学 位 論 文

Assessment of Automatic Software for Detecting Radiographic Joint Space Narrowing Progression in Rheumatoid Arthritis

（関節リウマチにおける単純 X 線写真を用いた関節裂隙狭小化進行の
自動検出ソフトウェアの評価）

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Chapter 1

Introduction

Rheumatoid arthritis (RA) is an autoimmune and chronic inflammatory joint disease that can cause cartilage, bone damage, and disability [1]. The estimated prevalence of RA is more than 700 thousand in Japan [2]. The ratio of male to female RA patients is 1:4, with the incidence between 30 and 50 [3,4]. After the onset of RA, joint destruction progresses rapidly, and daily life becomes difficult due to joint pain and deformity.

The progression of joint space narrowing (JSN) over time is one of the parameters used to evaluate joint destruction in RA patients. The gold standard for its assessment is the modified Sharp/van der Heijde score (SHS) or the Genant-modified Sharp score (GSS) [5,6]. This is evaluated visually by a physician. However, it is difficult to objectively and quantitatively assess the progression of slight JSN [7]. In addition, recent advances in anti-rheumatic drugs, such as biological agents have reduced the progression of symptoms, and in some cases, the progression of JSN is only a few millimeters per year [8]. Therefore, the objective and quantitative evaluation of JSN plays an important role in clinical trials in RA drug development and evaluation of efficacy in drug therapy.

This study verified whether a newly developed in-house software could automatically and quantitatively evaluate the slight progression of JSN on plain radiographs, which is difficult to evaluate visually.

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Chapter 2

Fully Automatic Software for Detecting Radiographic Joint Space Narrowing Progression in Rheumatoid Arthritis: Phantom Study and Comparison with Visual Assessment

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Abstract

Purpose: We have developed an in-house software with partial image phase-only correlation (PIPOC) that can automatically quantify radiographic joint space narrowing (JSN) progression. The purpose of this study was to evaluate the software in phantom and clinical assessments.

Materials and methods: In the phantom assessment, the software's performance on radiographic images was compared to the joint space width (JSW) difference using a micrometer as ground truth. A phantom simulating a finger joint was scanned underwater. In the clinical assessment, 15 RA patients were included. The software measured the radiological progression of the finger joints between the baseline and the 52nd week. The cases were also evaluated with the Genant-modified Sharp score (GSS), a conventional visual scoring method. We also quantitatively assessed these joints' synovial vascularity (SV) on power Doppler ultrasonography (0, 8, 20, and 52 weeks).

Results: In the phantom assessment, the PIPOC software could detect changes in JSN with the smallest detectable difference of 0.044 mm at 0.1 mm intervals. In the clinical assessment, the JSW change of the joints with GSS progression detected by the software was significantly greater than those without GSS progression ($p = 0.004$). The JSW change of joints with positive SV at baseline was significantly higher than those with negative SV ($p = 0.024$).

Conclusion: Our in-house software equipped with PIPOC can automatically and quantitatively detect slight radiographic changes of JSW in clinically inactive RA patients.

Keywords:

Connective tissue disease; Radiography; Joint space; Software; Ultrasonography

Introduction

Rheumatoid arthritis (RA) is characterized by synovial inflammation and bone destruction leading to the disability with potentially large socioeconomic consequences for the individual patient and society [1]. The emphasis is now on early intervention to prevent disability and irreversible damage. Early detection and diagnosis of RA are extremely important to avoid missing the "window of opportunity" to start effective therapeutic agents, resulting in long-term sustained benefits or, more importantly, the chance of "cure" [2].

Radiography has been the primary imaging modality for the evaluation of structural joint damage both in clinical practice and clinical trials. The advantages of radiography for RA include excellent skeletal structure imaging and comprehensive assessment of joints, as well as low cost and general accessibility [3, 4]. The gold standard to assess radiographic joint destruction in RA is the semi-quantitative van der Heijde-modified Sharp score or the Genant-modified Sharp score (GSS), in which radiologists and rheumatologists visually assess the progression of joint space narrowing (JSN) and bone erosion [5-7]. As Kato et al. reported, even for experienced rheumatologists in GSS assessment, it is difficult to detect joint space width (JSW) difference of 0.30 mm or less [8], making it extremely challenging to detect slight changes visually.

In the last two decades, a trend toward lower levels in disease activity, and hence in radiographic progression among the cohort of patients receiving methotrexate has been noted in trials [9], hypothesized to be due to a better standard of care for RA patients. Even

with the availability of high-resolution imaging, it is not uncommon for JSN progression to be less than a few pixels per year; a high level of accuracy and precision is therefore required to detect slight progression in clinical trials [10].

Several computer-based software methods have been developed and introduced [11-14]; however, most use traditional image processing and machine learning methods to detect the bone margin and then calculate JSW. Because of the two-dimensional nature of the radiograph, it is difficult to improve the accuracy of the bone margin. Algorithms based on margins have pixel-level errors, and it is theoretically almost impossible to detect early JSW changes that are less than one pixel in early-stage RA patients.

We, therefore, have developed in-house software equipped with partial image phase-only correlation (PIPOC), which can automatically calculate the displacements of multiple areas with sub-pixel accuracy. To validate the software, we conducted a phantom assessment. We then assessed JSN progression by the GSS and synovial vascularity (SV) by quantitative power Doppler ultrasonography (PDUS). The purpose of this study was to evaluate the in-house software with PIPOC in terms of detecting slight radiographic progression in finger JSN using the GSS and the PDUS assessments as well as in phantom finger JSN.

Material and methods

Phantom assessment

A phantom finger joint in a water tank was imaged by radiography. The JSW was changed at intervals of 0.1 and 0.01 mm. The delta (Δ) JSWs, or changes from JSN = 1.2 and 1.65 mm for 0.1 mm and 0.01 mm intervals, respectively, were used to evaluate the process of JSN by the PIPOC method.

