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Kroon, FPB, van Beest, S, Gandjbakhch, F et al. (2019) Longitudinal Reliability of the OMERACT Thumb Base Osteoarthritis Magnetic Resonance Imaging Scoring System (TOMS). *Journal of Rheumatology*, 46 (9). pp. 1228-1231. ISSN: 0315-162X

<https://doi.org/10.3899/jrheum.180949>

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Longitudinal reliability of the OMERACT Thumb Base Osteoarthritis Magnetic Resonance Imaging Scoring System (TOMS)

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Key Indexing Terms. OMERACT, hand, thumb base, osteoarthritis, magnetic resonance imaging, outcomes research

Sources of support. PGC is supported in part by the UK National Institute for Health Research (NIHR) infrastructure at Leeds. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Conflict of interest. None declared.

Running title. Longitudinal Reliability of TOMS

ABSTRACT

Objective. Assess OMERACT Thumb Base Osteoarthritis MRI Scoring System (TOMS) longitudinal reliability.

Methods. Paired MRIs of hand osteoarthritis patients were scored in two exercises (six-month and two-year follow-up) for synovitis, subchondral bone defects (SBDs), osteophytes, cartilage assessment, bone marrow lesions (BMLs), and subluxation. Inter-reader reliability of delta scores was assessed.

Results. Little change occurred. Average-measure intra-class correlation coefficients were good-excellent (≥ 0.71), except synovitis (0.55-0.83) and carpometacarpal-1 osteophytes/cartilage assessment (0.47/0.39). Percentage exact/close agreement was 52-92%/68-100%, except BMLs in two-years' time (28%/64-76%). Smallest detectable change was below the scoring increment, except in SBDs and BMLs.

Conclusion. TOMS longitudinal reliability was moderate-good. Limited change hampered assessment.

INTRODUCTION

The thumb base, including the first carpometacarpal (CMC-1) and scaphotrapeziotrapezoid (STT) joints, is often involved in hand osteoarthritis (OA). Thumb base OA is associated with particular risk factors and requires distinct therapeutic interventions compared to interphalangeal finger OA(1). Therefore, outcome measures specifically assessing thumb base OA are needed.

In response, the OMERACT MRI Working Group developed a scoring system of MRI findings in the thumb base: the Thumb base OA MRI Scoring system (TOMS)(2). This tool has been shown to exhibit good cross-sectional reliability, but data concerning longitudinal reliability are lacking(2). With the term 'longitudinal reliability' we mean the ability to reliably score sequential images taking into account inter-reader variability. Understanding the reliability of TOMS for measuring change is needed for effectively implementing this tool.

This study investigated the longitudinal reliability of TOMS in two settings: a prospective observational study with long-term and a clinical trial with short-term follow-up.(3, 4)

METHODS

Reliability exercises

Two reliability exercises were performed. An atlas was available to facilitate scoring(5). Features assessed were synovitis, subchondral bone defects (SBDs), osteophytes, cartilage assessment, bone marrow lesions (BMLs), and subluxation(2). All features but subluxation were evaluated on 0-3 scales in the CMC-1 and STT joints, with 0.5 increments for synovitis, SBDs and BMLs. Proximal and distal joint parts were scored separately for SBDs, osteophytes and BMLs. Subluxation was scored absent/present in the CMC-1 joint. In both exercises, MRIs were selected to represent a large range of pathology.

In the first exercise, paired MRIs (baseline, two-year follow-up) of 25 patients from the Hand Osteoarthritis in Secondary Care (HOSTAS) prospective cohort study (Leiden University Medical

Center, Leiden, Netherlands; for detail(6)) were scored in known time-order by three independent readers (one rheumatologist (FG) and two rheumatology fellows (SvB, FK), all experienced in using TOMS). Coronal and axial T1-weighted (T1w) fast spin echo (FSE), and T2w FSE images with fat-suppression (fs) were obtained on a 1.5T extremity MRI unit (ONI, GE) (Supplementary File). No contrast agent was used. Therefore, synovitis was scored on T2w-fs images, as per the original scoring system(2).

