

	Study	Year of publication	Objective	Diagnosis	Number of included patients	Control group	Examined joints	Involved centers	Reference method	Standardisation	Principle results
<b>Inflammatory arthritis</b>											
1	Fischer et al.	2010	Development of a new tool for detection of inflammation via fluorescence imaging in near-infrared spectral range	RA	10	Yes (5 volunteers und 5 patients with rheumatoid arthritis)	70 joints of the hand in 10 persons of study population	1	MRI	<p>Optical parametric oscillator (GWU-Lasertechnik, Erfstadt, Germany) using 0.1 mg/kg by weight of indocyanine green as an unspecific contrast agent</p> <p>Evaluation using the average or percentiles of the count rate in a region of interest over a joint and divided for normalization by the counts of a fluorescence standard</p> <p>Semiquantitative grading: no change and mild, moderate, and severe synovitis</p>	<ul style="list-style-type: none"> <li>NIR agent enriched in inflammatory joints</li> <li>Different kinetic behavior compared to normal joints: highest contrast in volunteers first in the fingertips; in patients, index joints with fast and high increases in fluorescence intensity</li> <li>Two different patterns for inflamed joints: strong increase in fluorescence intensity shortly after bolus arrival or no initial intensity spike but later stabilized high fluorescence intensity Good correlation with MRI findings (r = 0.84).</li> </ul>

2	<b>Werner et al.</b>	2012	Comparison of FOI to clinical examination (CE), musculoskeletal ultrasound (MSUS) and magnetic resonance imaging (MRI)	Different forms of arthritis (RA, PsA, UA, other inflammatory arthritis)	252	Yes  (6 healthy individuals, 6 patients with arthralgia without signs of inflammatory arthritis)	Center 1: 750 joints compared FOI to CE, 300 joints compared to MRI  Center 2: 1110 joints compared FOI to CE, 962 compared to MSUS  (wrist, MCP1-5, PIP2-5, DIP2-5, IP)	2  (center 1: 153 patients, center 2: 99 patients)	MRI, MSUS (GS/PDUS) and CE	Scoring in 3 phases  Semiquantitative grading (0-3) via FOIAS  One reader for FOI  Intrareader agreement ( $\kappa=0.73$ ) Interreader agreement ( $\kappa=0.73$ )	<ul style="list-style-type: none"> <li>Standardization by the definition of three phases (P1-P3)</li> <li>FOI sensitivity 76%, FOI specificity of 54% vs. MRT</li> <li>Greatest specificity of 94% in phase 1 (P1) vs. MRI</li> <li>Agreement rates up to 88% versus CE, 64% versus GSUS, 88% versus PDUS, 83% versus MRI</li> <li>More positive findings in FOI</li> </ul>
3	<b>Werner et al.</b>	2013	Comparison to MRI	Early and very early arthritis	32	Yes  (46 subjects without any signs of inflammatory joint disease)	960 joints compared FOI to CE, 382 joints to MRI  (wrist, MCP1-5, PIP2-5, DIP2-5, IP)	1	MRI	Scoring in 3 phases  Semiquantitative grading (0-3) via FOIAS  One reader for FOI  Intrareader agreement ( $\kappa=0.73$ ) Interreader agreement ( $\kappa=0.71$ )	<ul style="list-style-type: none"> <li>FOI sensitivity 86%</li> <li>FOI specificity 63% (for PVM 87%, P1 90%, P2 69%, P3 88%) vs. MRI</li> </ul>
4	<b>Meier et al.</b>	2012	Comparison of FOI with contrast-enhanced MRI for the detection of synovitis	Suspicion of an inflammatory arthropathy	45	No	1350 joints  30 joints in both hands (carpal, MCP, PIP, and DIP joints)		MRI	Evaluation of maximum-intensity projections of the stack of 360 optical images in FOI  Analysis of true-positive, true-negative, false-positive, and	<ul style="list-style-type: none"> <li>With as MRI standard of reference FOI-sensitivity of 39.6% (95% confidence interval [95% CI] 31.1–48.7%) and FOI-specificity of</li> </ul>