Phantom

A metacarpophalangeal joint-shaped two-layer (subchondral bone and cancellous bone) phantom with a water tank (Fig. 1.1) was used in the experiment. The phantom was made of titanium medical apatite (TMA) [15]. TMA is a recently introduced material that is easier to model than hydroxyapatite, and its CT value (Hounsfield units) is equivalent to that of subchondral and cancellous bones. The phantom mimics the metacarpophalangeal joint, and the JSW can be freely changed at 0.01 mm intervals. The composition of the phantom is shown in Table 1.1.

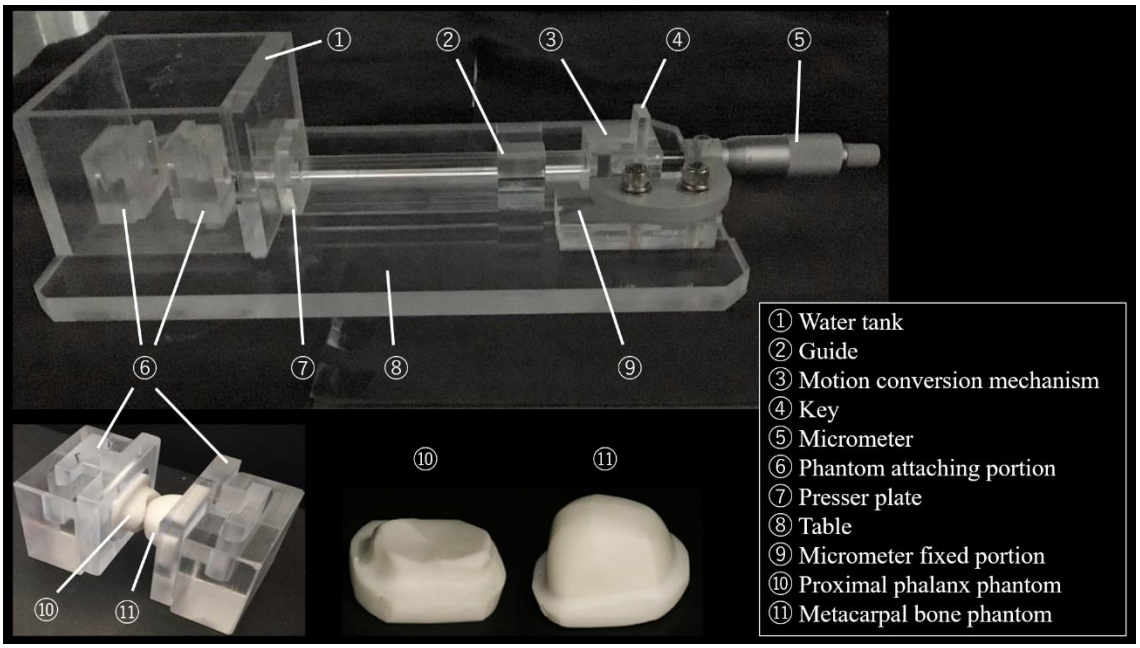

Fig. 1.1 A metacarpophalangeal joint-shaped two-layer phantom with a water tank

Table 1.1 Composition of the phantom

	Mixing ratio (TMA powder: adhesive)	Particle size of TMA powder, μm	TMA incineration temperature, °C
Subchondral bone	1:1.2	107～250	1100
Cancellous bone	1:5	107～251	1100

Imaging with radiography

The phantom's joint center was used as the imaging center. Imaging was performed using radiography where the attached water tank was full of water. Digital radiographs were acquired with CALNEO smart C47 (Fujifilm, Tokyo, Japan) under the following conditions: tube voltage = 50 kV; tube current = 100 mA; exposure time = 0.02 sec; source to detector distance = 100 cm; pixel size = 0.15 mm. Also, referring to the average JSW of

women within the RA prevalence age, the phantom JSW was changed at intervals of 0.1 mm between 1.2 and 2.2 mm and at intervals of 0.01 mm between 1.65 and 1.75 mm in water. In total, 21 measurements were taken.

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. [16, 17]. The FIPOC is an approach to estimating the relative translative offset between two similar images that relies on analyzing images in the frequency domain. The FIPOC-based JSW measurement requires the segmentation of the distal and proximal bones in the joint, and the in-painting algorithm is used to fill vacant space; this could lead to phase dispersion. The PIPOC method quantifies the displacement by segmenting the joint image in the frequency domain's phase spectrum to obtain a sharper delta function. Compared to the FIPOC combined image in-painting, the PIPOC can further improve the accuracy and robustness of JSW quantification by eliminating the impact of the image in-painting algorithm [18]. The analysis procedure was performed following five steps (Fig. 1.2).