The second exercise was conducted by an experienced radiologist (CP) and a rheumatology fellow (FK). Paired MRIs (baseline, six-months follow-up) of 24 hand OA patients from a multicenter randomized double-blind trial comparing lutikizumab to placebo(7) were scored for synovitis and BMLs. One reader (CP) scored in unknown and the other in known time-order (FK) for logistical reasons. Coronal and axial T1w-fs images with/without gadolinium-based contrast-enhancement, and short-tau inversion recovery (STIR) or T2w-fs images were obtained according to standardized protocol. Due to incomplete coverage the STT could only be assessed in 16 patients, and the trapezoid bone was not evaluated.

Data collection for both studies was approved by local ethics committees (P09.004, NCT02384538).

All participants provided written informed consent.

Statistical analyses

Separate scores of distal and proximal joint compartments were combined into one sum score per joint where applicable. Median and interquartile range (IQR; baseline status scores) or range (delta scores) was calculated for each feature, based on the average of the readers. Inter-reader reliability of delta scores was assessed by calculating intra-class correlation coefficients (ICC; average measure, mixed-effect models, absolute agreement), and percentage exact and close agreement (PEA/PCA). ICCs ≤ 0.20 were considered poor, >0.20 - <0.40 fair, ≥ 0.40 - <0.60 moderate, ≥ 0.60 - <0.80 good, and ≥ 0.80 excellent reliability(8). PEA/PCA were defined as a difference of $0/\leq 1$ between minimum and maximum scores across readers. For each feature the smallest detectable change (SDC) was

calculated(9). We determined how many patients changed beyond measurement error (i.e., change score>SDC), and whether the smallest scoring increment for each feature could be scored reliably (i.e., smallest increment>SDC).

RESULTS

Table 1 presents baseline characteristics of patients from both reliability exercises. Thirteen trial participants received placebo and 11 lutikizumab. Baseline scores of MRI features were generally low (Table 2). Highest scores were given for CMC-1 osteophytes. Overall, more MRI abnormalities were seen in the CMC-1 compared to the STT joint.

Baseline scores of synovitis and BMLs were comparable in the two studies. On average little change was observed after six months and two years (Table 2). However, individual patients showed change in synovitis and BMLs, both increasing and decreasing (Supplementary Figure 1). Cartilage and bone features generally showed less improvement and more deterioration over time.

Table 3 presents the longitudinal reliability in both studies. ICCs for most features in both thumb base joints were good to excellent. Fair to moderate ICCs were found for cartilage assessment and osteophytes in the CMC-1 joint. ICCs for synovitis in the different studies and joints varied from moderate to excellent. ICCs could not be estimated for some features (STT synovitis in the clinical trial, STT osteophytes, and subluxation).

Since calculation of ICCs was influenced by the small amount of change that occurred over time in both studies, PEA and PCA values were also calculated. PEA/PCA of all features in both joints ranged from 52-92% and 68-100%, except for BMLs in the CMC-1 in the three-reader exercise (PEA 28%/PCA 64%). PEA values in that exercise were all lower than for the clinical trial.

The SDC was calculated for all features and should be considered in light of the range and smallest increment of that feature's score (Table 3). Most SDCs were lower than that feature's smallest scoring increment, although the SDCs of in particular SBDs and BMLs were higher than the increment

of 0.5. In the cohort study, the SDC for BMLs in the CMC-1 was even higher than 1 (SDC=1.27), although in the clinical trial the SDC was better (SDC=0.87). Most participants did not change more than the SDC (Supplementary Table 1). The largest number of participants with a delta score larger than the SDC, either increasing or decreasing, occurred for synovitis and BMLs. Features related to cartilage and bone generally deteriorated. Of these, SBDs showed the most participants with change.

DISCUSSION

In this report, we show the longitudinal reliability of a recently developed OMERACT MRI scoring system to assess inflammatory and structural features in thumb base osteoarthritis (TOMS). Based on ICCs, PEA and PCA values, this investigation showed that reliability of assessment of delta scores using the TOMS was good.

The longitudinal reliability of the similar HOAMRIS, to evaluate interphalangeal joints, was previously published(10). Since HOAMRIS and TOMS assess similar features, similar reliability is expected.

