Evaluation of three scoring methods for Fluorescence Optical Imaging in erosive hand osteoarthritis and rheumatoid arthritis

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SUMMARY

Objective: Fluorescence Optical Imaging (FOI) demonstrates indocyanine green (ICG)-enhanced microcirculation in wrist and finger joints, as a sign of inflammation. We wanted to assess the reliability of three FOI scoring methods from Berlin, Stockholm, and Copenhagen, to assess the validity of FOI with MRI as reference and to compare enhancement in hand joints in erosive hand osteoarthritis (OA) vs. rheumatoid arthritis (RA).

Design: Five readers scored all finger and wrist joints of 26 patients with erosive hand OA and RA on semi-quantitative 0–3 scales using three different FOI scoring methods. To evaluate inter-reader reliability, we calculated the intraclass correlation coefficients (ICC) for sum scores and prevalence and bias adjusted kappa values for ordinal scales (Pabak-OS) on joint level. Enhancement in joint groups in erosive hand OA vs. RA was compared using Mann-Whitney test. Sensitivities and specificities of FOI was calculated with MRI as reference for hand OA patients only.

Results: We found moderate to good inter-reader reliability for all FOI scoring methods (Pabak-OS: 0.50–0.78, ICC: 0.43–0.85) and different patterns of enhancement in erosive hand OA vs. RA with significantly more FOI enhancement in DIP joints in erosive hand OA vs. RA. With MRI as reference the different FOI scoring methods reached similar sensitivities (63–65%) and specificities (76–91%).

Conclusion: FOI enhancement can be measured reliably in erosive hand OA and RA using three different scoring methods. More DIP enhancement in erosive hand OA patients and good agreement with MRI support the diagnostic performance of FOI.

1. Introduction

Joint inflammation plays an essential role in the pathogenesis of rheumatoid arthritis (RA) and in the last decade studies have suggested that synovitis also is an important pathological component in hand osteoarthritis (OA) [1–3]. Monitoring inflammation with sensitive and cost-effective imaging techniques is important in both diseases. Inflammation assessed by imaging is not included in current remission criteria for RA, but there is increasing interest on the value of imaging-based treat-to-target strategies [22]. For treatment of hand OA there are currently no disease-modifying OA drugs (DMOADs) available and in future trials with drugs targeting synovitis, imaging might be an important and relevant outcome measure. Magnetic resonance imaging (MRI) and musculoskeletal ultrasound (US) can reliably monitor synovitis in both diseases, however MRI is hampered by high cost and limited availability and US by potential operator dependency and the need for sufficient US training. Fluorescence Optical Imaging (FOI) is a novel imaging technique using near infrared light and the fluorophore agent indocyanine green (ICG) to demonstrate enhanced microcirculation due to inflammation in wrist and finger joints. The FOI device can be

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operated by trained medical personnel, emits no radiation and is relatively inexpensive and fast. FOI has since 2010 been applied in clinical research on inflammatory joint diseases [4–9] and in a previous study on patients with undifferentiated arthritis FOI demonstrated good sensitivity and moderate specificity with MRI (n = 25; sensitivity 76%, specificity 54%) and power Doppler ultrasound (n = 74; sensitivity 74%, specificity 42%) as reference [10].

A reliable scoring method is crucial in the assessment of FOI images. The ‘Berlin scoring’ method developed at the Charité Universitätmedizin Berlin as the fluorescence optical imaging activity score (FOIAS) is the most commonly used scoring method in available literature [6,10–12]. A previous study by Werner et al. found moderate to good inter-reader reliability for the Berlin method (k = 0.71) [10] whereas Meier et al. have presented lower weighted kappa values (k = 0.47) [5].

New scoring methods have been developed at Karolinska University Hospital in Stockholm (Sweden) and at Rigshospitalet in Copenhagen (Denmark), but reliability for these two scoring methods has not yet been published. Our primary aim was to assess the inter-reader reliability of these three methods in erosive hand OA and RA patients, and to compare the degree of enhancement in different joint groups in these two diseases. Secondly, we wanted to investigate the diagnostic performance of the different FOI scoring methods in erosive hand OA patients using MRI-defined synovitis as a reference standard.

