and swollen joint counts (*SJC-rho = 0.355,p = 0.002*), VAS scale (*rho = 0.383,p = 0.001*), DAS28-ESR (*rho = 0.361,p = 0.002*), and age (*rho = 0.385,p = 0.001*) (Table 2). Moreover, a weak association between OST and hand size (*rho = 0.267,p = 0.023*) was found.

Among control subjects, OST correlated moderately with hand size (*rho = 0.465,p < 0.001*) and weakly with BMI (*rho = 0.258,p = 0.01*) (Table 2).

Receiver operating characteristics (ROC) analysis and cut-off values

ROC analyses were done to test the diagnostic performance of OST. Because of the substantial difference in OST scores between males and females (Fig. 2), the ROC analysis was additionally stratified by sex. To test the diagnostic performance of OST, ROCs were performed twice, once comparing the whole RA group and once an RA-subgroup [patients with ≥1 acutely swollen wrist of finger joint(s)] with the two control groups, respectively.

In the comparison between the whole RA-group vs. healthy control group, the overall diagnostic performance of OST was found to be excellent by an AUC of *0.810* (*95%CI: 0.746–0.873*) and further improved during the comparison of the RA subgroup with ≥1 swollen wrist or finger joint vs. the healthy control subjects [*AUC 0.841 (95%CI: 0.773–0.908)*]. Interestingly, the diagnostic performance of OST was higher in the female group, by an AUC of *0.848* (*95%CI: 0.780–0.917*), compared with the male group (AUC *0.696*; *95%CI: 0.537–0.855*). These values were also found to be higher in the comparisons between the RA subgroup with ≥1 swollen wrist or finger joint(s) and the control group for both females [AUC *0.87 (95%CI; 0.797–0.943)*] and males [AUC *0.78 (95%CI; 0.606–0.954)*], respectively.

In the case of comparing RA- with non-inflammatory arthralgia patients as an additional control group, similar results were observed by a very good overall diagnostic performance [AUC of *0.788* (*95%CI: 0.709–0.867*)]. Also in this case, diagnostic performance further improved in the comparison between the RA subgroup with ≥1 swollen wrist or finger joint(s) and the non-inflammatory arthralgia patients by an AUC of *0.822* (*95%CI: 0.740–0.90*) [females: AUC: *0.823* (*95%CI: 0.727–0.918*) and males AUC *0.688 (95%CI; 0.441–0.934)*].

The determination of cut-off-values was based on the Youden index and the comparison between the RA group and healthy controls. The OST cut-off value in the female subgroup was *11.17* with a sensitivity of *85.1%* and specificity of *71.2%* (Youden index: 0.563). In comparison, in the male subgroup, a cut-off of *16.05* with a sensitivity of *72%* and specificity of *65%* (Youden index: *0.37*) was found. Overall sensitivity/specificity values improved when the RA subgroup with ≥1 swollen wrist or finger joint(s) was compared with the control group (cut-off of *11.17*; sensitivity *93%*, specificity *71.2%* for females, and cut-off of *18.21*; sensitivity *67%*, specificity *90% for males*).

Prediction models for the risk of RA

To predict the probability of a positive RA diagnosis, based on the measured OST score and the presence of possible OST influencing factors, we have pre-selected 4 different logistic regression models (Table 3, suppl. material). In the first model, OST (as the main variable), age, and gender were included. In the second model, smoking was added to the variables to rule out an influencing effect through blood-flow restriction. Models 3 and 4 included hand size and BMI respectively, which have been shown to correlate with OST in the past and the current study.

These 4 models were tested against each other using an LR test to find the optimal prediction model for the presence of RA. The four models, as presented in Table 3, were analyzed and compared using logistic regression. All models were first estimated for all patients, followed by a gender-specific estimation.

Statistic model regarding all patients

According to the omnibus test, all four models were statistically significant ($p<0.001$, Table 3, suppl. material).