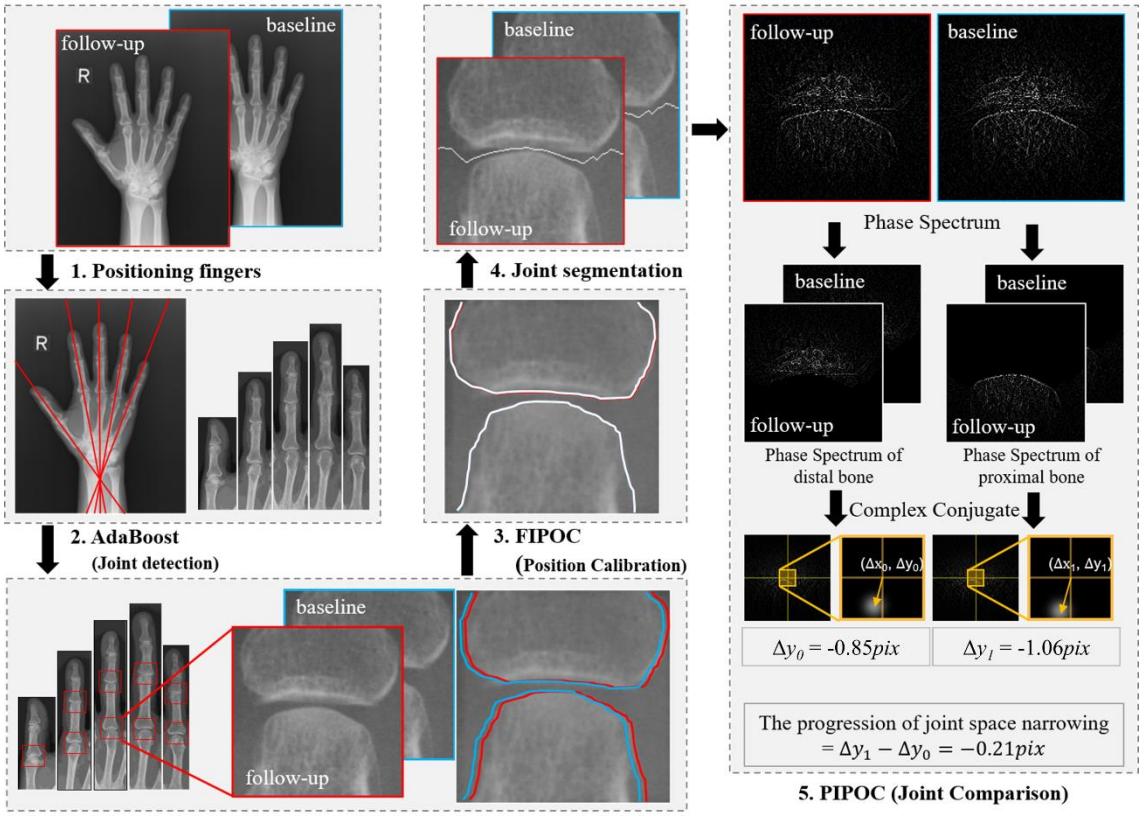

Fig. 1.2 The algorithm flow of in-house software equipped with PIPOC
FIPOC, full image phase-only correlation; PIPOC, partial image phase-only correlation

1. Positioning fingers

Initially, the background of radiographic images is subtracted using Otsu's method [19]. The morphological opening and closing are used to remove small objects and holes. Next, we find grooves and fingertips by the edge of the hand. Then, we calculate the area of the finger and fit a line through the center of this area. Last, we calculate the width of the fingers by the size of the finger area. Therefore, the finger area can 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 [20].

3. Position Calibration

As shown in step 3 of Fig. 1.2, 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 the FIPOC to calibrate the position of the joint. The deviation between the two joint windows can be mostly eliminated when their 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 Fig. 1.2, PIPOC is used to calculate the relative movement of the proximal and distal bones. Each joint image is divided into proximal and distal bones in the phase spectrum in this step. 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. Thus, the JSN between the baseline and follow-up images can be quantified according to the bone movement difference between proximal and distal bones.

A median filter is used to suppress the 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 describe the details of the PIPOC algorithm in a previous study [18].

Clinical assessment

Patients

Fifteen patients meeting the 1987 American College of Rheumatology classification criteria for RA [21] and long-term sustained clinical low disease activity (CLDA) were analyzed retrospectively. The patients had been treated with non-biologic disease-modifying antirheumatic drugs (DMARDs) (eight patients with methotrexate [MTX], three patients with MTX + tacrolimus) or with biologics (one patient with MTX + adalimumab, two patients with MTX + tocilizumab [TCZ] and one patient with TCZ monotherapy). The clinical and laboratory characteristics of the patients are presented in Table 1.2. This study was conducted in accordance with the Declaration of Helsinki. The local ethics committee approved the study, and informed consent was obtained from all patients.

Our patients' population overlaps with three previous reports [22-24]. The first study [22] aimed to investigate the relationship between synovial vascularity and structural changes assessed with conventional radiographic scoring of finger joints in rheumatoid

patients with CLDA. The second study [23] directly compared the performance of computer-based and conventional radiographic scoring methods using the relationship between synovial vascularity and future structural alterations. The third study [24] evaluated the automatic system that can detect joint locations and compute temporal changes of JSN. The current study investigated the performance of a fully automated in-house software equipped with the PIPOC, which can evaluate JSW with sub-pixel accuracy by calculating the joint edge peaks separately in the frequency domain.

Table 1.2. Clinical and laboratory characteristics of patients

	baseline	52nd week
Age, median (range) years	54 (32 - 69)	
Sex, female/male	13 / 2	
Duration of disease, median (range) months	50 (26 - 196)	
Duration of CLDA, median (range) months	15 (12 - 19)	
Swollen joint count, range	0-2	0-3
Tender joint count, range	0-2	0-3
DAS28-ESR, mean (SD)	2.03 (0.55)	1.96 (0.57)

CLDA, clinical low disease activity; DAS28, disease activity score with 28 joints; ESR, erythrocyte sedimentation rate; SD, standard deviation

Ultrasonography

All patients underwent 3D PDUS of metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints over the dorsal surface in the longitudinal plane at baseline and weeks 8, 20, and 52 by one of three US experts specialized in musculoskeletal ultrasonography who were blinded to other clinical information. A linear array transducer (13 MHz) and US equipment were used (EUP-L34P, HI VISION Avius; Hitachi, Tokyo,

Japan). Using quantitative PDUS, the SV value was determined by counting the number of vascular flow pixels in the region of interest (ROI). The ROI of a standardized box shape (5 mm × 10 mm) was placed to contain as many intraarticular flow pixels as possible, avoiding signals derived from artifacts and extraarticular vessels. Vascular flow pixels in the ROI were automatically measured using the program's Vascularity mode in the ultrasonographic machine. The details of the PDUS settings were described in the previous studies [22, 25-27].