2. Methods

2.1. Patients

The erosive hand OA patients (n = 13) were randomly selected from the Nor-Hand study, where 300 patients with hand OA were recruited from the rheumatology outpatient clinic at Diakonhjemmet hospital [13]. Inclusion criteria was proven hand OA by clinical examination and/or ultrasound and no clinical sign of inflammatory arthritis. RA patients (n = 13) with the indication to start or switch synthetic DMARDs or switch from synthetic to a combination of synthetic and biological DMARDs were recruited from the rheumatology outpatient clinic at Rigshospitalet, Copenhagen. New treatment was initiated after the FOI examination.

The data collection was approved by the regional ethics committee in Norway and Denmark and all patients signed informed consent.

2.2. FOI examination

The Xiralite-system is the only FOI device available for clinical use in rheumatology. To perform the FOI scan, the patient receives an intravenous injection with a fluorescent dye (ICG pulsion, 0.1 mg/kg body weight) and have near-infrared light from light-emitting diodes projected down on the hands for 6 minutes. With a highly sensitive camera, 360 images (one/second) are produced, showing the flooding in, distribution and washing out of the dye. All images can be scrolled through after the examination, and a composite picture (Prima Vista Mode, PVM) from the 240 first images is automatically generated by the XiraView software. Patients with poor liver function (transaminases above twice the upper reference limit), untreated hyperthyroidism with TFT above 21 pmol/L and thyroid-stimulating hormone (TSH) below 40 mL/min, reduced kidney function with glomerular filtration rate below 40 mL/min, pregnancy and breast-feeding or known allergy to iodine or indocyanine did not undergo FOI examination [13].

2.3. FOI scoring methods

A detailed description of the three scoring methods with an atlas and scoring sheets are available online (Supplementary file 1). In short, four images are assessed with the Berlin method; one composite picture (Prima Vista Mode, PVM) of the 240 first images (Fig. 1a) and three images representing phase 1, 2, and 3 based on the distribution and washing out of the fluorescent dye in relation to the fingertips. The readers registered which image in the sequence was defined as representative of the different phases.

The Stockholm method is evaluated in PVM of 240 and 120 images in a specific setting in the XiraView software (‘temperature’ palette setting, as opposed to the standard ‘rainbow’ palette setting), with additional scrolling through the image sequences to detect further joint enhancement. The ‘temperature’ palette setting is being applied as the developers of the scoring method have experienced that it might be easier to discern between enhanced and non-enhanced tissue with this setting (Fig. 1b).

Finally, the Copenhagen method assumes that inflamed tissues will demonstrate more rapid FOI enhancement than surrounding tissues. FOI enhancement is defined as the first sharply marginated enhancement over a joint area lasting ≥3 seconds when scrolling through the 360 images (Fig. 1c). When peak enhancement was detected in a joint, the readers registered which of the 360 images they assessed, and did not proceed scrolling through the remaining image sequence [14,15].

According to the Berlin and Stockholm methods each joint was graded on 0–3 scales based on color intensity and width of enhancement, while only the width of the enhancement was assessed with the Copenhagen method. The 2nd-5th distal interphalanageal (DIP), 2nd-5th proximal interphalanageal (PIP), 1st interphalanageal (IP1), 1st-5th metacarpophalanageal (MCP), first carpometacarpal (CMC1) joint and wrist were evaluated, with small differences across methods. Sum scores were based on 30 (Copenhagen, excluding the CMC1), 32 (Berlin) and 34 (Stockholm, excluding the CMC1) and interpreting the wrist as 3 joints; ulnar, radial and middle) joints. A mean FOI score from the five readers was calculated for each joint to be used in comparison with MRI.

2.4. Reliability exercise

We arranged a two-day meeting in Berlin (Germany) where all five readers (SO, DG, MA, YK, ØM) and other co-authors (IKH, ØM) participated. Two representatives from Xiralite GmbH offered technical assistance. The three FOI scoring methods were demonstrated and discussed. After the meeting, an FOI atlas was created with examples of grade 0–3 enhancement in all joint groups (except CMC1) for all methods. A calibration exercise was conducted via video conference where all participants scored one patient in consensus using the atlas. Subsequently, the reliability exercise of 26 patients was performed in which the readers were blinded for diagnosis, sex and age of the patients. Each reader scored all patients according to one by one scoring method with at least one week interval between each method and with rearrangement of the order of patients between each method. The readers started with different FOI scoring methods to avoid learning effects and better reliability favoring one method. Time spent on scoring each patient was noted to assess feasibility.

