SHORT REPORT

A Thermographic Disease Activity Index for remote assessment of rheumatoid arthritis

Isabel Morales-Ivorra 1, Javier Narváez 2, Carmen Gómez-Vaquero,2 Carmen Moragues,2 Joan M Nolla 2, José A Narváez,3 Manuel Alejandro Marin-López 4

ABSTRACT

Objectives Remote assessment of patients with rheumatoid arthritis (RA) has increased during recent years. However, telematic consultations preclude the possibility of carrying out a physical examination and obtaining objective inflammation. In this study, we developed and validated two novel composite disease activity indexes (Thermographic Disease Activity Index (ThermoDAI) and ThermoDAI-CRP) based on thermography of hands and machine learning, in order to assess disease activity easily, rapidly and without formal joint counts.

Methods ThermoDAI was developed as the sum of Thermographic Joint Inflammation Score (ThermoJIS), a novel joint inflammation score based on the analysis of thermal images of the hands by machine learning, the Patient Global Assessment (PGA) and, for ThermoDAI-CRP, the C reactive protein (CRP). Construct validity was tested in 146 patients with RA by using Spearman's correlation with ultrasound-determined grey-scale synovial hypertrophy (GS) and power Doppler (PD) scores, CDAI, SDAI and DAS28-CRP.

Results Correlations of ultrasound scores with ThermodoAI (GS=0.52; PD=0.56) and ThermoDAI-CRP (GS=0.58; PD=0.61) were moderate to strong, while the correlations of ultrasound scores with PGA (GS=0.35; PD=0.39) and PGA-CRP (GS=0.44; PD=0.46) were weak to moderate. ThermoDAI and ThermoDAI-CRP also showed strong correlations with Clinical Disease Activity Index (p>0.83), Simplified Disease Activity Index (p>0.85) and Disease Activity Score with 28-Joint Counts-CRP (p>0.81) and high sensitivity for detecting active synovitis using remission criteria.

Conclusions ThermoDAI and ThermoDAI-CRP showed stronger correlations with ultrasound-determined synovitis than PGA and PGA + CRP, thus presenting an opportunity to improve remote consultations with patients with RA.

INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory disease characterised by chronic synovitis, joint destruction and disability. Current therapies, the implementation of treat-to-target strategies and tight control assessments have all been shown to aid improved outcomes.1 2

Different disease activity measurement tools are used in clinical practice and trials. Disease Activity Score with 28-Joint Counts (DAS28), Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) involve formal joint counts performed by trained professionals, as well as Patient Global Assessment (PGA) of health and laboratory analysis.3 4 Recently, digital innovations in rheumatology have increased exponentially and the use of telemecine to follow-up of patients with RA has been explored.5 7 As telematic

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Remote assessment of patients with rheumatoid arthritis precludes the possibility of conducting a physical examination, making the determination of objective inflammation challenging.

⇒ Previous research shows that Thermographic Joint Inflammation Score (ThermoJIS), a novel joint inflammation score based on the computational analysis of thermal images of the hands by machine learning, assesses joint inflammation in patients with rheumatoid arthritis in a rapid, sensitive and automated manner.

WHAT THIS STUDY ADDS

⇒ The development and validation of Thermographic Disease Activity Index (ThermoDAI) and ThermoDAI-CRP, two novel composite disease-activity indexes based on ThermoJIS, the Patient Global Assessment and C reactive protein to assess disease activity without the need for formal joint counts.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These novel indexes could be used not only to improve clinical practice, but also to decentralised clinical trials.

1 Rheumatology Department, Hospital Universitari d‘Igualada, Igualada, Spain
2 Rheumatology Department, Hospital Universitàri de Bellvitge, L’Hospitalet de Llobregat, Spain
3 Radiodiagnosis Department, Hospital Universitàri de Bellvitge, L’Hospitalet de Llobregat, Spain
4 R&D Department, Singularity Biomed, Sant Cugat del Vallés, Spain

Correspondence to
Dr Isabel Morales-Ivorra; isabel.morales-ivorra@gmail.com
consultations do not allow for the possibility of making formal joint counts, the development of new techniques enabling rheumatologists to obtain objective inflammation in a fast and easy manner could improve remote evaluation of patients with RA.

Thermography is an emerging imaging technique that creates an image of the heat emitted by bodies by capturing the intensity of long wave infrared radiation, which increases with temperature. In recent years, a new generation of affordable uncooled thermal detectors has been developed. These thermal cameras are compact, easy to use and have shown good performance suitable for medical imaging. As inflammatory processes cause warmth and localised hyperaemia, thermography could be useful for detecting arthritis and disease activity. Previous research (both preclinical and clinical) showed thermographically detectable changes in inflamed joints. Furthermore, we recently developed a novel Thermographic Joint Inflammation Score (ThermoJIS) based on the computational analysis of thermal images of the hands by machine learning to assess joint inflammation in an automated and rapid manner.

The aim of this study was to develop and validate two new composite disease activity indexes (Thermographic Disease Activity Index (ThermoDAI) and Thermographic Joint Inflammation Score (ThermoJIS)) based on the computational analysis of thermal images of the hands by machine learning to assess joint inflammation in an automated and rapid manner.