										<p>false- negative values for detection of synovitis</p> <p>3 readers for MRI and 3 readers for FOI, 1 reader for repeated reading of FOI after 4 weeks: For pairwise assessment of interreader agreement: mean <math>k=0.473</math> (for carpal and MCP mean <math>k=0.332-0.656</math>; for PIP und DIP mean <math>k=0.096-0.537</math>); intrareader agreement of repeated measurement by one reader: <math>k=0.507</math></p>	<p>85.2% (95% CI 79.5–89.5%), accuracy of 67.0% (95% CI 61.4–72.1%) for the detection of synovitis in patients with arthritis</p> <ul style="list-style-type: none"> <li>• Limitation of diagnostic accuracy in the setting of mild synovitis</li> </ul>
5	Krohn et al.	2015	Comparison of FOI to MSUS (GS/PDUS) and MRI	Early RA	31	No	279 joints (wrist, MCP/PIP2-5)	1	MRI and MSUS (GS/PDUS)	<p>Scoring in 3 phases</p> <p>Semiquantitative grading (0-3) via FOIAS</p> <p>One reader for FOI</p>	<ul style="list-style-type: none"> <li>• MRI as reference: sensitivity/specificity of FOI: 0.81/0.00 (wrist), 0.49/0.84 (MCP), 0.86/0.38 (PIP)</li> <li>• PDUS as reference: sensitivity/specificity of FOI: 0.88/0.15 (wrist), 0.81/0.76 (MCP), 1.00/0.27 (PIP)</li> <li>• P2 with highest sensitivity, P1 with highest specificity</li> <li>• Best agreement of FOI with PDUS, especially with regard to MCP/PIP</li> </ul>

											(ICC of 0.57 and 0.53)
6	Schäfer et al.	2013	Quantitative assessment of FOI for synovitis and non-synovitis joints	RA	18	-	90 Wrist, MCP2+3, PIP2+3	1	MRI	3 phases of each 120s (1-120s, 121-240s, 241-360s) circular regions of interest (ROI), with the size of each ROI defined according to the anatomical size of the corresponding joint (a diameter of 22 pixel for wrists, 12 pixel for MCP- and 10 pixel for PIP-joints) – resulting in fluorescence readout (FLRO)  Calculation of fluorescence ratio (FLRA) for individual perfusion	<ul style="list-style-type: none"> <li>Overall, the analyses of FLRA higher discrimination compared to FLRO</li> <li>most significant differences in phases 2 and 3</li> <li>FLRA sensitivity 67% and specificity 77 of phase 3 using a cut-off value of more than 1.2 to detect MRI-confirmed synovitis with FOI</li> </ul>
7	Kisten et al.	2015	Diagnostic utility for detection of clinically non-apparent synovitis	Inflammatory arthritis	26	No	872 joints  (radiocarpal, midcarpal and ulnocarpal wrist regions, MCP1-5, PIP1-5 and DIP2-5)	1	MSUS	Evaluation of abnormal focal optical signal intensities by visual inspection of the entire image series, postprocessing image techniques for artefact reduction  Quantitative scoring for present or absence of abnormal signal intensity  Two readers of FOI in	<ul style="list-style-type: none"> <li>Detection of clinically silent synovitis, sensitivity of 80%, specificity 96%, positive and negative predictive values of FOI vs. MSUS 77% and 97%</li> </ul>

										consensus	
8	Thuermel et al.	2017	Comparison of FOI and MRI in the detection of synovitis of the wrist and finger joints in rheumatoid arthritis and to analyze the performance of FOI depending on the grade of synovitis.	RA	23	Yes (20 RA patients with wrist and/or finger joint involvement and moderate to high disease activity DAS28 of 3.2–5.1 or >5.1)  13 volunteers without arthritis, arthralgia or evidence of any other joint disease	956 joints of both hands (Carpal, MCP, IP, PIP, and DIP joints) of 20 patients and 13 healthy controls	1	MRI	Using FOI System (XiraView Software, version 3.7 Mivenion)  Semiquantitative grading according to color grading of FOI signal  Evaluation of inflammation of the joints via composite standard of reference  Three readers (2 radiologists and 1 rheumatologist): interreader agreement 0.79 (0.77–0.81) and 0.84 (0.83–0.86) for FOI and MRI; intrareader agreement 0.80 (0.83–0.86)	<ul style="list-style-type: none"> <li>FOI: overall sensitivity of 57.3%, specificity of 92.1%</li> <li>MRI: sensitivity of 89.2%, specificity of 92.6%.</li> <li>Increase of FOI sensitivity with the degree of synovitis to 65.0% for moderate and severe synovitis (specificity 88.1%) and 76.3% for severe synovitis (specificity 80.5%)</li> <li>Decrease for FOI with the degree of synovitis with false negative results predominantly for mild (156/343, 45.5%) and moderate (160/343, 46.6%) synovitis false positive FOI results based on weak (grade 1) signals (133/163, 81.6%)</li> </ul>