2.5. MRI

Patients with erosive hand OA from the Nor-Hand cohort underwent 1.5T MRI (Siemens Aera, Germany) of the dominant hand approximately 2 weeks after the FOI was obtained (mean (SD) 14 (8) days). The fingers and thumb base joints were covered by a 16-channel hand/wrist-coil and unless contraindications an intravenous contrast (Dotarem 279.3 mg/mL, 0.2 mL/kg body weight) was given. A T1-weighted volumetric interpolated breath-hold examination (VIBE) was reconstructed into three planes with 2 mm thickness [13], of which the axial and sagittal planes were used for evaluation of synovitis.

The images were assessed by two physicians: one experienced reader (IKH) and a PhD-student trained for assessing synovitis in the hand joints (ØM). Both readers were blinded to the FOI results and all clinical data. Synovitis in the DIP, PIP (incl. IP-1) and MCP joints were assessed on a 0–3 scale according to the Hand OA MRI scoring system (HOAMRIS) [16]. The MCP joints were scored as the PIP joints. The two readers
reviewed all joints with disagreement regarding absence/presence of synovitis or inter-reader difference of 2 or 3 grades. The final grade was decided by consensus and an experienced radiologist (KF) was consulted if needed. In joints with one grade difference (grade 1 vs grade 2 and grade 2 vs grade 3), we used the lowest value. Tenosynovitis was assessed by one reader (ØM) according to the Oslo hand OA MRI scoring system (OHOA-MRI) [17], and consulted with KF and IKH in cases of uncertainties.

2.6. Statistics

The average sum scores of FOI enhancement for all five readers in all methods were calculated for different joint groups and for all joints together and compared in erosive hand OA vs. RA using the Mann-Whitney U-test. The CMC1 was assessed by the Berlin method only and demonstrated no enhancement. Hence, we excluded CMC1 from all analyses. The IP1 was defined as a PIP joint in all analyses. To evaluate inter-reader reliability of sum scores, we calculated the intraclass correlation coefficients (ICC, two-way mixed-effects model, absolute agreement, average of 10 reader pairs). On joint level, we calculated linear weighted kappa values and prevalence and bias adjusted kappa values for ordinal scale (Pabak-OS) for pair of readers (ten pairs) and calculated mean kappa values across the four joint groups (DIP, PIP, MCP, wrist) and for all joint groups together. We assessed the percent exact agreement (PEA) and percent close agreement (PCA) with a maximum difference of one grade across the five readers. To compare FOI and MRI we calculated agreement rates for all joints together and in DIP, PIP, and MCP joints separately. The sensitivity, specificity, negative predictive and positive predictive values were calculated for FOI using MRI-defined synovitis as the reference. MRI-defined tenosynovitis was not included in the analysis due to low prevalence. For each of the three Berlin phases and the Copenhagen method we identified the images with the lowest and highest sequence number among the 5 readers. The average difference between maximum and minimum image per patient (Berlin) and per enhanced joint (Copenhagen) was then calculated for all 26 patients.

3. Results

3.1. Demographic and clinical characteristics

Demographic and clinical characteristics for common variables in both studies are presented in Table 1. All patients with erosive hand OA fulfilled the American College of Rheumatology criteria for hand OA and they had substantial radiographic hand OA with mean (SD) Kellgren-Lawrence sum score of 45.3 (9) (range 0–128). All RA patients fulfilled the ACR/EULAR 2010-criteria, 69% of the patients were diagnosed within the last 2 years and had high disease activity with mean (SD) disease activity score 28 (DAS28) of 5.3 (0.7) and median (IQR) number

| Table 1 | Demographic and clinical characteristics. |
|---------|------------------------------------------|
|         | Erosive hand OA (n = 13) | Rheumatoid arthritis (n = 13) |
| Age, mean (SD) | 62 (6) | 50 (12) |
| Sex, n (% female) | 12 (92) | 12 (92) |
| Body mass index, mean (SD) kg/m² | 25 (4) | n/a |
| NRS (0-100)/VAS (0-100) hand pain, median (IQR) | 2 (1, 3) | 60 (40, 72) |
| C-reactive protein, median (IQR) mg/l | 3 (1, 4) | 10 (7, 36) |

OA (Osteoarthritis), RA (rheumatoid arthritis), NRS (Numeric Rating Scale), VAS (Visual Analogue Scale).
of 7 (5.9) swollen and 8 (6.10) tender joints. Six of the patients initiated or switched synthetic DMARD and seven patients added biological DMARD to current synthetic DMARD treatment. Three patients were DMARD naïve.