ThermoJIS values and CRP (mg/dL) were limited from 0 to 20 and from 0 to 30, respectively. CRP values were expressed as follows: first, the images were processed for contrast enhancement, background removal and noise reduction. Subsequently, a collection of local thermal features containing distinctive patterns of inflammation was extracted. Finally, an algorithm based on machine learning was used to analyse the features and obtain the ThermoJIS value. The greater the ThermoJIS value, the greater the confidence of having active synovitis.

**Ultrasonography**

Ultrasonography of both hands was performed in all patients and was used as a reference standard for the detection and quantification of synovitis. Ultrasound was performed using a GE Logiq 9 with a 9–14 MHz linear array transducer (Milwaukee, Wisconsin, USA). Both the patient and the probe were positioned according to EULAR guidelines. All participants underwent an ultrasound assessment (blinded with respect to other study results) consisting of a systematic examination of the wrist, metacarpophalangeal and proximal interphalangeal joints of both hands. Each joint was scored using the Outcome Measures in Rheumatology (OMERACT)-EULAR semiquantitative scoring system (0–3) for grey-scale synovial hypertrophy (GS) and for power Doppler (PD). At the patient level, an ultrasound sum score of the joints examined was made for GS (GS sum score) and PD (PD sum score). Patients with a GS sum score grade >1 and PD sum score >0 were considered to have active synovitis.

**Clinical and laboratory assessments**

Clinical and laboratory assessments were performed and included the number of swollen and tender joints in the standard 28-joint count examination in an ungraded fashion (SJC28 and TJC28), the PGA and the Evaluator Global Assessment (EGA) of disease activity based on a visual analogue scale score (0–10), the erythrocyte sedimentation rate and the CRP value.

**Calculation of ThermoDAI and ThermoDAI-CRP**

ThermoDAI and ThermoDAI-CRP were developed based on the CDAI and SDAI with the aim of being intuitive, simple and available in a remote setting. Calculations of ThermoDAI and ThermoDAI-CRP are the simple linear sum of the outcome parameters: ThermoJIS, PGA and, for ThermoDAI-CRP, the CRP in mg/dL. Thus, the formulas for ThermoDAI and ThermoDAI are as follows:

\[
\text{ThermoDAI} = \text{ThermoJIS} + \text{PGA} \\
\text{ThermoDAI} - \text{CRP} = \text{ThermoJIS} + \text{PGA} + \text{CRP}
\]

ThermoJIS values and CRP (mg/dL) were limited from 0 to 10. Therefore, ThermoDAI and ThermoDAI-CRP ranged from 0 to 20 and from 0 to 30, respectively. ThermoDAI and ThermoDAI-CRP thresholds for remission, low disease activity (LDA) and high disease activity (HDA) were optimised to maximise weighted kappa coefficients with CDAI and SDAI, respectively (i.e., different cut-off points were tested and those with the...
best weighted kappa with the qualitative interpretation of the CDAI and SDAI were selected).

**Statistical analysis**

Subject characteristics were described using means with SD, medians with IQRs or frequencies with proportions, where appropriate. The number of participants exceeded the sample size in order to obtain robust results. The study population was independent from the development set used to develop ThermoJIS to prevent overfitting. The correlations were calculated using Spearman’s correlation coefficient. Agreements of ThermoDAI and ThermoDAI-CRP with CDAI and SDAI, respectively, were determined using weighted kappa coefficients. Statistical significance was set at p<0.05 (two-sided). The statistical analysis was performed using Python V.3.7, NumPy V.1.19, Scikit-learn V.0.24 and SciPy V.1.4.

**RESULTS**

**Characteristics**

All subjects tolerated the procedure well, and no adverse effects were observed. Characteristics of the patients are presented in table 1. The distribution of ThermoJIS is shown in online supplemental figure S2.

**Associations between ThermoDAI and ThermoDAI-CRP with ultrasound**

The Spearman’s correlation for the different indices and the ultrasound scores are shown in table 2. The PGA showed a weak correlation with the ultrasound scores. The sum of CRP to PGA only showed a small improvement. ThermoDAI showed a moderate correlation,

<table>
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<th>Table 1 Characteristics of the study population</th>
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<tbody>
<tr>
<td>RA (n=146)</td>
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<tr>
<td>Age (years) 57±14</td>
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<tr>
<td>Female (%) 80.1</td>
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<tr>
<td>ThermoJIS 5±2.5</td>
</tr>
<tr>
<td>TJC28 1 (0, 4)</td>
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<tr>
<td>SJC28 0 (0, 3)</td>
</tr>
<tr>
<td>PGA 5 (2, 7)</td>
</tr>
<tr>
<td>EGA 3 (1, 5)</td>
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<tr>
<td>ESR (mm/hour) 19 (10, 34)</td>
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<td>CRP (mg/dL) 0.24 (0.1, 0.76)</td>
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<tr>
<td>DAS28-CRP 3.1±1.4</td>
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<tr>
<td>CDAI 12.7±10.6</td>
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<tr>
<td>SDAI 13.4±11.1</td>
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<tr>
<td>GS sum score 3 (0, 8)</td>
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<tr>
<td>PD sum score 1 (0, 4)</td>
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<tr>
<td>SJC28&gt;0 (%) 48</td>
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<tr>
<td>Active synovitis (%) 53</td>
</tr>
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</table>

