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Title	Accurate quantitative assessment of synovitis in rheumatoid arthritis using pixel-by-pixel, time-intensity curve shape analysis
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Title; Accurate Quantitative Assessment of Synovitis in Rheumatoid Arthritis Using
Pixel-by-Pixel, Time-Intensity Curve Shape Analysis

Short title; Quantification of synovitis Using Time-Intensity Curve Shape Analysis

Abstract

Objectives: To improve on the reproducibility and sensitivity of the assessment of rheumatoid arthritis (RA) patients, two semi-automated measurement methods of the area of enhancing pannus (AEP), based on thresholding (AEP_THRES) and pixel-by-pixel time-intensity curve analysis (AEP_TIC), were evaluated as an alternative for the gold standard manual contouring method (AEP_MANUAL).

Methods: Eight patients (7 women and 1 man) with RA of the wrist or finger joints participated in the study. A three-dimensional contrast-enhanced dynamic sequence was used at 3T. After identifying the most relevant time-intensity curve shape in terms of synovitis by comparing with the synovitis score using the RA-MRI scoring (RAMRIS) system, three different approaches for measuring the AEP were performed. Spearman's test of rank correlation was used to compare AEPs via two semi-automated methods (AEP_THRES and AEP_TIC) against manual segmentation (AEP_MANUAL) in the entire hand region as well as the wrist and the finger regions.

Results: The time-intensity curve shape of “washout after fast initial enhancement” had excellent correlation with synovitis score ($r=0.809$). The correlation coefficient between AEP_TIC and AEP_MANUAL was evaluated to be better than that of AEP_THRES and AEP_MANUAL in the wrist region (AEP_THRES: $r=0.716$, AEP_TIC: $r=0.815$),

while these were of comparable accuracy for the entire hand and the finger regions.

Conclusion: This study suggests that TIC analysis may be an alternative to manual contouring for pannus quantification and provides important clinical information of the extent of the disease of RA patients.

Advances in knowledge: Time-intensity curve shape analysis can be applied for new quantitative assessment for RA synovitis in the wrist.

1. Introduction

Magnetic resonance (MR) imaging provides important clinical information regarding the extent of the disease and the degree of inflammatory tissue in rheumatoid arthritis (RA) (1-3). The amount of synovial membrane (pannus) is probably related to disease activity and severity, and a reliable quantification may be useful in the assessment of RA patients and as a therapy evaluation (4-6). The Outcome Measures in Rheumatology Clinical Trials (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS) system has been extensively utilized as the gold standard of MR scoring for inflammatory and destructive changes in the hands and wrists of RA patients (7,8). However, the reliability of this system suffers from great inconsistency, with interreader correlation coefficients from 0.45 to 0.98, which may be insufficient in demonstrating noticeable progression (9-13).

In an effort to improve on the reproducibility and sensitivity of a biomarker for RA disease activity, various techniques have been put forward for the direct measurement of the volume of enhancing pannus (VEP) (14). A method for estimating VEP by manual computer-assisted segmentation based on visual analysis of pre- and post-gadolinium-DTPA MR images was introduced in previous studies and showed an acceptable correlation coefficient ranging from $r=0.7$ to 0.88 (15,16). However, this

method is subjective and requires the interpretation of experienced rheumatologists or radiologists. Thresholding in combination with rough manual outlining of pannus doesn't require interpretation by experts and can substantially reduce analysis times. However, the reproducibility of this method is poorer than manual outlining and is significantly affected by the threshold selected (17,18). On the other hand, pixel-by-pixel time-intensity curve (TIC) shape analysis is a new dynamic contrast-enhanced MR imaging technique to help visualize differently shaped TICs (19,20). Previously, Type 4 TIC shape expression, characterized by fast initial enhancement followed by early washout, was reported to be increased in rheumatoid patients compared with healthy subjects (20). Although the feasibility of measuring the extent of pannus formation using this approach has not been determined in the hand, we hypothesize that this technique can accurately quantify the size of the synovial pannus.

In this study, we compared the area of enhancing pannus (AEP) via segmentation using thresholding (AEP_THRES) and pixel-by-pixel TIC analysis (AEP_TIC) against manual contouring (AEP_MANUAL) as the gold standard to evaluate the accuracy of AEP quantification.

2. Methods

2.1. Patients

Eight subjects (7 women and 1 man) with RA of the wrist or finger joints participated in the study. The geometric mean of the age was 57 years with a range from 38 to 67 years.