Reliability of change scores in the HOAMRIS exercise (20 patients, 3 readers) for erosive damage and cysts were similar to those for SBDs in TOMS. BMLs were also reliably assessed in both studies.

However, our results for synovitis, osteophytes and cartilage assessment were better compared to HOAMRIS. Observed differences between the studies may partly be explained by a higher number of assessed joints for HOAMRIS, leading to lower PEA/PCA values. Interphalangeal joints are also smaller, and the field strength of the MR scanner was lower, which made reliable assessment more difficult.

ICCs of the previous cross-sectional reliability exercise of the TOMS were generally higher, while PEA/PCA values were lower(2). These differences can be attributed to the fact that assessment of ICCs of delta scores in a cohort with little change over time generally results in lower values, because ICC values are not only dependent on measurement error, but also on between-subject variability. Between-subject variability is part of the calculation used to produce ICC values, and low between-

subject variability can cause unreasonably low ICC values(11). Results of the two exercises performed in this study were generally comparable, although the difference in blinding for time-order among readers of the clinical trial may have resulted in lower results for agreement between these readers. PEA values in the three-reader exercise were all lower than for the two-reader exercise, which can at least partially be attributed to the higher number of readers that have to reach exact agreement in the first case.

Assessment of longitudinal reliability was hampered by the small magnitude of change. Continuous change scores and the number of patients changing more than the SDC were low. Both cohorts reflect natural disease course. In the cohort study no intervention was given, and inflammatory features were not expected to change. However, over a two-year period, cartilage and bone damage was expected to increase, which it did, though only mildly. Generally, radiographic progression in the CMC-1 over two years is slow(12). Moreover, we selected participants with and without thumb base OA for this methodological exercise, which may have attributed to the low amount of change that was observed over time.

Most SDCs were low and below the feature's smallest scoring increment, showing that a change of one increment reflects a measurable change in that feature. Only SBDs and BMLs had an SDC above their defined smallest increment of 0.5, and it could be argued that 0.5 increments are too small to be reliably assessed for these features.

In conclusion, results from this study provide evidence that the OMERACT TOMS can be used to evaluate thumb base MRIs in studies of different settings. Future studies, in particular positive clinical trials, to evaluate sensitivity-to-change, as well as validation studies, are warranted.

ACKNOWLEDGEMENTS

We are indebted to AbbVie (North Chicago, IL) and the Department of Radiology of the Leiden University Medical Center (Leiden, the Netherlands) for providing the Magnetic Resonance Images for the reliability exercises.

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TABLES

Table 1. Baseline characteristics of hand osteoarthritis patients in two reliability exercises.

Clinical characteristic	HOSTAS cohort (n=25)	Clinical trial (n=24)
Women, n (%)	23 (92)	20 (83)
Age, years, mean (SD)	60.0 (7.5)	65.9 (6.8)
Fulfilling ACR hand OA criteria, n (%)	24 (96)	24 (100)
Pain on palpation thumb base, n (%)	16 (64)	14 (58)
KL grade CMC-1, n (%)		
Grade 0	10 (40)	7 (29)
Grade 1	5 (20)	0 (0)
Grade 2	5 (20)	8 (33)
Grade 3	3 (12)	5 (21)
Grade 4	2 (8)	4 (17)
Osteophyte STT[†], n (%)	2 (8)	7 (44)*
Joint space narrowing STT[†], n (%)	6 (24)	6 (38)*

*STT data from n=16 patients. [†]According to OARSI atlas(13).

ACR, American College of Rheumatology; CMC-1, first carpometacarpal; KL, Kellgren-Lawrence; n, number; OA, osteoarthritis; STT, scaphotrapeziotrapezoid.

Table 2. Baseline status (median, IQR) and change scores (median, range) of each MRI feature for the CMC-1 and STT joint in two reliability exercises.