9	<b>Hirano et al.</b>	2018	Comparison of CE, MSUS, FOI with MRI	RA	6	Yes 3 healthy subjects	30 joints (wrist, MCP1-5, PIP2-5, DIP2-5, IP)	1	MRI	Scoring in 3 phases Semiquantitative grading (0-3) using FOIAS One reader for FOI	<ul style="list-style-type: none"> <li>Sensitivity and specificity: FOI phase 1 85%/94%, FOI phase 2 69%/94%, CE 100/35%, GSUS 92/41%, PDUS 77/100%</li> </ul>
10	<b>Kawashiri et al.</b>	2020	Investigation of significance of FOI findings based on association between FOI and MSUS and serum biomarkers	RA	50	No	18 joints per patient Bilateral Wrist, MCP2-5, PIP2-5	1	MSUS	Scoring in 3 phases Semiquantitative grading (0-3) via FOIAS One reader for FOI	<ul style="list-style-type: none"> <li>Differences in positive findings and diagnostic performance of FOI among phases and affected joint regions</li> <li>Severity of FOI-proven synovitis associated with presence of MSUS-proven bone erosion</li> </ul>
11	<b>Ammitzbøll-Danielsen et al.</b>	2021	Develop and validate a new semi-quantitative FOI scoring system, for assessing synovitis by evaluating inter-scan, inter- and intra-reader agreement, smallest detectable change (SDC), responsiveness	RA	46	Yes, 11 healthy controls	32.434 joints including all visits 22 joints per patient Bilateral Wrist, MCP1-5, PIP2-5, IP	1	MSUS and clinical joint count	Scoring in 1 phase Semiquantitative grading (0-3) via FOIE-GRAS Two readers for FOI Inter-scan, intra- and inter-reader intraclass correlations coefficients (ICC) were good-excellent for all baseline scores (0.76-0.98) and moderate-to-	<ul style="list-style-type: none"> <li>Moderate agreement with ultrasound (ICC 0.30-0.54) for total score</li> <li>A good standardized response mean (&gt;0.80),</li> <li>Moderate correlation with clinical joint assessment and DAS28-CRP.</li> </ul>

			and feasibility  Agreement of FOI assessed synovitis with ultrasound, clinical and patient reported outcomes of disease activity.  Comparison of FOI findings in RA patients and healthy controls.							good for change (0.65-76).	<ul style="list-style-type: none"> <li>The median (IQR) reading time per FOI examination was 133 (109;161) seconds.</li> <li>Scores were significantly lower in controls 1(0;4) than RA patients 1(6;19).</li> </ul>
12	<b>Erdmann-Keding et al.</b>	2019	Comparison of MSUS and FOI in detection of joint inflammation in diagnosed and suspected PsA	PsA	60	Yes  6 patients with PsO without joint symptoms	Wrist, MCP 2-5, PIP 2-5, DIP 2-5	1	MSUS	Scoring in 3 phases  Semiquantitative grading (0-3) via FOIAS	<ul style="list-style-type: none"> <li>FOI more sensitive than MSUS for detection of inflammation in PIP/DIP joints (<math>p = 0.035</math>)</li> <li>More findings in FOI P2 and P3 in confirmed PsA, more findings in P1 in suspected PsAs</li> </ul>
13	<b>Schmidt et al.</b>	2020	Evaluation of subclinical skin inflammation by FOI	PsA/PsO	80	Yes  78 patients with RA, 25 healthy subjects	-	1	-	Sequence of image 0-120, Semiquantitative grading of subclinical skin enhancement in 5 regions  One reader for FOI  Interreader reliability for the diagnosis ( $\kappa = 0.35$ , absolute agreement 59.6%), agreement of	<ul style="list-style-type: none"> <li>Subclinical skin enhancement on the back of hands: PsO/PsA 72.5%, RA 20.5%, healthy 28% (<math>p &lt; 0.001</math>)</li> <li>72.5% PsO/PsA, 76.9% and 68% classified correctly in FOI in comparison to physician-based diagnosis as</li> </ul>

