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Title

Subtle Radiographic Progression at Six Months Can Be Detected Using Automated Quantitative Software in Rheumatoid Arthritis While Receiving Tocilizumab

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ABSTRACT

Objectives: We investigated whether our in-house software equipped with partial image phase-only correlation (PIPOC) can detect subtle radiographic joint space narrowing (JSN) progression at six months and predict JSN progression in rheumatoid arthritis (RA) patients receiving Tocilizumab.

Methods: The study included 39 RA patients who were treated with Tocilizumab. Radiological progression of the metacarpophalangeal and the proximal interphalangeal joints was evaluated according to the Genant-modified Sharp score (GSS) at 0, 6, and 12 months. Automatic measurements were performed with the software. We validated the software in terms of accuracy in detecting the JSN progression.

Results: The success rate of the software for joint space width (JSW) measurement was 96.8% (449/464). The 0-12-month JSW change by the software was significantly greater in joints with the 0-6-month PIPOC (+) group than the 0-6-month PIPOC (-) group ($p < 0.001$). The 0-12-month JSW change by the software was 0-12-month GSS (+) than with 0-12-month GSS (-) ($p = 0.02$). Here, "(+)" indicates the JSN progression during the follow-up period. Meanwhile, "(-)" indicates no JSN progression during the follow-up period. Linear regression tests showed significant correlations between the 0-6-month and

the 0-12-month PIPOC in the left 2nd and 3rd MCP joints (R^2 = 0.554 and 0.420, respectively).

Conclusions: Our in-house software equipped with PIPOC could predict subsequent JSN progression with only short-term observations.

KEYWORDS: Finger joint; joint space narrowing; radiography; rheumatoid arthritis; software

Introduction

The treatment of early rheumatoid arthritis (RA) has caused a paradigm shift in the past decades with the introduction of tight-control and treat-to-target strategies and the advent of biological disease-modifying anti-rheumatic drugs (DMARDs) [1-4]. With these advances in effective treatment techniques, radiographic progression of joint damage in early RA is difficult to detect in short-term clinical trials [5-7].

Nevertheless, radiographic joint damage is still an important finding widely used in clinical practice and trials because of its accessibility and ease of longitudinal comparison [8]. The gold standard for its evaluation is the modified Sharp/van der Heijde score (SHS) or the Genant-modified Sharp score (GSS), in which radiologists and rheumatologists visually evaluate the radiographic progression of joint space narrowing (JSN) and bone erosion [5, 9, 10]. However, visual evaluation has several disadvantages, such as the scoring results depending on the reader, its time-consuming nature and difficulty detecting subtle changes with the human eyes in radiographs with limited resolution and contrast [11, 12].

To address these issues, various computer-based and automated techniques have been developed to detect changes in finger joint space width (JSW) using hand radiographs achieving some promising results [13-17]. However, most of them first detect

and delineate the joint bone edges using conventional image processing and machine learning methods and then calculate the JSW. The definition of the joint edge by delineating it contains pixel-level errors, especially when there is an overlap of the bony edge in the joint [16]. It is, therefore, theoretically difficult to detect changes of less than the pixel size of approximately 0.1 millimeters (mm) in early RA patients. In the past, we successfully overcame this problem by superimposing images to quantitatively detect the change in JSW, avoiding potential errors derived from inaccurate edge delineation. However, this method has some drawbacks, such as the semi-automation nature still requiring operator intervention [12, 18-20] and the inability to measure JSW in the mm unit [21].

Phase-only correlation (POC) is a method to estimate the relative translative offset between two similar images. It is commonly used in image registration utilizing a frequency-domain representation of the data calculated by fast Fourier transforms. It is superior in robustness and positional accuracy to other methods. In high-precision image matching with POC, the displacement of an image can be estimated with an accuracy of 1/10 to 1/100 pixel by a function fitting technique using the closed-form representation of the POC function's peak [22]. We have developed in-house software equipped with partial image phase-only correlation (PIPOC) that can automatically calculate the

displacements of multiple areas with sub-pixel accuracy [23, 24].