MRI feature [range CMC-1/STT]	HOSTAS cohort (n=25)				Clinical trial (n=24)			
	CMC-1		STT		CMC-1		STT*	
	Baseline	Change (2 years)	Baseline	Change (2 years)	Baseline	Change (6 months)	Baseline	Change (6 months)
Synovitis [0-3/0-3]	1.3 (0.7;1.7)	0 (-1.7;1)	0.7 (0.3;1.3)	0 (-0.7;1)	1.5 (1;2)	0 (-1;1)	0.5 (0;1)	0 (0;0.5)
Subchondral bone defects [0-6/0-9]								
Osteophytes [0-6/0-9]	2.3 (1.7;4)	0 (0;0.7)	0.7 (0.3;1)	0 (0;0.3)				
Cartilage assessment [0-3/0-3]	1 (0.7;1.7)	0 (-0.3;0.7)	0.7 (0;1.3)	0 (-1.7;1)				
Subluxation [absent or present]	8 (32%)†	0 (0;0.3)						
Bone marrow lesions [0-6/0-9]	1.7 (0.7;4.3)	0 (-3.2;4.7)	1 (0.3;2.3)	0 (-2.7;3)	1.3 (0.5;2.5)	0 (-5;4)	0 (0;1.3)	0 (-2.5;3)

Based on average score of all readers, except subluxation†. Separate scores for the distal and proximal part of the joint combined into sum score per joint. *STT scored in n=16 patients, trapezoid not included. †number (%) with subluxation scored by at least two readers. CMC-1, first carpometacarpal; IQR, interquartile range; MRI, magnetic resonance imaging; n, number; STT, scaphotrapeziotrapezoid.

Table 3. Inter-reader reliability of change scores of MRI features for the CMC-1 and STT joint in two reliability exercises.

HOSTAS cohort (n=25)								
MRI feature [smallest increment]	<i>AvmICC</i> (95% CI)	CMC-1			<i>AvmICC</i> (95% CI)	STT		
		<i>PEA</i> <i>n (%)</i>	<i>PCA</i> <i>n (%)</i>	<i>SDC</i>		<i>PEA</i> <i>n (%)</i>	<i>PCA</i> <i>n (%)</i>	<i>SDC</i>
Synovitis [0.5]	0.83 (0.68;0.92)	14 (56)	25 (100)	0.45	0.56 (0.12;0.79)	15 (60)	24 (96)	0.48
Subchondral bone defects [0.5]	0.72 (0.47;0.87)	13 (52)	17 (68)	0.73	0.71 (0.44;0.86)	16 (64)	22 (88)	0.63
Osteophytes [1]	0.47 (-0.02;0.75)	22 (88)	25 (100)	0.22	†	23 (92)	25 (100)	0.18
Cartilage assessment [1]	0.39 (-0.18;0.71)	16 (64)	25 (100)	0.39	0.72 (0.47;0.87)	20 (80)	24 (96)	0.43
Subluxation [1]	†	23 (92)		0.18				
Bone marrow lesions [0.5]	0.84 (0.69;0.93)	7 (28)	16 (64)	1.27	0.92 (0.83;0.96)	7 (28)	19 (76)	0.67
Clinical trial (n=24)*								
Synovitis [0.5]	0.55 (-0.07;0.80)	17 (71)	23 (100)	0.65	†	14 (88)	16 (100)	0.37
Bone marrow lesions [0.5]	0.89 (0.75;0.95)	17 (71)	22 (92)	0.87	0.90 (0.68;0.97)	13 (87)	14 (93)	0.77

*STT scored in n=16 patients, trapezoid not included. †Reliable estimation of ICC not possible due to low variability. AvmICC, average measure intra-class correlation coefficient; CI, confidence interval; PCA, percent close agreement; PEA, percent exact agreement; SDC, smallest detectable change.