Radiography

Plain radiographs of the hands at baseline and at the 52nd week for all patients using Radnext 32 (Hitachi, Tokyo, Japan) under the following conditions: tube voltage = 50 kV; tube current = 100 mA; exposure time = 0.025 sec; source to detector distance = 100 cm; pixel size = 0.15 mm. All radiographs were scored by an expert rheumatologist with more than 15 years of experience who was blinded to other clinical information for the 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 [6, 28]. The intra-observer reliability of the GSS method for this study population has already been shown in previous studies [8, 23].

Statistical analysis

Statistical analyses were performed using Microsoft Excel 2019 (Microsoft, Redmond, WA, USA) and EZR software version 1.40 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [29], which is a graphical user interface for R software package version 3.5.2 (The R Foundation for Statistical Computing, Vienna, Austria). A p-value < 0.05 was considered to indicate a significant difference.

In the phantom assessment, the mean error and the standard deviation (SD) of the differences between theoretically true JSW derived from the measurement via the micrometer and measured JSW were calculated as an index to evaluate the random error. The smallest detectable difference (SDD) represents the smallest difference between two independently obtained measures which can be distinguished from measurement error. The SDD for measured JSW was calculated according to the following formula:

$$\mathrm{SDD} = 1.96 \times \mathrm{SD}_{\mathrm{diff}}$$

where $\mathrm{SD}_{\mathrm{diff}}$ was the SD of the difference between theoretical and measured JSW [30-32]. A linear regression test validated the relationships between the theoretically true JSW and the measured JSW differences.

In the clinical assessment, quantitative variables were given as median and interquartile range (IQR) or mean and SD. Differences in parameters were examined using the Mann–Whitney U test. We defined the interval difference of the GSS and the JSW between baseline and follow-up as the ΔGSS and the ΔJSW, respectively. First, we compared ΔJSW (mm) calculated by in-house software between the progressive and non-

progressive finger joints according to the ΔGSS. Then, the ΔGSS was compared to confirm that the in-house software can detect interval JSN progression in the visual assessment results. We finally compared the ΔGSS and the ΔJSW in the positive and negative SV finger joints in the ultrasonographic findings at baseline. Joints with positive SV at baseline [b-SV (+)] were defined as those with positive SV detected in the ROI at baseline. In contrast, joints without SV signals during the follow-up period were defined as negative SV [SV (-)]. This analysis demonstrated that finger joints with positive SV at baseline cause structural destruction in RA.

The sum-SV value, the total value of SV signals, was calculated for joints with positive SV during the follow-up period. To ascertain whether structural destruction depends on synovial blood flow inflammation, we divided the positive SV joints into sum-SV high and low groups by the median value and examined differences in JSN progression.

Results

Phantom assessment

The mean error, SD and SDD for JSW measurements at 0.1 mm and at 0.01 mm intervals are shown in Table 1.3. The correlations between true JSW and measured JSW differences are shown in Fig. 1.3. There were significant correlations between true JSW and measured

JSW differences ranging from 1.2 to 2.2 mm at 0.1 mm intervals ($R^2 = 0.996$; $p < 0.001$), and from 1.65 to 1.75 mm at 0.01 mm intervals ($R^2 = 0.553$; $p = 0.009$).

Table 1.3. Systematic error and SDDs underwater in phantom assessment

	0.1mm interval	0.01mm interval
Mean error, mm	0.001	-0.037
SD of the differences, mm	0.023	0.028
SDD, mm	0.044	0.055

SD, standard deviation; SDD, smallest detectable difference

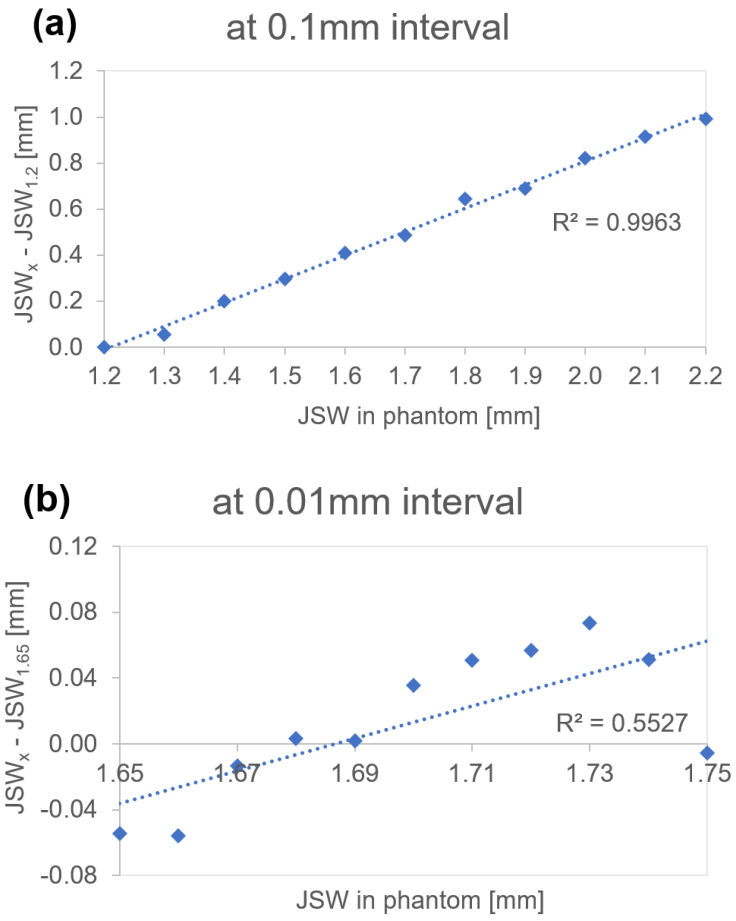

Fig. 1.3 Correlations between true JSW and measured JSW differences based on 1.2 mm at 0.1 mm (a) and on 1.65 mm at 0.01 mm (b) intervals
JSW, joint space width

Clinical assessment

We analyzed the 1st to 5th MCP joints and the 2nd to 5th PIP joints in 15 RA patients. Out of 270 joints, we targeted 261 finger joints after excluding nine damaged joints (ankylosis, complete luxation, and subluxation). The success rate of the in-house software JSW analysis was 99.6% (260/261). The software analysis failed to locate one joint. Subsequent analyses were therefore performed for the remaining 260 joints.