										63.4% in the classification of PsO/PsA, 65.4% of RA, 41.2% of healthy	reference (overall agreement of 74%, kappa = 0.57) <ul style="list-style-type: none"> <li>• Body weight as CV factor associated with subclinical skin enhancement (OR 1.04, 95% CI 1.02–1.06; <math>p &lt; 0.001</math>)</li> </ul>
14	Wiemann et al.	2019	Classification of extra-articular signal intensities in PsA by FOI, systematic study in PsA	PsA	187 (241 image sequences)	Yes 31 patients with RA (36 FOI sequences)	-	1	-	Scoring in 3 phases  Extraarticular signal intensity patterns of 40 sites (20 per hand) in defined areas: nail, nail fold, middle phalanx, proximal phalanx, hand dorsum	<ul style="list-style-type: none"> <li>• Three different fluorescence optical signal patterns in the nail regions: green, cold and hot nail</li> <li>• Green nail: highly specific (97%) for PsA</li> <li>• In follow-up study: specificity of green nail 87% in comparison to control group</li> </ul>
<b>Osteoarthritis (OA)</b>											
15	Glimm et al.	2016	Comparison of frequency and distribution of enhancement in FOI in two diseases	RA OA	90	No	1170 joints (wrist, MCP 1-5, PIP 2-5, DIP 2-5, IP)	1	MSUS	Scoring in 3 phases  Semiquantitative grading (0-3) via FOIAS  One reader for FOI	<ul style="list-style-type: none"> <li>• Depending on the phase different distribution of joints in RA vs. OA</li> <li>• P1: grades 1–3 more frequently in RA, especially in wrist</li> <li>• P2: wrist as leading affected joint group,</li> </ul>



											<p>same in both groups. MCP with lowest percentage rates, higher percentage in RA. DIP joints more affected in OA.</p> <ul style="list-style-type: none"> <li>• P3: wrist and PIP joints most affected with higher levels in the OA cohort</li> <li>• PVM: Leading joint groups were wrist and PIP. Higher percentage rates in PIP and DIP detected in patients with OA</li> </ul>
16	<b>Maugesten et al.</b>	2020	Diagnostic performance Comparison of FOI and MRI/MSUS	OA	221	No	(MCP1-5, PIP2-5, IP, DI2-5)	1	MRI	<p>Scoring in 3 phases</p> <p>Semiquantitative grading (0-3) via FOIAS</p> <p>One reader for FOI</p> <p>Intrareader reliability (intraclass correlation coefficient for sum scores; PVM = 0.89, phase 1 = 0.10, phase 2 = 0.87, phase 3 = 0.89); good interreader reliability, except phase 1 (ICC = 0.10)</p>	<ul style="list-style-type: none"> <li>• Poor to fair correlations with MRI (rho 0.01–0.24) and GS synovitis sum scores (rho 0.12–0.25)</li> <li>• AUC from 0.50–0.61 (MRI) and 0.51–0.63 (GSUS)</li> </ul>

17	<b>Maugesten et al.</b>	2021	Association of FOI and MRI defined synovitis with pain and physical function	OA	221	No	MCP1-5, PIP2-5, IP, DI2-5, CMC1, STT)	1	MRI	<p>Scoring in 3 phases</p> <p>Semiquantitative grading (0-3) via FOIAS</p> <p>One reader for FOI</p> <p>MCP and thumb base excluded from analysis due to no or low enhancement</p>	<ul style="list-style-type: none"> <li>• Joints with FOI enhancement on PVM with higher odds (95% confidence interval) of pain in the same finger during the last 6 weeks (grade 1: 1.4 (1.2-1.6), grade 2-3: 2.1 (1.7-2.6))</li> <li>• Similar results for joint pain during the last 24 hours and joint tenderness in fingers</li> <li>• Numerically stronger associations between MRI-defined synovitis and finger joint pain/tenderness</li> <li>• No/weak associations between FOI/MRI sum scores and hand pain and physical function</li> </ul>
<b>Juvenile Arthritis (JIA)</b>											
18	<b>Beck et al.</b>	2017	Assessment of the predictive power of FOI for discrimination between	JIA, juvenile patients with arthralgia	76 patients in 3 groups Group I: 29 patients with active	-	Group I: 870 Group II: 690 Group III: 1590	3 different centres in Berlin, Germany	MSUS, CE	<p>Scoring in 3 phases</p> <p>Semiquantitative grading (0-3) via FOIAS</p>	<ul style="list-style-type: none"> <li>• JIA: FOI sensitivity of 67.3%/72.0%; specificity of 65.0%/58.8% with GSUS/PDUS as reference; highest</li> </ul>