This study aimed to investigate whether the in-house software equipped with PIPOC can detect subtle JSN progression six months after baseline and predict the JSN progression at 12 months in RA patients under tocilizumab (TCZ) treatment. JSN progression at baseline, 6, and 12 months was assessed by GSS and compared with the automated results.

Materials and Methods

Patients

This study included 39 RA patients (35 female and four male) who satisfied the American Rheumatism Association 1987 revised criteria for the classification of RA [25]. All patients had been treated with biological DMARDs (TCZ + methotrexate [MTX], n = 19; TCZ + MTX + bucillamine [BUC], n = 8; TCZ + MTX + tacrolimus [TAC], n = 4; TCZ +MTX + Salazosulfapyridine, n = 2; TCZ + BUC + TAC, n = 1; TCZ + BUC, n = 1; TCZ + TAC, n = 1; TCZ monotherapy, n = 3). Prednisolone was administered to 23 of these patients. The clinical characteristics of RA patients are shown in Table 1. The study was conducted in compliance with the Declaration of Helsinki and approved by the ethics

review committee at the Faculty of Health Sciences, Hokkaido University. Informed consent was obtained in the form of opt-out on the website.

Radiography

Bilateral hand radiographs were acquired at baseline, 6 and 12 months. The mean and standard deviation (SD) between baseline and follow-up was 6.3 (±0.8) months and 13.3 (±2.1) months, respectively. The imaging conditions are shown in Table 2. The center of the incident beam was the hand's 3rd metacarpophalangeal (MCP) joint. All images were displayed as digital imaging and communications in medicine (DICOM) with 2010 × 1490 pixels and a 0.175 × 0.175 mm pixel size at 12-bit grayscale resolution. All radiographs were scored by an expert rheumatologist with more than 20 years of experience who was blinded to other clinical information for assessment of JSN progression using the GSS system as follows: 0 = normal; 0.5 = subtle or equivocal narrowing; 1.0 = focal or mild narrowing; 1.5 = mild-to-moderate narrowing; 2.0 = moderate narrowing; 2.5 = moderate-to-severe narrowing; 3.0 = complete loss of joint space or dislocation in the presence of erosion; 3.5 = partial or equivocal ankylosis; 4.0 = definite ankylosis [9, 26].

In-house software equipped with PIPOC

We have developed in-house software equipped with PIPOC. The PIPOC method is an improvement over the full image phase-only correlation (FIPOC) method proposed by Ou et al. [23, 27]. FIPOC is an approach to estimating the relative translative offset between two similar images that relies on analyzing images in the frequency domain. The analysis procedure followed five steps (Figure. 1) [28].

1. Positioning fingers

The background of radiographic images is first subtracted using Otsu's method [29]. Morphological openings and closings are used to remove small objects and holes. Next, we find grooves and fingertips at the edge of the hand. We then calculate the area of the finger and fit a line through the centre of this area. Finally, we calculate the width of the fingers by the size of the finger area. The finger area can then be cut out to detect the position of the joint.

2. Joint detection

The next step is the detection of the joints. We use AdaBoost's machine learning algorithm to train our joint classifier [30].

3. Position Calibration

As shown in step 3 of Figure 1, the cyan and red lines are the bone edges of the

baseline and follow-up images, respectively. The white line represents coincidental parts. Before position calibration, detection results of the same joint in sequential radiographic images have a deviation in the position of joint windows. We use FIPOC to calibrate the position of the joint. The deviation between the two joint windows is eliminated when the bone edges are almost completely coincident.

4. Joint segmentation

We propose an algorithm to segment joint images so that the movement of the proximal and distal bones can be detected separately. To avoid mutual interference, a dividing line is drawn in the gully to calculate the movement of the proximal and distal bones separately.

5. Joint Comparison

As shown in step 5 of Figure 1, PIPOC calculates the relative movement of the proximal and distal bones. This step divides each joint image into proximal and distal bones in the phase spectrum. We then calculate the phase difference spectrum of proximal and distal bones between the baseline and follow-up images. The bone movement can be obtained by calculating the peak position of the Dirac delta function in the phase difference spectrum. The JSN between the baseline and follow-up images can thus be quantified according to the bone movement difference between proximal and distal bones.