All patients were diagnosed with RA according to the American College of Rheumatologists' 1987 criteria (21). The inclusion criteria of this arthritis cohort consisted of active arthritis, based on clinical findings, of at least the wrist, or finger joint, but without the knowledge of the extent of the disease, with disease duration of under 1 year. All patients were managed in a dedicated rheumatologic therapy clinic in a university hospital and were evaluated for continuation on biological agent treatment or switching to another biological agent or termination of treatment. All subjects were recruited from consecutive patients. Ethics board permission and written informed patient consent were obtained for this study.

2.2. MR Imaging

Images were acquired with a 3.0-T MR imager (Discovery MR750w, GE Medical Systems, Milwaukee, WI, USA). A 16-channel GE Musculo-Skeletal Flex small coil was adapted for image acquisition. Patients were situated on the examination table in the prone position with the arm extended over the head. The hand and the wrist were

firmly fixed by use of sand bags. The hand and the wrist of the dominant side with the joint of strongest clinical symptoms were examined for all subjects.

Three-dimensional contrast-enhanced liver acquisition with volume acceleration (LAVA) dynamic sequence (repetition time/ echo time 7.769-9.114 ms/ 2.328-2.604 ms, slice thickness 2.0 mm, matrix size 360×360, field of view (FOV) 160mm×160mm, bandwidth 244.141 Hz/pixel, flip angle 12, acquisition time per phase 13.27 sec, number of slices 40-52, phase 26, coronal orientation) was used for assessing the AEP. A bolus of a contrast agent (0.2 ml per kilogram of body weight of gadopentetate dimeglumine (Magnevist , Bayer HealthCare, Osaka, Japan) followed by a 20-mL saline chase was delivered at an injection rate of 2 mL/sec by using an automatic MR injection device (Sonic Shot, Nemoto Kyorindo co. Ltd. Tokyo, Japan).

2.3. MR imaging data analysis

Identification of the most relevant TIC shape in terms of synovitis

Thirty four out of 40 metacarpophalangeal (MP) joints in 8 patients were analyzed for correlation between TIC shape and synovitis score. Synovitis was scored using the RA-MRI scoring (RAMRIS) system (22) by an experienced musculoskeletal radiologist.

Scores of synovitis ranged from zero (normal) to three (severe). Six MP joints were not assessed because they were out of the FOV and not fully identified. An oval region of interest (ROI) of approximately 2500 pixels was placed on each slice of the MP joint, resulting in a three dimensional ellipsoid ROI (Figure 1).

AEP_MANUAL

The image-processing viewer system EV Insite (PSP Corporation, Tokyo, Japan) allowed outlining and calculation of the areas of the regions of interest. The pannus formation located from the distal radio-ulnar joint to carpometacarpal joints of each coronal MRI slice was outlined manually, using a computer mouse. The areas were calculated automatically. Outlining was done on post-gadolinium-DTPA images obtained 4-5 min after IV gadolinium-DTPA by a musculoskeletal radiologist with more than 15 years of experience, based on visual analysis of pre- and post-contrast images.

AEP_THRES

This method was conducted following a previous study (17) and included two steps, both performed using the image-processing software ImageJ (National Institutes of Health, Bethesda, MD, USA, <http://rsbweb.nih.gov/ij/>). Firstly, a rough manual

outlining of the areas including synovial tissue was performed on post-gadolinium-DTPA images obtained 4-5 min after IV gadolinium-DTPA. Extra-articular enhancing tissues, particularly vessels, were excluded. Secondly, a pixel-by-pixel segmentation algorithm was applied, by means of which ImageJ showed and counted pixels fulfilling the criteria.

The criteria chosen were as follows:

1. A relative post-gadolinium-DTPA signal intensity increase (enhancement) above 40%.
2. A post-gadolinium-DTPA absolute synovial signal intensity that exceeds the mean pre-gadolinium-DTPA synovial membrane signal intensity minus 2 S.D. This criterion was included in all measurements to avoid noise from low-intensity pixels.