			inflammatory and non-inflammatory juvenile joint diseases		JIA in hand region Group II: 23 patients with arthralgia Group III: 53 patients with JIA regardless activity (including 29 patients of group I)					2 readers of FOI imaging in consensus	<p>specificity highest P3 (GSUS 94.3%/PDUS 91.7%)</p> <ul style="list-style-type: none"> <li>FOI more sensitive in detecting clinically active joints than GSUS/PDUS (75.2% vs 57.3%/32.5%). predictive value for discrimination between inflammatory and non-inflammatory joint diseases 0.79 for FOI and 0.80/0.85 for GSUS/PDUS</li> </ul>
19	Klein et al.	2017	Evaluation of monitoring via FOI in JIA	JIA	37 (DMARD and biological cohort)	-	1110	3 centers in Germany	CE, MSUS	<p>Scoring in 3 phases</p> <p>Semiquantitative grading (0-3) via FOIAS</p> <p>One reader for FOI</p>	<ul style="list-style-type: none"> <li>Decrease of mean JADAS 10 significantly from 17.7 at( baseline) to 12.2 (week 12) and 7.2 (week 24) respectively</li> <li>PedACR 30/50/70/100 response rates at week 24 85%/73%/50%/27%</li> <li>FOI at baseline/week 12/week 24, 430 (38.7%)/280 (29.2%)/215 (27.6%)</li> <li>highest numbers of signals detected by FOI with 32% of</li> </ul>

joints, especially in phase 2, (MSUS 20.7%, CE 17.5%) of joints were active

- 21.1% and 20.1% of joints in FOI were inactive clinically or in active in MSUS
- specificity of FOI compared with clinical examination/US/PD was high (84-95%), sensitivity moderate

### Treatment Monitoring\*

20	Glimm et al.	2019	Treatment monitoring	RA	35	No	Wrist, MCP1-5, PIP1-5, DIP2-5,	1	MSUS	<p>Scoring in 3 phases</p> <p>Semiquantitative grading (0-3) via FOIAS</p> <p>2 readers of FOI imaging in consensus</p>	<ul style="list-style-type: none"> <li>• Significant reduction of FOIAS in P1 from baseline (median 5.0, IQR 24.96) to follow-up (median 1.0, IQR 4.0, <math>p = 0.0045</math>) in responders and non-responders according to EULAR response criteria by DAS28</li> <li>• No significant correlation of phase 1 and DAS28(ESR), TJC, or SJC</li> </ul>
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21	<b>Meier et al.</b>	2014	Evaluation of quantitative perfusion measurement under treatment	Different forms of inflammatory arthritis (RA, SpA, PsA, undifferentiated arthritis)	28	No	840 Wrist, MCP1-5, PIP1-5, DIP2-5,	1	MRI	360 images in FOI with region of interest; Rate of early enhancement (REE) during first 60s  2 readers	<ul style="list-style-type: none"> <li>Significant reduction of early enhancement in responders after 24 weeks in FOI and MRI (mean -21.5%, 41.0%, P&lt;.001 both)</li> <li>Increasing enhancement in non-responders (mean FOI 10.8%, P=.075, MRI: 8.7%, P=.03)</li> <li>Significant correlation between FOI and MRI (p=0.80, P&lt;.001)</li> </ul>
<b>Systemic Sclerosis (SSc)</b>											
22	<b>Pfeil et al.</b>	2015	Visualization of Soft Tissue inflammation in SSc patients  Detection of therapeutic response to iloprost or alprostadil	SSc	47 (21 SSc patients)	Yes 26 healthy subjects	-	-	-	Scoring in 3 phases: phase 1 from beginning of examination to first visible enhancements, phase 2 with intensity maximum, phase 3 till end of examination  Scoring of 38 segments per hand  3 readers in consensus  Interreader reliability kappa 0.90 (<0.001), interreader kappa 0.95 (p<0.001)	<ul style="list-style-type: none"> <li>FOI in detection of enhancement: sensitivity 95%, specificity 96%</li> <li>Baseline: 31.5% of hand segments with ICG enhancements, 7 days after therapy 24.7% to 40.9% with enhancement</li> </ul>