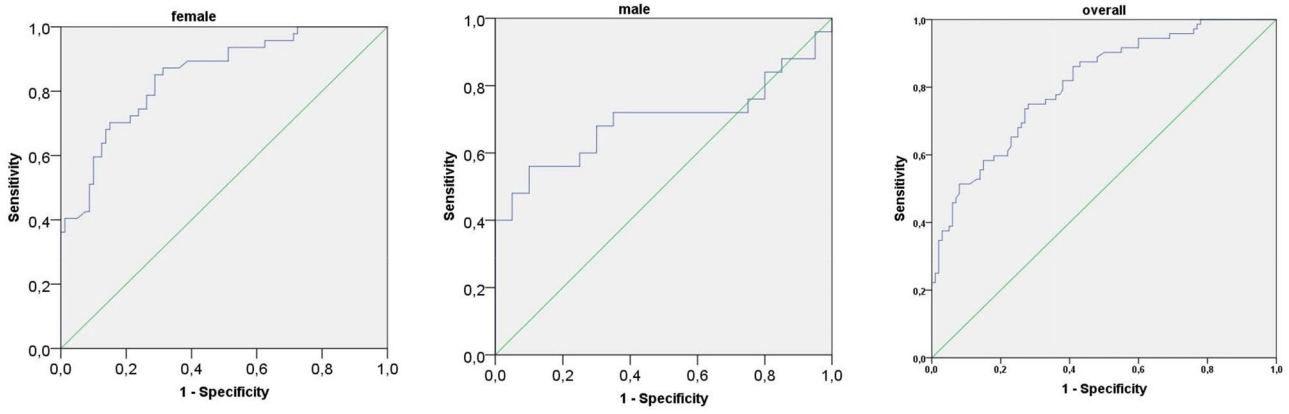

Fig. 2 Top left. ROC of OST in females between RA-group and control group (reference). Top middle. ROC of OST in males between RA-group and control group (reference). Top right. ROC of OST overall (male and female together) between RA-group and control group (reference). OST-AUC for females (0.848; 95% CI 0.780–0.917); males (AUC 0.696; 95% CI 0.537–0.855); overall (AUC 0.81; 95% CI 0.746–0.873) *ROC: Receiver-operating characteristic; OST: optical spectral transmission; RA: rheumatoid arthritis; AUC: area under the curve*

Table 3 Selected prediction models for RA in male and female group. P(Y): the estimated risk for RA with the parameter

	Prediction equation to estimate the risk for RA
All patients	$P\,(RA) = \frac{e^{(-7.173+(0.065*age)+(0.259*OST)+(-0.172*male))}}{1+e^{(-7.173+(0.065*age)+(0.259*OST)+(-0.172*male))}}$
Female patients	$P\,(RA) = \frac{e^{(-7.813+(0.057*age)+(0.344*OST))}}{1+e^{(-7.813+(0.057*age)+(0.344*OST))}}$
Male patients	$P\,(RA) = \frac{e^{(-5.553+(0.087*age)+(0.084*OST))}}{1+e^{(-5.553+(0.087*age)+(0.084*OST))}}$

P = Risk/Probability, e = exponential function. The individual predicted risk for RA can be derived by putting in the respective age in years, OST-value and a dummy for gender: 0 for females and 1 for males

RA: rheumatoid arthritis

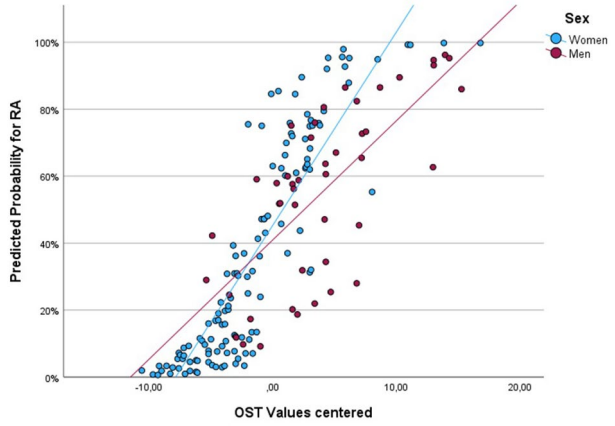

Fig. 3 Plot showing the association of predicted probabilities for RA and mean-centered OST-values stratified by sex.Respective lines showing the association for men and women based on a logistic regression model with predictors: sex, mean-centered OST-values, interaction term of sex and OST-values. *RA: rheumatoid arthritis; OST: optical spectral transmission*

Compared with model 1, the second model including smoking status as an additional variable, did not yield a significantly better risk estimation of RA (LR-Test: *1.804*, $p=0.179$). The sum of the percentage of overall correct predictions was *80.2%* for model 2 and *78.5%* for model 1. Adding hand size and BMI in models 3 and 4 led to no significant improvement in the prediction of RA compared to model 1 (model 3 vs. 1: LR-test: *1.996*, p=*0.158*; model 4 vs. 1: LR-test: *2.264*, $p=0.132$), with the sum of the percentage of overall correct predictions being the same for models 3 and model 4: *80.2%*.