Based on the number of pixels, the area of tissue meeting the criteria could be calculated by the following formula:

$$\text{area of the pannus} = \text{number of pixels} \times \text{pixel size}$$

AEP_TIC

Images were processed using MATLAB (MathWorks, Natick, MA, USA). This program evaluates the time-dependent relative signal intensity changes of every pixel in

the volume imaged after contrast administration resulting in a TIC. The TIC of each pixel was classified into one of seven predefined TIC shape categories (Figure 2), after ruling out and designating in black the pixels classified with a signal below noise level. Type 1 shows no enhancement. Type 2 shows enhancement. Types 3, 4 and 5 show a fast initial increase followed by a plateau phase, a washout phase, or a slow constant enhancement phase, respectively. Among these, Type 4 is reported to be relevant to RA (19,20). Type 6 shows rapid enhancement followed by a sharp signal drop. Type 7 shows all others. Each TIC shape type was assigned a color. The TIC shape distribution of each image section was visualized in color-coded maps (23).

The total number of Type 4 TIC shapes was calculated because it has been reported that the Type 4 TIC shape is associated with RA (20). In this study, we regarded the Type 4 TIC shape as the area of the pannus. The area of the pannus can therefore be calculated by the following formula:

$$\text{Area of the pannus} = \text{number pixels with Type 4 TIC shape} \times \text{pixel size}$$

2.4. Statistical analysis

PASW Statistics ver. 18.0 (IBM Co., Armonk, NY, USA) was used for statistical analysis. Thirty four MP joints were analyzed for TIC shape and RAMRIS synovitis

scoring by Pearson's product-moment correlation. Spearman's test of rank correlation was used to compare AEPs via two semi-automated methods (AEP_THRES and AEP_TIC) against manual segmentation (AEP_MANUAL) gold standard. Analysis of statistical correlation was performed in the entire hand region as well as the wrist and the finger regions, separated by the line connecting the center of the 1st through 5th metacarpal bones. Pearson's and Spearman's correlation coefficients were set as follows: $r < 0.2$, poor correlation; $r = 0.2 - 0.4$, fair correlation; $r = 0.41 - 0.6$, moderate correlation; $r = 0.61 - 0.8$, good correlation; $r > 0.81$, excellent correlation (24).

3. Results

There was an excellent correlation between the pixel number of Type 4 curve shape in the ROI and RAMRIS synovitis score in MP joints (Table 1, Figure 3). Five out of eight patients showed apparent pannus formation on dynamic images. Two out of eight patients showed a limited extent of hyperemia of pannus. One out of eight patients didn't show enhanced pannus on post-contrast images. The images of this patient were excluded from investigation because the criteria for AEP_THRES could not be determined without the synovial membrane signal intensity. Consequently, Spearman's test of rank correlation was performed on 292 images. A typical image outlining the

AEP is shown in Figure 4. Analysis of statistical correlation is shown in Table 2. In the entire hand, there were significant correlations between semiautomatic methods and manual segmentation (AEP_THRES: $r=0.714$ $p<0.001$, AEP_TIC: $r=0.791$ $p<0.001$). In the finger region, correlation of AEP_THRES and AEP_TIC with manual segmentation showed a comparable correlation coefficient (AEP_THRES: $r=0.591$ $p<0.001$, AEP_TIC: $r=0.568$ $p<0.001$). On the other hand, the correlation coefficient between AEP_TIC and AEP_MANUAL was evaluated as better than that of AEP_THRES and AEP_MANUAL in the wrist region (AEP_THRES: $r=0.716$ $p<0.001$, AEP_TIC: $r=0.815$ $p<0.001$).

4. Discussion

Accurate disease quantification of RA is of great importance for the evaluation of treatment efficacy and prognostication of the outcome (1-3). A direct measurement of the area of enhancing pannus provides important clinical information with respect to the extent of the disease and may evaluate inflammatory changes more sensitively than the scoring system. The method for estimating AEP by manual outlining is regarded as a leading direct measurement but requires interpretation by experienced rheumatologists

or radiologists. In order to assess the degree of the pannus without expertise in interpretation, it is necessary to demonstrate semiautomatic methods replacing manual segmentation for the quantification of pannus formation.