### 3.2. Reading of the FOI image sequence

For the Berlin method, the difference between the highest and lowest chosen image across the five readers was smallest for phase 1 with a median (IQR) of 10 (5, 22) images for the 26 patients. The difference was large for phase 2 with median (IQR) of 83 (66, 105) images and phase 3 with median (IQR) of 92 (62, 124) images. For the Copenhagen method the readers differed with median (IQR) 6 (3,10) to 10 (5,21) images for different joint groups.

The median (IQR) reading time per patient was shorter for the Copenhagen method (12 (11,14) minutes) than for the Stockholm (15 (14,17) minutes) and Berlin (17 (16,18) minutes) methods. In total the 5 readers scored 4368 joints with the Stockholm method (n = 52 missing), 3860 joints with the Copenhagen method (n = 40 missing) and for Berlin Phase 1–3 and PVM 4091 to 4123 joints (n = 37–69 missing).

### 3.3. Comparison of FOI-enhancement between erosive hand OA and RA patients

Comparing the two diseases we found numerically more FOI enhancement in the DIP and PIP joints in the hand OA patients, while the RA patients demonstrated more FOI enhancement in the MCP joints. Statistical significance was not reached for all methods (Table 2). No consistent differences were observed in the wrists for erosive hand OA and RA patients. The erosive hand OA patients demonstrated more enhancement in the hands than the RA patients by the Berlin PVM (p < 0.001), Berlin Phase 2 (p = 0.12) and Stockholm method (p = 0.03).

### Table 2

Comparison of sum scores (IQR) for 5 readers across different joint groups in erosive hand OA patients vs RA patients.

| Method       | Diagnosis          | DIP P | PIP P | MCP P | Wrist P |
|--------------|--------------------|-------|-------|--------|---------|
| Berlin PVM   | Erosive hand OA    | 4.8 (2,8,7.6) | 0.01   | 12.6 (11.2, 13.6) | -0.001  | 1.4 (0.6, 2.2) | 0.41   | 0.4 (0.0, 1.4) | 0.51   |
|              | RA                 | 1.0 (0.2, 2.8) |       | 6.0 (3.8, 9.0)    | 0.57    | 0.8 (0.4, 1.0) | 0.23   | 0.0 (0.0, 0.8) | 0.28   |
| Berlin Phase 1| Erosive hand OA   | 3.0 (2.4, 4.2) | <0.001 | 4.0 (3.0, 6.2)    | 0.57    | 0.8 (0.4, 1.0) | 0.23   | 0.0 (0.0, 0.8) | 0.28   |
|              | RA                 | 1.4 (0.6, 2.0) |       | 3.6 (2.4, 5.6)    | 2.2 (0.6, 5.0) | 0.4 (0.0, 1.8) |       |
| Berlin Phase 2| Erosive hand OA   | 10.2 (8.6, 11.6) | 0.01  | 20.0 (18.8, 23.8) | 0.23    | 6.6 (4.4, 8.8) | 0.47   | 3.6 (2.4, 4.4) | 0.01   |
|              | RA                 | 6.4 (5.6, 6.8) |       | 15.0 (11.6, 22.2) | 0.23    | 10.0 (5.0, 10.8)| 1.8 (0.8, 2.4) |       |
| Berlin Phase 3| Erosive hand OA   | 2.6 (1.4, 2.8) | 0.59   | 8.4 (6.4, 12.6)   | 0.94    | 2.6 (1.6, 4.0) | 0.39   | 1.6 (0.6, 2.2) | 0.03   |
|              | RA                 | 1.2 (0.6, 3.4) |       | 7.8 (5.4, 12.2)   | 0.32    | 3.2 (2.6, 6.8) | 0.4 (0.4, 1.4) |       |
| Stockholm    | Erosive hand OA    | 6.4 (5.4, 9.8) | <0.001 | 15.2 (12.8, 17.6) | 0.01    | 1.2 (0.8, 2.4) | 0.03   | 1.0 (0.4, 4.2) | 0.80   |
|              | RA                 | 1.6 (0.8, 3.4) |       | 9.4 (6.6, 12.6)   | 0.68    | 3.8 (2.2, 7.0) | 1.12   | 1.2 (0.8, 1.6) | 0.12   |
| Copenhagen   | Erosive hand OA    | 4.4 (3.4, 6.4) | <0.001 | 10.0 (7.2, 11.0)  | 0.68    | 2.6 (1.0, 4.8) | 0.11   | 1.2 (0.8, 1.6) | 0.12   |
|              | RA                 | 1.8 (1.0, 2.6) |       | 7.6 (4.4, 11.4)   | 0.5 (2.8, 10.4) | 1.8 (1.0, 3.0) |       |