Thus, model 1 proved to be the optimal one for the prediction of RA for all patients. Among the analyzed predictors, only OST score (*OR=1.296 95%-CI: 1.163–1.444*, $p<0.001$) and age (*OR=1.067, 95%-CI: 1.033–1.103,p<0.001*) were significant. The sum of the percentage of overall correct predictions was *78.5%* (RA-patients: *70.8%*). The prediction equation for the risk of RA for all patients can be found in Table 3. An additional analysis showed a significant interaction effect between gender and OST score for all patients. For increasing OST values above the respective mean, the risk for RA was higher in females versus males. For decreasing OST values below the respective mean, the risk for RA was higher in males versus females (Fig. 3).

Stratified for gender

For females and males separately, the first model including OST values and age proved to be the optimal prediction model for RA (females: Chi-Square: *62.47*, $p<0.001$, males: Chi-Square: *17.01,p<0.001*). Adding smoking, hand size, and BMI did not significantly improve the risk prediction (LR-test not significant for model 2, 3, 4 vs. model 1). The sum of the percentage of overall correct predictions for females was *81.9%* (RA-patients: *70.2%*) and for males *73.3%* (RA-patients: *84.0%*). OST score was shown to be a significant predictor for RA in females (*OR=1.411; 95% CI: 1.225–1.624,p<0.001*) but not in males (*OR=1.411; 95% CI: 1.225–1.624,p<0.323*). Moreover, age was a significant predictor for RA both in females (*OR=1.059, 95% CI: 1.018–1.101,p=0.004*) and males (*OR=1.091, 95% CI: 1.027–1.160, p=0.005*).

The association of predicted probabilities for RA and mean-centered OST values stratified by sex is shown in Fig. 3 and the prediction equation for the risk of RA stratified by gender is in Table 3.

Discussion

In this pilot study, we have suggested OST cut-off values which are adjusted for the effect of OST influencing factors and thus of higher diagnostic value in comparison to a universal cut-off. Moreover, we presented statistical models that inform the physician about the probability of a positive RA/inflammatory arthritis diagnosis for every patient, based on the individual measured OST value and patient-associated OST influencing factors, such as gender and age.

To our knowledge, this is the first study to provide "patient-tailored" OST cut-off values. Moreover, it is the first study to suggest statistical models that could assist in estimating the percentual likelihood of a positive RA/inflammatory arthritis diagnosis for every examined patient individually.

In the past, Verhoeven et al., in cooperation with our research group, have suggested mathematical models to assess a composite activity score called DAS-OST [29].

In this activity index, tender and swollen joint counts were replaced by OST values and both VAS and age were included in the model. During internal and external validation high intraclass correlation coefficients and high sensitivity/specificity values were found. Results of this corporate study and of the present exploration point to an increase in OST diagnostic performance, when patient and disease-associated characteristics are combindly taken into account, and are included in the OST mathematical models.

The majority of further studies having examined OST influencing factors, concluded that the right interpretation of OST values requires the consideration of patient age and -gender. The effect of gender on OST has been examined also in the past by our group [21]. As we were then able to show, female patients seem to have statistically significantly lower OST values compared to males, both in healthy cohorts and in RA groups. Verhoeven et al. were also able to confirm these results in two further cohorts, evaluating RA patients and control subjects respectively [23]. However, in the present study, an additional important element was found: the performance of OST seems to be higher in females compared to male patients, meaning that OST could differentiate between patients and controls with higher accuracy in the female subgroup. Additionally, further statistical analysis showed a significant interaction effect between gender and OST score in the model for all patients. This reinforced the assumption, that the influence of OST-score on the risk of RA is different in women compared to men. A possible explanation for this finding could lie in anatomical differences between males and females regarding joint structure and size. As well known, males have often larger and more robust joints than females and these anatomical characteristics could have affected light passage through the joint and subsequently light absorption. Of course, a better diagnostic performance in the female group, also due to the higher count of included female subjects may have also contributed to this result.

Interestingly, an increase in OST diagnostic performance was observed in the current study when control subjects were compared with an RA subgroup of patients having at least one swollen wrist or finger joint, pointing to better diagnostic behavior in cases of higher disease activity. Based on the background technology of OST which detects hypervascularity, this result seems plausible. Nevertheless, OST showed acceptable diagnostic performance during the examination of the whole cohort which was characterized by overall lower disease activity.

Even though hand size (control and patient group) and BMI (control group) were associated significantly with OST, as they also did in our previous study and the work of Verhoeven [21, 23], these correlations were statistically poor. By this, we found that both BMI and hand size (as part of the discussed models three and four) couldn't statistically enhance the RA risk estimation. Indeed, the effect of these patient characteristics on OST seems somewhat unclear. For example, the effect of hand size is difficult to examine, because male patients often have larger hands than females. Interestingly, in our previous work, hand size did not show a confounding effect on OST after adjustment of the results for the effect of gender [21].