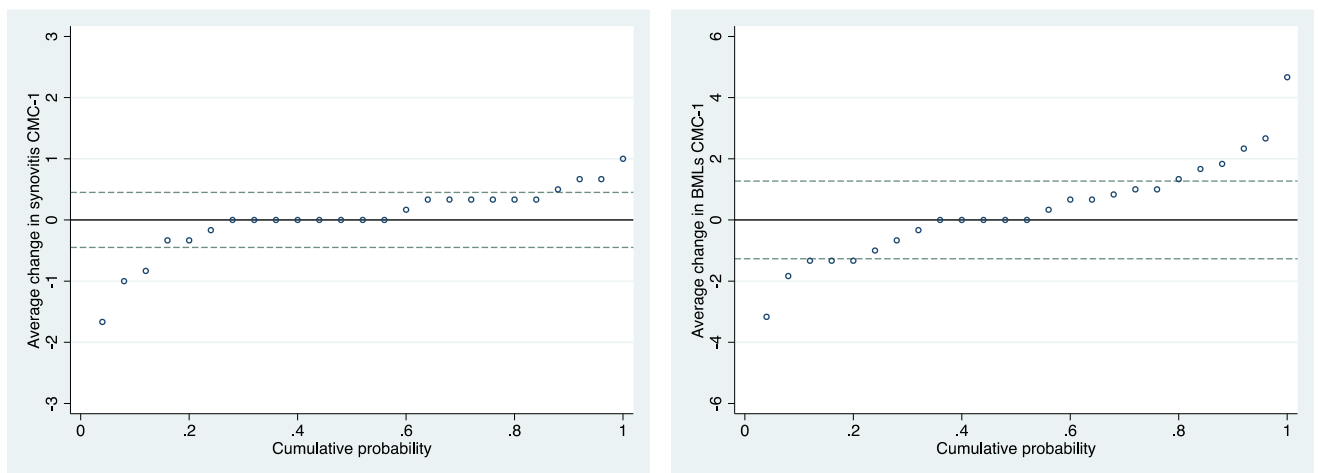
SUPPLEMENTARY FILE

MRI sequences HOSTAS cohort

MR sequences in the HOSTAS cohort included T1-weighted (T1w) fast spin echo (FSE) images in coronal and axial planes (TR/TE 575/11.2, slice thickness 2.0 and 3.0 mm, slice gap 0.2 and 0.3 mm), and T2w FSE images with frequency-selective fat-saturation in coronal and axial planes (TR/TE 3000/61.8, slice thickness 2.0 and 3.0 mm, slice gap 0.2 and 0.3 mm).

Changes of synovitis and bone marrow lesions (BMLs) in individual patients

In Supplementary Figure 1 (below) cumulative probability plots of the change scores of synovitis (left panel) and BMLs (right panel) in the CMC-1 joint are shown. In these plots, each dot represents the change score of an individual patient (based on average scores of all readers). Scores are ordered from the lowest (0) to the highest (1) cumulative probability on the x-axis. The red horizontal line denotes a change score of 0 (i.e., no change over time). Data from the HOSTAS cohort are presented. This figure shows that, despite no average change over time, in individual patients these features did show change over time, both positively and negatively.



Supplementary Figure 1. Cumulative probability plots of change scores in synovitis (left) and BMLs (right) in the CMC-1 joint in the HOSTAS cohort. Dotted lines represent smallest detectable change (SDC).

Change above the smallest detectable change (SDC)

The number of participants with a change score above the SDC are presented in Supplementary Table 1.

Supplementary Table 1. Number (%) of patients with change score of each MRI feature greater or lower than the smallest detectable change (SDC).

MRI feature	HOSTAS cohort (n=25)				Clinical trial (n=24)			
	CMC-1		STT		CMC-1		STT*	
	+ SDC	- SDC	+ SDC	- SDC	+ SDC	- SDC	+ SDC	- SDC
Synovitis	4 (16)	3 (12)	3 (12)	2 (8)	1 (4)	3 (13)	2 (13)	0 (0)
Subchondral bone defects	6 (24)	0 (0)	4 (16)	0 (0)				
Osteophytes	3 (12)	0 (0)	2 (8)	0 (0)				
Cartilage assessment	2 (8)	0 (0)	1 (4)	1 (4)				
Subluxation	2 (8)	0 (0)						
Bone marrow lesions	6 (24)	5 (20)	4 (16)	4 (16)	5 (21)	3 (13)	4 (25)	1 (6)

Based on average score of all readers. * STT scored in n=16 patients, trapezoid not included.

CMC-1, first carpometacarpal; MRI, magnetic resonance imaging; n, number; STT, scaphotrapeziotrapezoid.