23	<b>Friedrich et al.</b>	2017	Assessment of disturbed microcirculation in SSc via FOI and comparison to clinical findings	SSc	89	Yes 26 healthy subjects	-	1	CE Capillaroscopy	<p>360 images Analysis of</p> <ul style="list-style-type: none"> <li>- Region of initial enhancement (IE)</li> <li>- Region of maximum distal distribution (MDD)</li> <li>- Disruption</li> </ul> <p>8 regions per finger, 5 for thumb</p> <p>One reader for FOI</p> <p>Intrareader <math>\kappa = 0.786</math> and interreader reliability for FOI <math>\kappa = 0.834</math></p>	<ul style="list-style-type: none"> <li>• Initial enhancement in SSc in 78.5% (limited SSc) and 43.2% (diffuse SSc), 93.6% in healthy</li> <li>• FOI findings in SSc significantly associated with a late capillaroscopic pattern, disseminated SSc features, a diffuse SSc subtype, and the presence of digital ulcers or pitting scars</li> </ul>
24	<b>Friedrich et al.</b>	2019	Evaluation of predictors for Digital Ulcers (DU) by clinical and imaging methods	SSc	76	-	-	1	CDUS Capillaroscopy	<p>360 images Analysis of</p> <ul style="list-style-type: none"> <li>- Region of initial enhancement</li> <li>- Region of maximum distal distribution (MDD)</li> <li>- Disruption</li> </ul> <p>8 regions per finger, 5 for thumb</p>	<ul style="list-style-type: none"> <li>• 22 of 76 patients (28.9%) with new ulcers during follow-up (diffuse SSc 48.1%; limited SSc 18.4%)</li> <li>• FOI: fingers with pathologic staining with higher risk for new ulcer development in the same finger (<math>p = 0.0153</math>)</li> <li>• General future DU associated with a missing FOI signal in the right digit III at baseline (<math>p = 0.048</math>)</li> <li>•</li> </ul>

25	Friedrich et al.	2020	Development of a composite score for prediction of DU	SSc	79	-	-	1	-	360 images Analysis of <ul style="list-style-type: none"> <li>- Region of initial enhancement</li> <li>- Region of maximum distal distribution (MDD)</li> <li>- Disruption</li> </ul> 8 regions per finger, 5 for thumb	<ul style="list-style-type: none"> <li>• New digital ulcers in 29% of SSc patients in follow-up (48.1% diffuse, 18.4% limited SSc)</li> <li>• Good diagnostic performance of CIP DUS (AUC after cross-validation: 0.83, 95%CI 0.74 to 0.92), sensitivity and specificity at <math>\geq 10</math> points resulting in a sensitivity of 100% and specificity of 74%</li> </ul>
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**Supplementary Table 1:** Overview of included studies sorted by disease categories. FOI: Fluorescence Optical Imaging, MRI: Magnetic Resonance Imaging, MSUS: Musculoskeletal ultrasound. GSUS: Greyscale Ultrasound, PDUS: Power Doppler Ultrasound. CE: Clinical Examination. FOIAS: Fluorescence Optical Imaging Activity Score. ICG: Indocyanine Green. \* Treatment Monitoring is also part of study 12. RA: Rheumatoid Arthritis, PsO: Psoriasis, PsA: Psoriatic Arthritis, OA: Osteoarthritis, JIA: Juvenile Arthritis, SpA: Spondyloarthritis, SSc: Systemic Sclerosis. DIP: distal Interphalangeal joint, PIP: proximal Interphalangeal joint, IP: interphalangeal joint 1, MCP: metacarpophalangeal joint, CMC: first carpometacarpal joint, STT: scaphotrapezotrapezoidal joint. TJC: tender joint count, SJC: swollen joint count, DAS28: Disease Activity Score of 28 joints. CI: Confidence Interval. CV: cardiovascular.