A median filter is used to suppress noise before calibrating the minute displacement using PIPOC. From these steps, we can calculate the progression of JSN according to the vertical movements of the proximal and distal bones. We have described the details of the PIPOC algorithm in a previous study [24, 28]. All results calculated from the software were converted to mm units by multiplying the pixel spacing (0.175 mm/pixel).

Statistical analysis

Statistical analyses were performed with the use of JMP software version 16.2.0 (SAS Institute, Cary, NC, USA) and EZR software version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [31]. EZR is a graphical user interface for the R software package version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria). A p-value < 0.05 was considered to indicate a significant difference.

To ensure homogeneity of the subjects, we targeted the joints with GSS = 0 at baseline for the software analysis. The following statistical analyses were performed using the Mann-Whitney U tests. We compared the 0-12-month GSS/PIPOC with and without JSN progression according to the 0-6-month GSS/PIPOC assessment. Here, "(+)" indicates the JSN progression during the follow-up period. Meanwhile, "(-)" indicates no JSN progression during the follow-up period. The GSS (+)/PIPOC (+) were defined as

joints with JSN progression according to the GSS assessment and the software analysis, respectively. Otherwise, joints were defined as the GSS (-)/PIPOC (-), non-progressive JSN. We then compared the 0-6-/0-12-month PIPOC between the 0-6-/0-12-month GSS (-) and GSS (+).

The relationships between the 0-6-month and the 0-12-month PIPOC for each joint were investigated using linear regression tests. The joints within 1.5 mm of the JSW difference were included in the linear regression tests. The relationships for each joint were indicated according to the coefficient of determination (R^2) [32].

Results

Out of 624 MCP and proximal interphalangeal (PIP) joints of the 2nd through 5th finger in 39 RA patients, 553 joints were available for both GSS assessment and software analysis, excluding missing data and unevaluable joints. "Unevaluable joints" are joints that were determined to be N/A (not available) in the software analysis, including joints with severely progressive bone destruction. Out of 553 joints, we targeted 464 joints with GSS = 0 at baseline in the software analysis. The success rate of the in-house software for JSW measurement was 96.8% (449/464).

The median interquartile range (IQR) GSS of the 449 joints was 0 (0－0) at all time points (Table 3). Median IQR PIPOC for 0-6 and 0-12-months were -0.00 (-0.08－0.08) and -0.01 (-0.08－0.06), respectively (Table 3).

A comparison of JSN progression measured with GSS and the software is shown in Table 4. The 0-12-month GSS with the 0-6-month GSS (+) group showed significantly more JSN progression than the 0-6-month GSS (-) group (Mann-Whitney U test, $p < 0.001$). Similarly, the 0-12-month PIPOC with the 0-6-month PIPOC (+) group showed significantly more JSN progression than the 0-6-month PIPOC (-) group ($p = 0.001$). There was no significant difference in the 0-6-month JSW change of finger joints detected by the software between the 0-6-month GSS (+) and the 0-6-month GSS (-) ($p = 0.886$). The 0-12-month JSW change of finger joints with the 0-12-month GSS (+) detected by the software was significantly greater than the 0-12-month GSS (-) ($p = 0.020$).

As for the relationships between the 0-6-month and the 0-12-month PIPOC for each joint, linear regression tests showed significant correlations between the 0-6-month and the 0-12-month PIPOC in the left 2nd and the left 3rd MCP joints ($R^2 = 0.554$, $p < 0.001$ and $R^2 = 0.420$, $p = 0.004$), respectively (Figure 2). In contrast, there were no significant correlations in other finger joints. In addition, the joints larger than 1.5 mm were excluded to ensure that early changes could be detected sensitively and stably.