Images of 260 joints in 15 patients regarding GSS, JSW, and SV of the finger joints were scored or measured. The medians of GSS at baseline, at follow-up and the ΔGSS were 1 (IQR 1-2, n; the number of joints = 260), 1 (IQR 1-2, n = 260) and 0 (IQR 0-0, n =260), respectively. Out of 260 joints, ΔGSS (+) was assigned to joints with positive ΔGSS according to the GSS results (n = 37, 14.23%). Otherwise, ΔGSS (-) was assigned to the others (n = 223, 85.77%). The median of ΔJSW was 0.001 mm (IQR -0.491 mm – 0.496 mm, n = 260). The medians of SV at baseline, the 8th week, the 20th week, and the 52nd week were the same values (0 [IQR 0-0, n = 260]). The number of joints with baseline positive and negative SV were 32 and 211, respectively.

The ΔJSW of the finger joints with GSS progression [ΔGSS (+)] detected by the in-house software was significantly greater than those without GSS progression [ΔGSS (-)] (Mann-Whitney U test, p = 0.004). The median ΔJSW of ΔGSS (-) and ΔGSS (+) were 0.029 mm (IQR -0.434 mm – 0.496 mm, n = 223) and -0.443 mm (IQR -1.434 mm – -0.102 mm, n = 37), respectively (Fig. 1.4).

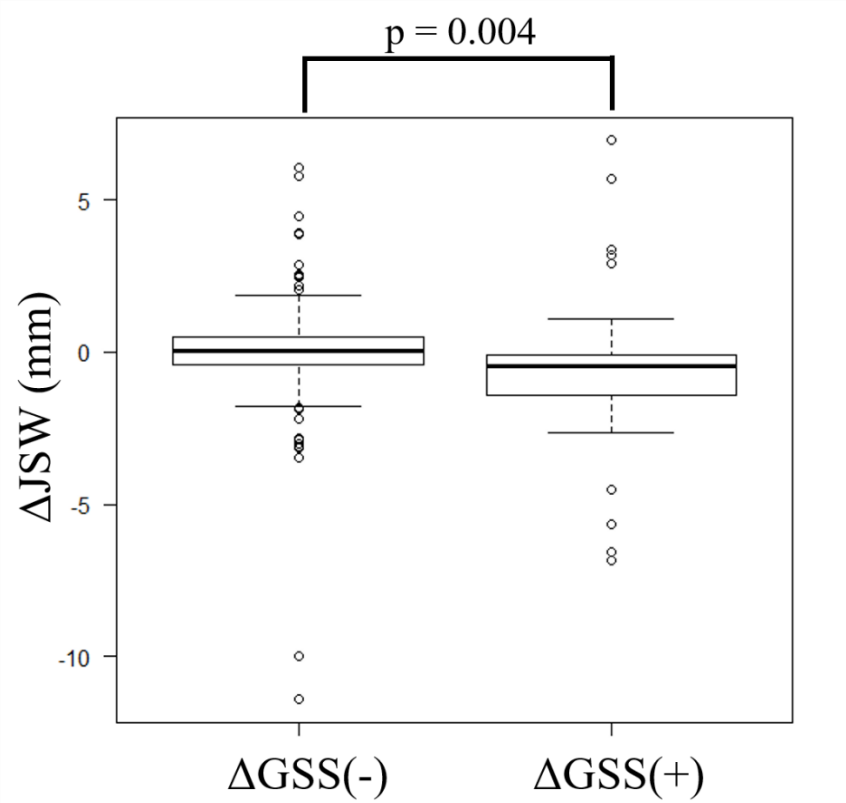

Fig. 1.4 Comparison of the ΔJSW derived from PIPOC analysis in terms of radiographic JSN progression
ΔJSW (mm), the difference in joint space width at baseline and the 52nd week; ΔGSS, the difference in Genant-modified Sharp score at baseline and the 52nd week; PIPOC, partial image phase-only correlation; JSN, joint space narrowing

The ΔGSS of finger joints with positive SV at baseline [b-SV (+)] were significantly higher than those with negative SV [SV (-)] ($p < 0.001$) (Fig. 1.5a). The ΔJSW of finger joints with positive SV at baseline [b-SV (+)] was significantly higher than those with negative SV [SV (-)] ($p = 0.024$) (Fig. 1.5b).