Distributions are presented as mean±SD or median (IQR). CDAI, Clinical Disease Activity Index; CRP, C reactive protein; DAS28, 28-joint Disease Activity Score; EGA, Evaluator Global Assessment; ESR, erythrocyte sedimentation rate; GS, grey-scale synovial hypertrophy; PD, power Doppler; PGA, Patient Global Assessment; SDAI, Simplified Disease Activity Index; SJC28, swollen joints in standard 28-joints count; ThermoJIS, Thermographic Joint Inflammation Score; TJC28, tender joints in standard 28-joints count.

<table>
<thead>
<tr>
<th>Table 2 Correlation between different indices and ultrasound scores</th>
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<tr>
<td>Index Formula</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>PGA</td>
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<tr>
<td>PGA + CRP</td>
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<tr>
<td>ThermoJIS</td>
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<tr>
<td>ThermoDAI</td>
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<tr>
<td>ThermoDAI-CRP</td>
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<tr>
<td>DAS28-CRP</td>
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<tr>
<td>CDAI</td>
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<td>SDAI</td>
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</table>

CDAI, Clinical Disease Activity Index; CRP, C reactive protein; DAS28, 28-joint Disease Activity Score; GS, grey-scale synovial hypertrophy; PD, power Doppler; PGA, Patient Global Assessment; SDAI, Simplified Disease Activity Index; SJC28, swollen joints in standard 28-joints count; ThermoDAI, Thermographic Disease Activity Index; ThermoJIS, Thermographic Joint Inflammation Score; TJC28, tender joints in standard 28-joints count.
and the ThermoDAI-CRP showed a strong correlation with the PD sum score. Both ThermoDAI and ThermoDAI-CRP showed a higher correlation than ThermoJIS. ThermoJIS correlation with TJC28 + SJC28 + EGA was 0.37 (p<0.001) (online supplemental figure S3).

**Discrimination assessments of ThermoDAI and ThermoDAI-CRP**

Optimal thresholds for remission, LDA and HDA were 5.3, 10.3 and 13.2 for ThermoDAI and 6.4, 10.9, 14.1 for ThermoDAI-CRP. Weighted kappa coefficients of ThermoDAI and ThermoDAI-CRP with CDAI and SDAI were both 0.73.

The sensitivity for detecting active synovitis using the remission thresholds was 88% for CDAI, 88% for SDAI, 81% for DAS28-CRP, 96% for ThermoDAI and 88% for ThermoDAI-CRP. The specificity was 29% for CDAI, 30% for SDAI, 65% for DAS28-CRP, 30% for ThermoDAI and 35% for ThermoDAI-CRP.

**DISCUSSION**

In this study, we have characterised ThermoDAI and ThermoDAI-CRP, two novel disease activity indexes based on the analysis of thermal images of hands by machine learning (ThermoJIS), the PGA and the CRP. ThermoDAI has been developed to be intuitive and simple to use (linear sum of the components). ThermoDAI-CRP can be easily calculated from ThermoDAI by summing the CRP.

ThermoDAI and ThermoDAI-CRP showed higher correlations with ultrasound scores than PGA or PGA + CRP. ThermoDAI-CRP even showed a strong correlation with PD, similar to common indices used in clinical practice. These findings suggest that ThermoJIS, PGA and CRP are synergic and can overcome the correlations of the individual components, thereby providing an accurate evaluation of synovitis. Furthermore, ThermoDAI and ThermoDAI-CRP showed strong correlations with CDAI, SDAI and DAS28-CRP.

In 2011 the American College of Rheumatology, the EULAR and the OMERACT groups published the most influential and authoritative definitions of remission: the Boolean-based and SDAI index-based definitions, which are considered to be stringent. The selected remission criteria of ThermoDAI and ThermoDAI-CRP were at least as stringent as SDAI for detecting active synovitis. All of these properties make these novel indexes promising for assessing disease activity remotely, especially when physical examinations are not possible. However, this study is cross-sectional in nature. Therefore, longitudinal studies involving a new cohort of patients with RA are needed to validate sensitivity-to-change and to determine treatment response thresholds before applying them for patient follow-up.

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**Contributors**

IM-I and MAM-L conceived and designed the study. IM-I, CM and JAN acquired the data. IM-I and MAM-L analysed the data, interpreted the results and drafted the manuscript. JN, CG-V and JMN provided critical comments on the manuscript. ThermoDAI-CRP with DAS28-CRP (p=0.81; p<0.001) was also strong (figure 1C).
design and results. All the authors revised and approved the final version of the manuscript. IM-1 is the guarantor for this paper.

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Competing interests IM-1 and MAM-L are cofounders and shareholders of Singularity Biomed.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by (1) Name: CEIM del Hospital Universitar de Bellvitge ID: PR307/19 and AC044/16. (2) Name: Comissió de Recerca del CSA ID: PR0/2019. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

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