Discussion

This study aimed to determine whether in-house software with PIPOC can detect subtle JSN progression and predict it in RA patients undergoing potent biologic DMARD treatment with TCZ at six months from baseline. In the assessment by the software and the conventional scoring method, JSN progression at 0-12 months was significantly greater in the JSN progression group than in the non-progression group at 0-6 months. In comparison, at 0-12 months, the degree of JSN progression by the software was significantly greater in joints with JSN progression than in joints without JSN progression using the conventional scoring method. In addition, there was a significant correlation in the software measurement between 0-6-month and 0-12-month JSN progression in the left 2nd and 3rd MCP joints. The results suggest that the software could detect subtle JSW changes at six months and might predict JSN progression at 12 months.

Previously, computer-based JSW assessments of hand radiographs of RA patients have been performed by several research groups using various methods [6, 13-17, 33]. These analyses are often cross-sectional assessments [13, 15-17], while only a few studies have focused on temporal changes [6, 14, 33]. Several studies that

investigated temporal changes had relatively long follow-up periods of more than one year; Pfeil et al. had data for one year [33], Huo et al. for 1-2 years [6], and Finckh et al. for four years [14]. In contrast, the present study suggests that the software can detect changes in JSW at a relatively early stage (0-6-month) and predict the degree of subsequent JSN progression based on radiographic evaluation at 0, 6, and 12 months. In the previous study using the phantom simulating a joint, the mean error and the smallest detectable difference of our software were revealed to be 0.001 mm and 0.044 mm, respectively [28]. Earlier detection of destructive changes using the software could be useful for the judgment of treatment efficacy and prediction of prognosis. Huo et al. also reported several studies using fully automatic software, although they mentioned that the overlap in joints of the upper and lower bones makes analysis difficult [6, 16]. Few software systems can perform automatic analysis with overlapped bones. The advantage of our software [24] is that it handles overlapping bones by using images taken at two points over time, evaluating the difference between the upper and lower bones with subpixel accuracy with POC and calculating the JSW changes.

There was no significant difference in the JSN progression on software in the 0-6-month period between joints with and without JSN progression by GSS. This might be attributed to the fact that the amount of change in JSW was too slight in the visual

assessment at six months. To support this explanation, Shimizu et al. reported that early-stage RA generally has a JSN of less than 1 mm that generally progresses to 3 months in a study using high-resolution peripheral quantitative computed tomography [34]. It has also been reported that even expert rheumatologists find it difficult to visually assess changes in JSW of 0.3 mm or less [12]. The software has been shown to have a mean error of 0.001 mm and SDD of 0.044 mm in a previous study using a phantom that simulated a joint. On the other hand, the significant difference between the software and GSS assessment in the 0-12-month period suggests that a visually detectable change in JSW had occurred.

In clinical trials in RA patients, the magnitudes of change in JSW have become lower than previously, owing to the advancement of innovative therapeutic agents such as biologic DMARDs and other treatment strategies. It has therefore become increasingly difficult for conventional radiographic scoring systems with the human eye to detect statistically significant changes in joint deterioration. Moreover, it has been reported that it takes 25 minutes to score all seven radiographs of the hands and feet using the conventional SHS method [35]. The conventional scoring method may soon be replaced by fully automated software that enables subpixel analysis, such as the one used in this study, reducing the busy physicians' workload.

There were several limitations to our study. First, our study was conducted retrospectively using patient data from a single centre. Furthermore, only a single therapeutic agent (TCZ) was considered. It is necessary to investigate further whether our software can be a useful tool for determining therapeutic efficacy in patients using other therapeutic agents and to confirm whether the results can be generalized by a multicentre prospective study. A second limitation of our study was that the in-house software analysis only included JSN and not bone erosion. Further software improvement is needed to evaluate bone erosion, a crucial finding in rheumatoid arthritis. A third limitation of this study was that our software targeted joints with GSS = 0 at baseline; cases with severe joint destruction were not considered. However, since this software was developed to detect early-stage JSN that is difficult to assess visually, it was a reasonable approach. The fourth limitation of our study was that the success rate of the software analysis depends on the quality of the radiographic images obtained. It has been reported that technical factors frequently cause the failure of computerized JSW analysis during image acquisition [36]. In particular, finger joint flexion, oblique X-ray entry, and the difference between baseline and follow-up positioning need to be specifically considered. In this study, the reason for the no significant correlation between the 0-6-month and 0-12-month software assessments, except for the left 2nd and 3rd MCP joints, may be due to patient-

specific factors including positioning, as described above. In addition to acquiring images based on standardized imaging protocols, introducing indicators to determine the acceptability of software analysis would eliminate false results as much as possible and provide highly valid analysis results.