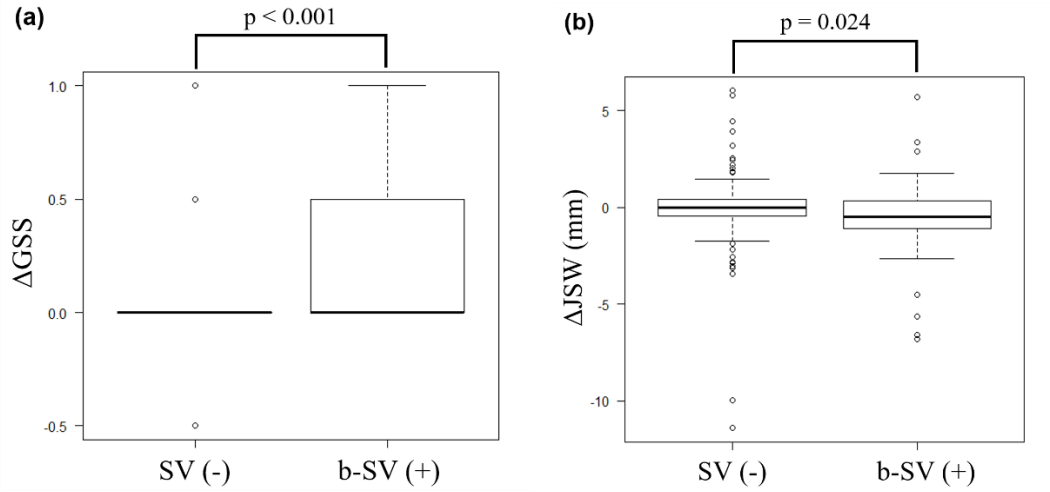

Fig. 1.5 Comparison of GSS (a) and ΔJSW (b) in terms of baseline SV findings
GSS, Genant-modified Sharp score; JSW, joint space width; SV, synovial vascularity; b-SV, synovial vascularity at baseline

We calculated the sum-SV value by summation of the sequential SV value of each joint. The median of the sum-SV value was 147 pixels (IQR 49-367.5, n = 32). The median ΔGSS of the high group and the low group of the sum-SV were 0.25 (IQR 0 – 0.5, n = 16) and 0 (IQR 0 – 0.125, n = 16), respectively. The median ΔJSW of the high group and the low group of the sum-SV were -0.350 mm (IQR -1.026 mm – 0.383 mm, n = 16) and -0.636 mm (IQR -1.140 mm – 0.096 mm, n = 16), respectively. There were no significant differences between the high and low group of sum-SV joints with both analyses using the GSS and the in-house software (p = 0.192 and p = 0.926) (Fig. 1.6). In joints with positive SV, changes in JSN progression did not relate to the sum-SV.

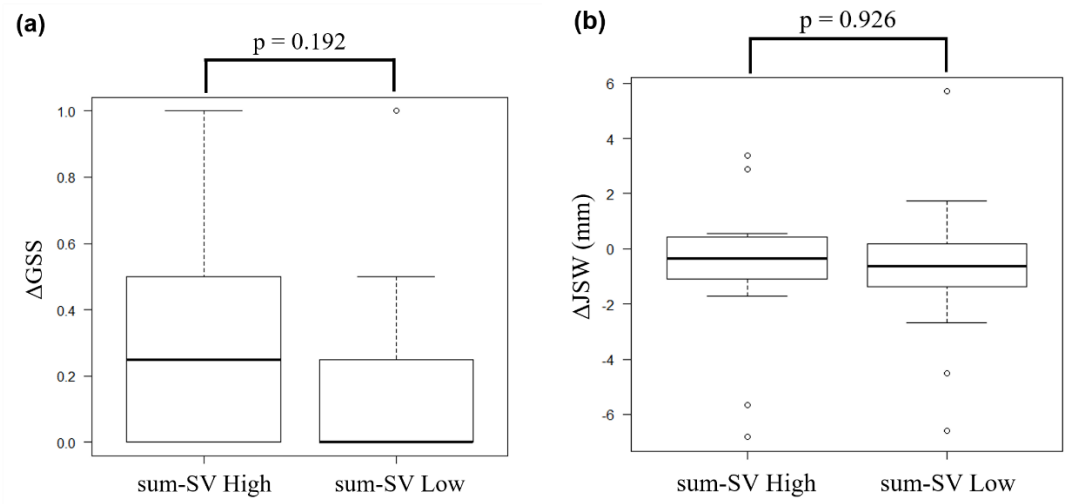

Fig. 1.6 Comparison of ΔGSS (a) and JSW (b) between the High group and Low group of the sum-SV

GSS, Genant-modified Sharp score; JSW, joint space width; sum-SV, summation of synovial vascularity

Discussion

In this study, our in-house software equipped with PIPOC could automatically and quantitatively detect slight JSN progression. The results were comparable to conventional scoring methods. The present study is novel in that it applies the PIPOC technique to joint detection and directly compares the software and the doctor's visual assessment based on ultrasound findings.

Several groups have researched JSW quantification using software with clinical practice cases and have achieved promising results [33, 34]. Huo et al. performed JSW quantification in early RA patients using the automated JSW quantification software 'JSQ'

[33]. Comparing the SHS method with the software evaluation, a similar trend was seen with the yearly progression rate of JSW change. However, they reported that the software might fail to detect JSW in some cases, such as when joint edges overlap or the distal bone margin cannot be identified.

A computer-based method named joint space difference index (JSDI) has been developed and examined, which can semi-automatically calculate an index showing the degree of JSN progression [23, 35]. The software was designed to avoid distal bone margin problems by superimposing two images between baseline and follow-up. However, the software using JSDI had some drawbacks. Since the JSDI calculated the difference in pixel values, it is strongly affected by image density and acquisition conditions. In addition, the superimposition of two images and the region's setting of interest were done manually and could not be fully automated. Kato et al. modified this software to enable the automatic calculation of JSDI [24]. The JSDI displays the absolute value of the change in JSW between two images, so it remains a drawback that it cannot identify whether the JSW was widening or narrowing.

To address these issues, we tried a completely new approach. The phase-only correlation (POC) method is superior in robustness and positional accuracy. 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 [36]. We have developed an in-house software equipped with PIPOC, which can automatically calculate the displacements of multiple

areas with sub-pixel accuracy. We, therefore, used an underwater phantom to confirm the performance of the fundamental software and performed a clinical assessment to determine how close the software could come to conventional scoring methods.