IQR (Inter-quartile range), DIP (distal interphalangeal joint), PIP (proximal interphalangeal joint), MCP (metacarpophalangeal joint), PVM (Prima Vista Mode), RA (Rheumatoid Arthritis), OA (Osteoarthritis).

### Table 3

Inter-reader reliability for sum scores in different joint groups. Average ICC values with range of minimum and maximum score for ten reader pairs.

| Method       | All joints ICC (min., max.) | DIP ICC (min., max.) | PIP ICC (min., max.) | MCP ICC (min., max.) | Wrist ICC (min., max.) |
|--------------|-----------------------------|----------------------|----------------------|----------------------|------------------------|
| Berlin PVM   | 0.85 (0.75, 0.97)           | 0.73 (0.41, 0.95)    | 0.88 (0.79, 0.97)    | 0.71 (0.47, 0.96)    | 0.66 (0.46, 0.92)      |
| Berlin Phase 1| 0.43 (0.17, 0.96)           | 0.24 (0.08, 0.67)    | 0.32 (0.11, 0.85)    | 0.79 (0.48, 0.99)    | 0.70 (0.68, 0.99)      |
| Berlin Phase 2| 0.70 (0.32, 0.98)           | 0.75 (0.56, 0.94)    | 0.72 (0.36, 0.98)    | 0.57 (0.08, 0.95)    | 0.80 (0.69, 0.93)      |
| Berlin Phase 3| 0.61 (0.25, 0.89)           | 0.63 (0.29, 0.83)    | 0.65 (0.35, 0.92)    | 0.55 (0.17, 0.95)    | 0.71 (0.55, 0.90)      |
| Copenhagen   | 0.46 (0.09, 0.92)           | 0.64 (0.43, 0.90)    | 0.42 (0.06, 0.90)    | 0.76 (0.52, 0.93)    | 0.60 (0.35, 0.86)      |
| Stockholm    | 0.65 (0.44, 0.84)           | 0.73 (0.59, 0.88)    | 0.77 (0.69, 0.96)    | 0.76 (0.53, 0.90)    | 0.51 (0.10, 0.80)      |

ICC (Intraclass correlation coefficient), DIP (distal interphalangeal joint), PIP (proximal interphalangeal joint), MCP (metacarpophalangeal joint), PVM (Prima Vista Mode).
3.5. Agreement between MRI and FOI in erosive hand OA patients

A total of 182 joints (13 patients, 14 joints per patient) were assessed with MRI, with no joints missing. The 13 erosive hand OA patients had substantial MRI-defined synovitis in the finger joints (DIP, PIP and MCP) with median (IQR) HOAMRIS sum score of 14 (13,15). There were only 4–107 DIP and PIP joints with no MRI-defined synovitis. Only one patient showed mild to moderate tenosynovitis in the MCP joints, thus tenosynovitis was not included in the analyses. We found the highest specificities for the Berlin PVM and Phase 1 and the Stockholm method, while Berlin Phase 2 had the highest sensitivity with a corresponding low specificity (Table 5). Among the different joint groups, the highest specificities and sensitivities were found in the PIP joints (supplement table 2).

MRI defined synovitis was present in 45/94 joints without FOI enhancement of which the majority (30 joints) was grade 1. When looking at agreement between MRI defined synovitis grade 2 and 3 vs. FOI grade 2 and 3 we found slightly improved specificity for all methods with corresponding lowering of the sensitivity (data not shown).