In conclusion, subtle radiographic JSN progression in RA patients under TCZ treatment is detectable by our automatic software equipped with PIPOC. Our results suggested that the software could predict subsequent JSN progression with only short-time observations at six months from baseline.

Conflicts of Interest: T.K. reports grants from Chugai Pharmaceutical. The other authors have no conflict of interest.

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Figure Legends

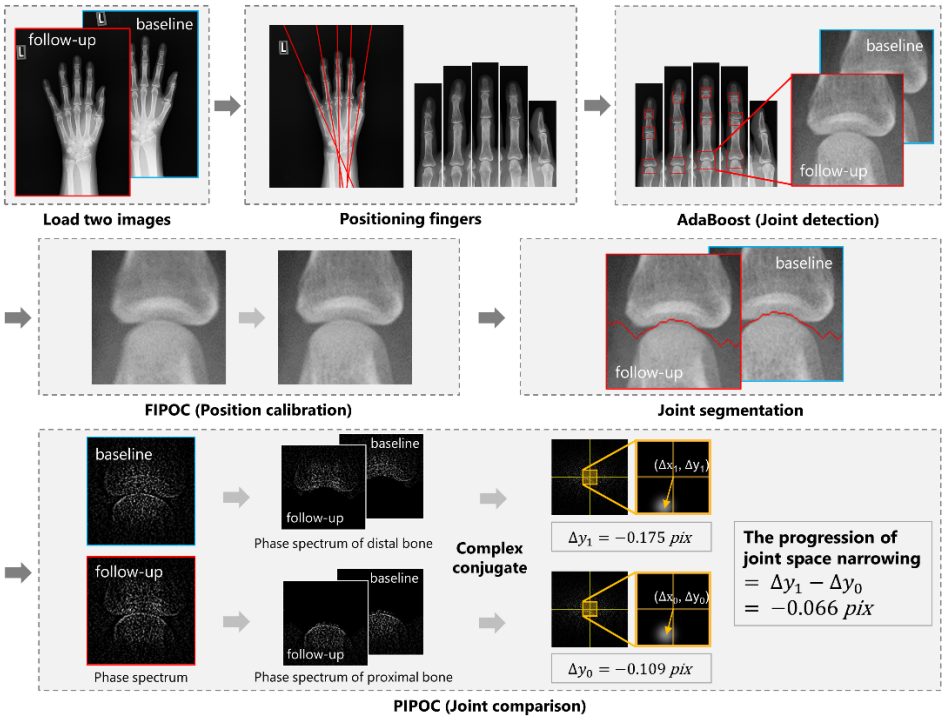

Figure 1. Algorithm flow of in-house software equipped with PIPOC.

Figure 1 is reprinted with minor modifications from “Japanese Journal of Radiology. 2023;41(5):510-520. Fig. 2.” [28]

FIPOC: full image phase-only correlation; PIPOC: partial image phase-only correlation