In the phantom assessment, the mean error and SDD underwater at 0.1 mm intervals were 0.001 mm and 0.044 mm, respectively. We also found significant correlations between true JSW and measured JSW differences in all measurement conditions. A similar phantom experiment was executed by Huétink et al., who studied the systematic error and sensitivity (defined as the SDD) of the computerized JSW measurements in an acrylic phantom joint and human cadaver-derived phalangeal joints both surrounded by the air [37]. The mean systematic error and SDD in an acrylic phantom/human cadaver phantom were 0.054 mm and 0.037 mm / 0.210 mm and 0.226 mm, respectively. Our software can perform JSW analysis with an order of magnitude finer accuracy than previous phantom studies, despite the more unfavorable underwater condition. Furthermore, the TMA phantoms were made to mimic human bones in terms of shape and CT values, which enables us to examine the structure of the real human anatomy more closely than simple acrylic phantoms.

In the clinical assessment, our in-house software compared to the GSS in radiographic JSN progressions was consistent with the conventional scoring method. The software and the doctor's visual assessment showed that the joints with positive SV at baseline were associated with JSN progression. However, in the positive SV joints, there was no significant difference in JSN progression depending on the total value of the signal.

This means that the joint with positive SV at baseline, i.e., synovial inflammation joints in the early stages of RA, will have progressive subsequent bone destruction, regardless of its degree of inflammation. Fukae et al. reported in joints with smoldering inflammation, structural damage progresses independently of the level of synovial vascular summation [27]. It is, therefore, clinically meaningful that the software can detect a slight JSN progression in patients with CLDA.

In clinical trials of patients with RA, it has become increasingly difficult for conventional radiographic scoring systems to detect statistically significant changes in joint deterioration. This is attributed to early escape study designs and the shorter duration of treatment in the placebo group, which leads to a lower radiographic progression rate [34, 38]. In contrast, hand radiographs' computer-based methods seem more sensitive to detecting subtle changes in progressive JSN [8, 23, 24]. Fully automatic software, such as the one we have developed here, enables early disease detection and helps physicians with extensive routine reading tasks. Using such effective tools is also expected to reduce the burden of health care costs [39]. In addition, we are working on further refinement of the software to make it applicable to the MCP/PIP joints and the other joints, such as the carpal bones.

There are several limitations to this study. First, the clinical assessment was conducted retrospectively. There is a risk that the radiographs may not be optimal for the software analysis, e.g., the difference in the finger angle between baseline and follow-up. In contrast, it is meaningful to test our software on the images acquired in a real clinical

setting, even if the images are unsuitable for software analysis. Second, the sample size was small and limited to a single hospital. We need to confirm our observations with a large-scale population in multiple institutions. Third, the software analysis is quite accurate in JSW measurements but not perfect. Certain joint structures and positioning might result in incorrect edge detection; this might be a factor that reduces the accuracy of the results in JSW measurements. Schenk et al. reported that the failure of computerized JSW analysis was more frequently caused by technical factors during image acquisition, such as differences between baseline and follow-up hand positioning, than by the automatic analysis system [40]. Therefore, it is important to standardize the imaging technique and further improve the software for commercialization in clinical practice.

In conclusion, our in-house software equipped with PIPOC can automatically and quantitatively detect slight radiographic changes of JSW in RA patients with CLDA. The clinical results in this study were confirmed using a specially designed phantom underwater, although further evaluation and refinement are needed.

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Chapter 3

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

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Abstract

Purpose: To investigate 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 joint destruction in rheumatoid arthritis (RA) patients receiving Tocilizumab.

Materials and 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 GSS/PIPOC with the 0-6-month GSS (+)/PIPOC (+) group was significantly more JSN progression than the 0-6-month GSS (-)/PIPOC (-) group ($p < 0.001$, respectively). The 0-12-month JSW change by the software was significantly greater in joints with 0-12-month GSS (+) than with 0-12-month GSS (-) ($p = 0.02$). The 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).

Conclusion: Our in-house software equipped with PIPOC can predict subsequent joint destruction with only short-term observations.

Keywords:

Rheumatoid arthritis; Radiography; Finger joint; Joint space narrowing; Software; Tocilizumab

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 unit of mm [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 an 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 prognosis of bone destruction 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.

Material 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 2.1. 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.

Table 2.1. Clinical characteristics of RA patients under TCZ treatment

variable	baseline	Six 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

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 2.2. 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 the 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].

Table 2.2. 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

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 was performed following five steps (Fig. 2.1).