Evaluation of the performed correlation analyses examining relationships of OST with disease activity parameters showed congruent results with previous studies [16, 18, 21]. In particular, OST correlated significantly with DAS28-ESR, SJC, and VAS, pointing to an association with well-established disease activity markers. The missing statistical correlation with TJC points to the fact that OST detects joint inflammation and not accompanying features, such as joint tenderness/pain. Missing correlations with inflammation markers could be explained by the fact that CRP and ESR represent systemic inflammation of multiple joins spread throughout the body and thus beyond the level of the wrist, MCP, and PIPs. On the other hand, OST focuses on located inflammation in these three aforementioned joint categories. In our previous study, however, which included a higher count of patients, OST correlated significantly with laboratory disease activity markers [21].

This study has some limitations. Firstly, stratification by gender led to a relatively low count of patients in the male subgroup, due to the more prominent female prevalence of RA and the consecutive recruitment of patients in a real-life setting. This could have influenced the calculated diagnostic performance in male subjects. However, estimated AUC and sensitivity/specificity values pointed to an acceptable diagnostic utility of the device in both genders. Secondly, even though the US was performed in the context of the diagnostic process for most of the included patients, we decided to include patients who could be diagnosed with RA on the strict basis of the clinical ACR/EULAR classification criteria. The reason for that was the fact that correlations of OST with joint US have been already thoroughly examined by our group in previous works and have be found to be statistically significant [21, 30]. In the context of the present study, we wanted to apply a slightly different methodology and evaluate the utility of OST also in settings where only clinical and laboratory diagnostic assessments can take place. Thirdly, even though OST showed a good diagnostic performance in detecting joint inflammation at the MCP, PIP, and wrist joint levels, which are typically affected by RA, we cannot exclude the possibility that other inflammatory diseases (such as PsA/seronegative spondyloarthropathies, etc.) would not have shown similar results. The case-control design and exclusion

of other types of inflammatory arthritis may have led to an overestimation of diagnostic accuracy and therefore the findings are not fully generalizable to the overall RA diagnostic process. Thus, while the results support OST's ability to differentiate between RA and non-inflammatory conditions, future studies should include a broader spectrum of arthritis types to validate OST's comprehensive diagnostic utility across various inflammatory conditions. Additionally, the evaluation of other clinical and laboratory parameters, such as anti-CCP and RF, remains essential for a valid diagnosis.

Conclusion

To summarize, herein, we propose gender-specific OST cut-off values and two different statistical models that could assist clinicians during RA/inflammatory arthritis patient screening. Given the fact that isolated OST evaluation seems to be inferior to a more combined approach that blends OST with specific patient-associated characteristics, we can conclude that the present methodology can lead to a significant increase in OST diagnostic value. Further patient recruitment and research regarding additional confounders are currently taking place intending to improve the diagnostic capabilities of this new and promising diagnostic technology.

Abbreviations

OST	Optical spectral transmission
RA	Rheumatoid arthritis
DAS28	Disease Activity Score calculated on 28 joints
AUC	Area under the curve
Ultrasound	US
MRI	Magnetic Resonance Imaging
GSUS	Grey Scale Ultrasound
PDUS	Power Doppler Ultrasound
ACR	American College of Rheumatology
EULAR	European League Against Rheumatism
TJC	Tender joint count; SJC: Swollen joint count
VAS	Visual analogue scale
BMI	Body-Mass-Index
CRP	C-reactive protein
ESR	Erythrocyte Sedimentation Rate
RF	Rheumatoid factor
anti-CCP	Anti-cyclic citrullinated peptide antibodies
MCP	Metacarpophalangeal joints
PIP	Proximal interphalangeal joints
CMOS	Metal oxide semiconductor
ROI	Regions of interest
ROC	Receiver operating characteristic
OR	Odds ratio

Supplementary Information

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Supplementary Material 1

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Author contributions

KT designed the study and wrote the manuscript. KA was involved in patient recruitment, data acquisition, and manuscript writing. FS performed statistical explorations and was involved in data analysis and interpretation. AS revised co-designed the study and revised the manuscript critically. All authors have read and approved the final version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The assessment was reviewed and approved by the Standing Committee for Clinical Studies of Rhineland-Palatinate, Germany in adherence to the Declaration of Helsinki (Nr.: 13042). All patients gave their informed consent to the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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