As Type 4 curve shapes showed an excellent correlation with synovitis score in MP joints in previous studies, we compared the measurement of the area of enhancing pannus via segmentation using thresholding and pixel-by-pixel TIC analysis against manual segmentation as the gold standard. As a result, the correlation coefficient between AEP_TIC and AEP_MANUAL was evaluated as better than that of AEP_THRES and AEP_MANUAL in the wrist region. Segmentation using thresholding tended to overestimate the area of pannus because some parts of other high-intensity tissues, such as the skin surface and the muscle tissue and peripheral vessels, fulfilled the pre-set criteria and was regarded as the enhancing pannus. On the other hand, as every pixel was classified in a step-by-step manner in pixel-by-pixel TIC analysis (Fig. 2b), pannus formations were strictly distinguished from surrounding tissue. Skin surface and muscle were mostly regarded as Type 2 or Type 7, and peripheral vessels were classified as Type 6 due to a sharp signal drop. TIC measurements could recognize precisely the tissue characteristics related to changes in MR signal intensity and show excellent correlation with manual segmentation.

In the finger region, the correlation of both AEP_THRES and AEP_TIC against AEP_MANUAL was lower than the correlation obtained in the wrist region. On the AEP_THRES, the existence of a high proportion of areas with incomplete fat suppression, such as skin surface, was incorrectly recognized as AEP in the finger region. In addition, vessels running along the wrist region, such as the radial and the ulnar artery, tend to be located at a distance from intra-articular synovial tissue and are relatively easy to be ruled out, while the tiny peripheral vessels adjacent to the finger joints could not be fully excluded by a rough manual outlining. With AEP_TIC, it was recognized that the partial pannus formation was regarded as Type 2, Type 3 and Type 5 rather than Type 4, which is a typical TIC shape indicating synovial tissue. Different TIC shapes have the common feature of showing no washout phase. In a previous study, the early washout phase was explained by the back flux of contrast agent due to increased vascular permeability and/or the passive diffusion of contrast agent into effusion fluid (19). In the knee and wrist, the washout phase is seen because contrast agent flows directly into the pannus from the vessels with high blood flow. On the other hand, as the partial synovial pannus in the finger joint is gradually supplied with blood via narrow peripheral arteries, the back flux of contrast agent due to increased vascular permeability may not necessarily have occurred. These results suggest that it is difficult

to quantify the pannus formation using thresholding segmentation and TIC shape analysis in the finger joint.

In a previous study, it was investigated whether the fast, automated 'threshold' method could replace the time-consuming 'manual' segmentation method in knees as well as wrists, setting the main criterion of a relative post-gadolinium-DTPA signal intensity increase (enhancement) above a pre-set threshold of 30, 40, 45, 50 or 60% (17). This previous study showed relatively higher correlations than our study in the wrist region ($r=0.5\sim0.95$). We selected the pre-set threshold of 40% due to its having shown the best correlation in the previous study ($r=0.95$), but derived a lower correlation coefficient ($r=0.716$). The lower correlation is explained by insufficient exclusion of extra-articular enhancing tissues using a rough manual outlining on the thresholding segmentation. It is possible to rule out the surrounding enhancing tissues located at a distance from intra-articular synovial tissue. On the other hand, high-intensity tissues adjacent to pannus formation could be incompletely excluded by the outlining. Additional explanation for the lower correlation is provided by the MR imaging parameters. In the previous study, the T1-weighted spin-echo MR images to conduct quantification of the synovial membrane were obtained in the axial plane using a 1.5 T Siemens MR unit or a 1.0 T Siemens Impact MR unit (17). Conversely, we performed MR imaging using

T1-weighted gradient-echo dynamic sequence in the coronal plane with a 3.0-T MR imager manufactured by GE Medical Systems. These differences at a stage prior to quantification of the synovial tissue may influence contrast enhancement of each tissue as well as the efficacy of outlining. The selection of adequate criteria and careful outlining are challenging and severely affect accuracy.

One of the main problems regarding the quantification of synovial membrane volume is finding an appropriate gold standard. Manual MRI segmentation, a direct measurement of the area of enhancing pannus, has been used as a gold standard. In order to reveal the reproducibility and reliability of this method, various studies have been performed. A previous study has demonstrated that changes of as little as 20% in synovial volume are detectable in the wrist, better than that achievable using OMERACT scoring. In addition, the correlation between scoring and direct measurement has shown a good correlation coefficient ranging from $r=0.7$ to 0.88 (15,16). In one study, the synovitis volume measurement is a better predictor of erosive progression than the OMERACT score (25). As indicated by previous examinations, manual outlining has been widely acknowledged as a credible measurement assessing the extension of the synovial membrane in RA.