4. Discussion

No previous studies have evaluated the reliability and validity of different FOI scoring methods in patients with erosive hand OA and RA. In this study we found moderate to very good inter-reader reliability on patient level for all methods and moderate to good agreement on joint level for all three methods. Our findings of best agreement between two readers from the same center underlines the importance of calibration before scoring. The Berlin PVM showed consistently the strongest inter-reader reliability on patient and joint level for all methods and moderate to good agreement on joint level for all three methods. Negative predictive values were low to moderate across all methods, suggesting that a lack of enhancement cannot exclude synovitis. The Copenhagen method was the fastest scoring method. However, in this exercise the readers had to report which image frame they scored for each enhanced joint and in patients with much activity this added several minutes to the final scoring time compared to regular scoring with the Copenhagen method [14,15]. For the Berlin method the readers reported which image they defined as phase 1, 2, and 3 which also added extra time to the total, whereas no additional information was reported for the Stockholm method. Nevertheless, our results indicate that all three methods are feasible with scoring times ranging from 12 to 17 minutes.

There are several limitations to this study. We had MRIs from the erosive hand OA patients (n = 13) only. These patients had moderate to high level of inflammation with very few joints with no synovitis, making analysis on sensitivity and specificity difficult to interpret. Thus, a larger sample and more variety of MRI findings is needed in order to explore FOIs validity in hand OA. Secondly, we only assessed one patient per scoring method in the calibration exercise and we could possibly have reached higher reliability if

### Table 5

| FOI-/MRI | FOI-/MRI | Sens. | Spes. | PPV | NPV | PEA | Pabak |
|----------|----------|-------|-------|-----|-----|-----|-------|
| Berlin PVM | 83/128 | 49/54 | 65 | 91 | 94 | 52 | 73 | 0.45 |
| Berlin Phase 1 | 45/128 | 49/54 | 35 | 91 | 90 | 37 | 52 | 0.03 |
| Berlin Phase 2 | 117/128 | 20/54 | 91 | 37 | 78 | 65 | 75 | 0.51 |
| Berlin Phase 3 | 65/128 | 40/54 | 51 | 74 | 82 | 39 | 58 | 0.15 |
| Copenhagen | 81/128 | 41/54 | 63 | 76 | 86 | 47 | 67 | 0.34 |
| Stockholm | 97/128 | 46/54 | 68 | 85 | 92 | 53 | 73 | 0.46 |

FOI (Fluorescence Optical Imaging), MRI (Magnetic Resonance Imaging), PPV (Positive Predictive Value), NPV (Negative Predictive Value), PEA (Percent Exact Agreement), Pabak (Prevalence and Bias Adjusted Kappa values), PVM (Prima Vista Mode).

* Joints with FOI enhancement in joints with MRI synovitis

* Joints without FOI enhancement in joints without MRI synovitis
a larger number of patients had been scored by consensus before the reliability exercise. Third, intra-observer agreement was not included in the reliability exercise due to feasibility reasons. Finally, our findings cannot be generalised to the general hand OA population as we only included patients with erosive hand OA who had been referred to specialist health care. The FOI technology also has its limitations [6,11,21], with 2D-images only and no available device for combining radiographic and optical images. Near infrared light also has limited tissue penetration, and from our findings the frequently inflamed CMC-1 joint was not possible to visualise with the FOI device. Finally, several precautions must be taken before performing the FOI exam, as dry skin, wounds, tattoos, nail polish, cold fingers, excessive use of the hands before the examination and ambient light in the room might influence the final result on FOI.

In conclusion, FOI enhancement can be measured reliably in erosive hand OA and RA using three different scoring methods and from our findings the Berlin PVM was the most reliable method. Numerically more DIP and PIP enhancement in erosive hand OA patients, more MCP enhancement in RA patients and good agreement with MRI support the diagnostic performance of FOI. Future larger studies are needed to confirm these findings.

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Author contributions

ØM: Study design, data collection, analyzing the data, interpretation of results, drafting the work and final approval of the paper. IKH: Study design, data collection, interpretation of results, revising the work critically and final approval of the paper. SO, MA, DG, YK: Study design, data collection, interpretation of results, revising the work critically and final approval of the paper. LT, TKK, TU, MØ: Study design, interpretation of results, revising the work critically and final approval of the paper.

Conflicts of interest

No relevant disclosures.

Role of xiralite GmbH

The meeting before the reliability exercise was held in the Xiralite GmbH offices in Berlin. Xiralite GmbH has not contributed to the study design, collection or interpretation of the data, the writing of the manuscript or the decision to publish the data. None of the participants have received funding from Xiralite GmbH.

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Appendix A. Supplementary data

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