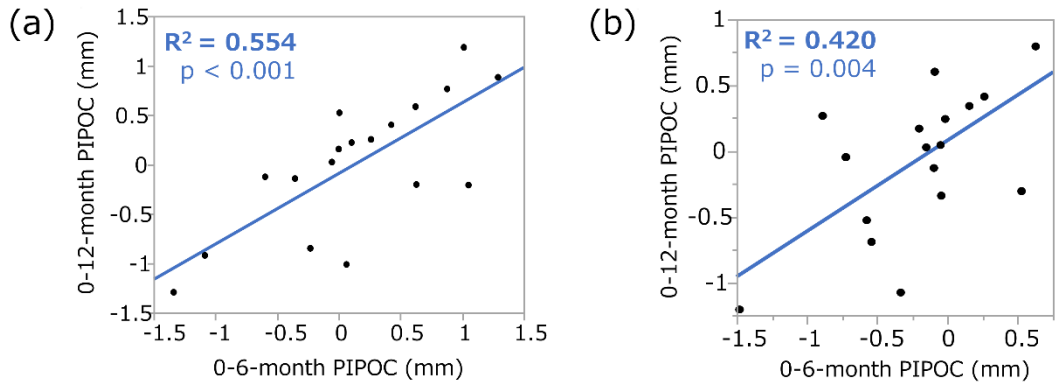

Figure 2. Linear regression tests between the 0-6-month and the 0-12-month PIPOC in the left 2nd MCP joints (a) and the left 3rd MCP joints (b).

PIPOC: partial image phase-only correlation; R^2: coefficient of determination;

MCP: metacarpophalangeal

Tables

Table 1. Clinical characteristics of RA patients under TCZ treatment

variable	baseline	6 months	12 months
Total number of patients	39		
Sex, female/male	35/4		
Rheumatoid factor status, positive/negative	29/10		
Age, mean (SD) years	61.5 (14.6)		
Duration of disease, mean (SD) months	111.4 (85.0)		
Tender joint count, mean (SD)	6.0 (4.7)	3.5 (3.5)	2.9 (4.0)
Swollen joint count, mean (SD)	6.4 (3.5)	2.9 (2.2)	1.9 (2.0)
DAS28-ESR, mean (SD)	4.9 (1.2)	3.0 (1.1)	2.6 (1.0)
DAS28-CRP, mean (SD)	4.4 (1.1)	3.0 (0.9)	2.6 (0.8)

RA: rheumatoid arthritis; TCZ: Tocilizumab; SD: standard deviation; DAS28: disease activity score with 28 joints; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein

Table 2. X-ray imaging parameters

Device	DR-155HS2-5
Manufacturing Company	Hitachi
Tube voltage, kV	42
Tube current, mA	100
Exposure, sec	0.02
Source to image distance, cm	100
Pixel size, mm	0.175

Table 3. Assessment of JSN progression for the GSS and the software

variable	baseline	6 months	12 months	0-6-month	0-12-month
Out of 553 joints GSS, median (IQR, range)	0 (0－0, 0－4)	0 (0－0, 0－4)	0 (0－0, 0－4)	0 (0－0, 0－2)	0 (0－0, 0－2)
Out of 449 joints GSS, median (IQR, range)	0 (0－0, 0－0)	0 (0－0, 0－2)	0 (0－0, 0－2)	0 (0－0, 0－2)	0 (0－0, 0－2)
PIPOC, median (IQR, range) mm				-0.00 (-0.08－0.08, -3.16－ 2.93)	-0.01 (-0.08－0.06, -3.19－2.88)

JSN: joint space narrowing; GSS: Genant-modified Sharp score; IQR: interquartile range;

PIPOC: partial image phase-only correlation

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Table 4. Comparison of JSN progression for the GSS and the software

variable	0-6-month GSS (-)		0-6-month GSS (+)		p-value
	median	IQR	median	IQR	
0-12-month GSS	0	0－0	2	2－2	< 0.001*
0-6-month PIPOC, mm	-0.00	-0.08－0.08	-0.01	-0.06－0.05	0.886
0-12-month PIPOC, mm	-0.01	-0.08－0.06	-0.09	-0.62－-0.01	0.109
	0-6-month PIPOC (-)		0-6-month PIPOC (+)		p-value
	median	IQR	median	IQR	
0-12-month PIPOC, mm	0.02	-0.05－0.09	-0.02	-0.12－0.04	0.001*
0-6-month GSS	0	0－0	0	0－0	0.666
0-12-month GSS	0	0－0	0	0－0	0.576
	0-12-month GSS (-)		0-12-month GSS (+)		p-value
	median	IQR	median	IQR	
0-12-month PIPOC, mm	-0.01	-0.08－0.06	-0.11	-0.31－-0.01	0.020*

2 JSN: joint space narrowing; GSS: Genant-modified Sharp score; IQR: interquartile range;

3 PIPOC: partial image phase-only correlation

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