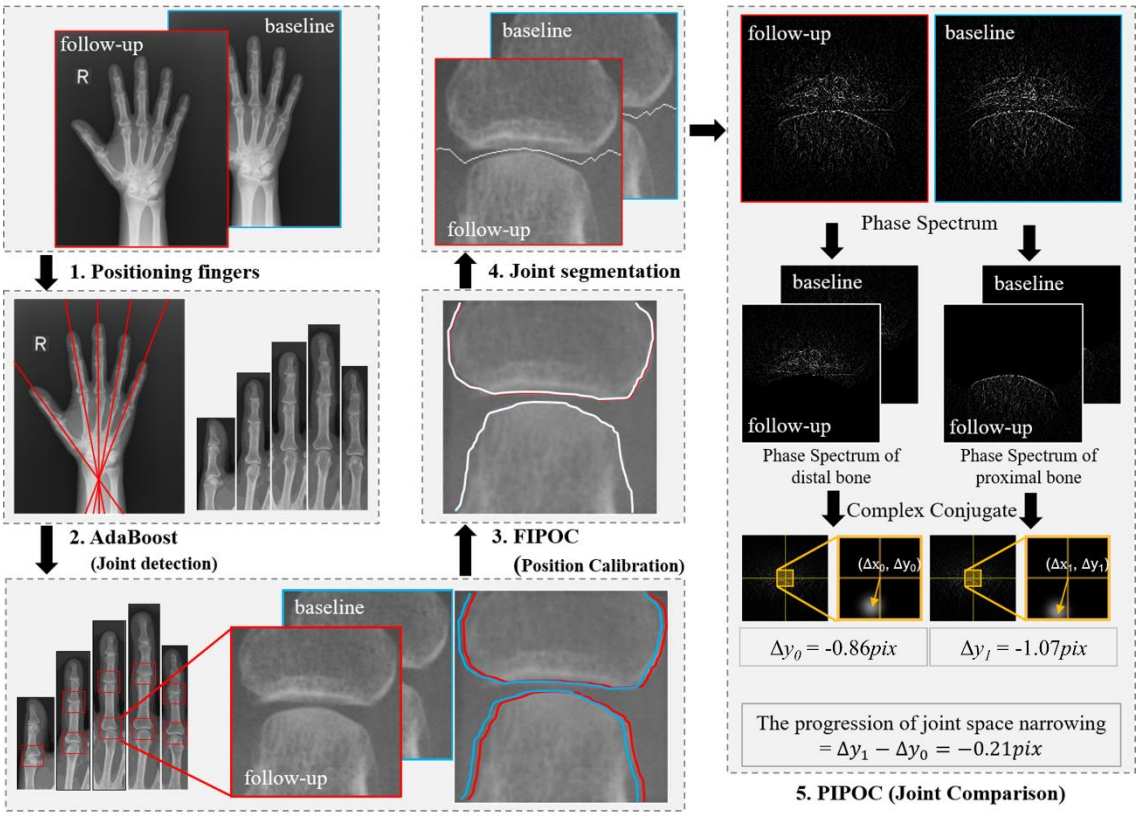

Fig. 2.1. Algorithm flow of in-house software equipped with PIPOC.
FIPOC: full image phase-only correlation; PIPOC: partial image phase-only correlation

1. Positioning fingers

The background of radiographic images is first subtracted using Otsu's method [28]. 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 center 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 [29].

3. Position Calibration

As shown in step 3 of Fig. 2.1, 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.

5. Joint Comparison

As shown in step 5 of Fig. 2.1, 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]. 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) [30]. EZR is a graphical user interface for 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 the 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. 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) [31].

Ethics approval and consent to participate

All procedures performed in studies involving human participants followed the institutional research committee's ethical standards and the 1964 Helsinki Declaration. Informed consent was obtained from all patients.

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. 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 2.3). 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 2.3).

Table 2.3. Assessment of JSN progression for the GSS and the software

variable	baseline	Six 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

A comparison of JSN progression measured with GSS and the software is shown in Table 2.4. 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).

Table 2.4. 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*

JSN: joint space narrowing; GSS: Genant-modified Sharp score; IQR: interquartile range; PIPOC: partial image phase-only correlation

The relationships between the 0-6-month and the 0-12-month PIPOC for each joint are shown in Table 2.5. 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. In contrast, there were no significant correlations in other finger joints.

Table 2.5. The relationship between 0-6-month and 0-12-month PIPOC (*p < 0.05)

Joints	R^2	p-value
Left 2nd MCP	0.554	< 0.001*
Left 3rd MCP	0.420	0.004*
Left 4th MCP	0.034	0.340
Left 5th MCP	0.005	0.740
Right 2nd MCP	0.005	0.780
Right 3rd MCP	0.088	0.248
Right 4th MCP	0.007	0.672
Right 5th MCP	0.175	0.075
Left 2nd PIP	0.009	0.678
Left 3rd PIP	0.177	0.051
Left 4th PIP	0.017	0.529
Left 5th PIP	0.019	0.638
Right 2nd PIP	0.008	0.672
Right 3rd PIP	0.026	0.488
Right 4th PIP	0.062	0.193
Right 5th PIP	0.032	0.622

PIPOC: partial image phase-only correlation; R^2: coefficient of determination; MCP: metacarpophalangeal; PIP: proximal interphalangeal

Discussion

This study aimed to determine whether in-house software with PIPOC can detect subtle JSN progression and predict its bone destruction prognosis 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 can detect subtle JSW changes at six months and 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, 32]. These analyses are often cross-sectional assessments [13, 15-17], while only a few studies have focused on temporal changes [6, 14, 32]. 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 [32], 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 bone destruction progression based

on radiographic evaluation at 0, 6, and 12 months. 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 time points over time, evaluating the difference between the upper and lower bone 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 six-month visual assessment. 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 [33]. 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]. 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 [34]. 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 center. 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 multicenter prospective study. A second limitation of our study was that the in-house 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 third 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 [35]. In particular, finger joint flexion, oblique X-ray entry, and the difference between baseline and follow-up positioning need to be specifically considered. 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 can predict subsequent joint destruction with only short-time observations at six months from baseline.

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Chapter 4

Summary

The main results of this study were as follows.

First, as shown in chapter 2, this study clarified the accuracy to which automated in-house software is able to precisely measure JSW. The potential for clinical application was demonstrated in terms of both phantom validation and comparison of visual evaluation. In the phantom assessment, the software could detect changes in JSN with the smallest detectable difference of 0.044 mm. In the clinical assessment, the software was comparable to the conventional scoring method regarding the detectability of JSN progression in RA patients. The in-house software equipped with PIPOC can automatically and quantitatively detect slight radiographic changes of JSW in clinically inactive RA patients.

Second, as shown in chapter 3, this study revealed whether in-house software could detect subtle JSN progression and predict the subsequent joint destruction with only short-term observation in RA patients undergoing potent biologic DMARD treatment with TCZ. 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 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 can detect subtle JSW changes at six months and predict JSN progression at 12 months.

In conclusion, the automated software used in this study, which can automatically and quantitatively detect slight radiographic RA lesions, is expected to be a powerful tool for the prevention and early detection of the disease and for making appropriate medication decisions and inducing remission.

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