Another main problem regarding quantification using TIC analysis is to determine the

TIC shape representing the synovial membrane. The Type 4 TIC shape, which consists of a rapid enhancement phase followed by an early washout, has been regarded as an indicator of pannus tissue. It was reported that the relative number of Type 4 TIC shapes were significantly greater in RA patients than in healthy control subjects; hence Type 4 TIC shapes were associated with RA (19,20,26). Although these studies were performed in the knee, pannus formations were mainly classified as Type 4 in the RA hand as well due to the characteristics of inflamed synovial tissue related to increased tissue vascularization and permeability. However, as pointed out above, a part of pannus tissue located in the finger region was classified into other TIC types. It is necessary to examine the reliability of TIC shape analysis in the finger in detail in future studies.

Limitations to this study must be addressed here. Because the number of cases is small, the TIC classification procedure and categorization code using MATLAB may not fit every patient. In addition, it may be necessary to modify the program with a different MRI unit or imaging parameters. However, as the analyzing code can be flexibly changed according to the circumstances of MR imaging, such as contrast enhancement or number of slices, it is possible to perform TIC shape analysis with calculation software.

Another limitation of this study is the influence of noise and artifacts related to MR

imaging. Pixels with a signal below noise level were ruled out from TIC classification in advance. However, noise showing equivalent MR signal intensity to that of body tissues was found in some images (like Fig. 4c) and involved in TIC shape analysis. These noisy pixels were mostly classified as Type 1 and Type 2, or Type 7 rather than Type 4. The quantification of the pannus formation thus seems to be unaffected by noise. Our TIC shape analysis is also limited by the difficulty of discriminating intraosseous pannus from extraosseous pannus. The clinical importance of this aspect needs to be elucidated in the future. Another limitation of this study is that patient movement could theoretically have been a confounder on the pixel-by-pixel analysis. However, imaging time of LAVA dynamic was approximately 6 minutes and the hand and the wrist were tightly fixed with sand bags throughout the imaging. In the images for this investigation, no noticeable motion artifact was observed.

Conclusion

In summary, pixel-by-pixel TIC shape analysis for quantification of the synovial membrane has strong correlation with manual contouring in the wrist. This technique can precisely characterize the tissues related to changes in MR signal intensity during and after intravenous injection of contrast agent. In addition, it is possible to distinguish

pannus formation from other tissues according to TIC shape types. On the other hand, segmentation for the area of enhancing pannus using thresholding could not thoroughly rule out the pixels of other high-intensity tissues from enhancing pannus. Finally, these results suggest that TIC shape analysis may be an alternative to the gold standard of manual contouring for pannus quantification and provide important clinical information of the extent of the disease in the RA wrist.

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Table

Table 1. Identification of the most relevant TIC shape in terms of synovitis

	r	p	correlation
Type1	-0.626	<0.001	good
Type2	0.236	0.179	poor
Type3	NA	NA	NA
Type4	0.809	<0.001	excellent
Type5	0.337	0.051	poor
Type6	0.111	0.534	poor
Type7	0.526	0.01	moderate

r, Pearson's product-moment correlation coefficient; p, p-value; NA, not applicable

Thirty four MP joints were analyzed between TIC shape and RA-MRI scoring (RAMRIS) system by Pearson's product-moment correlation. Type 3 shape type is excluded from consideration due to the lack of number of relevant pixel.

Table 2. Comparison of AEP_THRES and AEP_TIC with AEP_MANUAL as the gold standard

		r	p	correlation
entire hand	AEP_THRES	0.714	<0.001	good
	AEP_TIC	0.791	<0.001	good
finger region	AEP_THRES	0.591	<0.001	moderate
	AEP_TIC	0.568	<0.001	moderate
wrist region	AEP_THRES	0.716	<0.001	good
	AEP_TIC	0.815	<0.001	excellent

r, Spearman's rank correlation coefficient; p, p-value; AEP_THRES, area of enhancing pannus (AEP) measurement via segmentation using thresholding; AEP_TIC, AEP measurement via segmentation using pixel-by-pixel TIC analysis; AEP_MANUAL, measurement via segmentation by setting AEP by manual contouring

Figure Legend

Figure 1. ROI for measurement of TIC shape type

In post-gadolinium-DTPA MR images, ROI analysis with three-dimensional ROI fitted to cover the head of the metacarpal and basis of the phalangeal bones was performed using ImageJ software.

Figure 2. TIC shape categories (a) and the classification procedure (b)

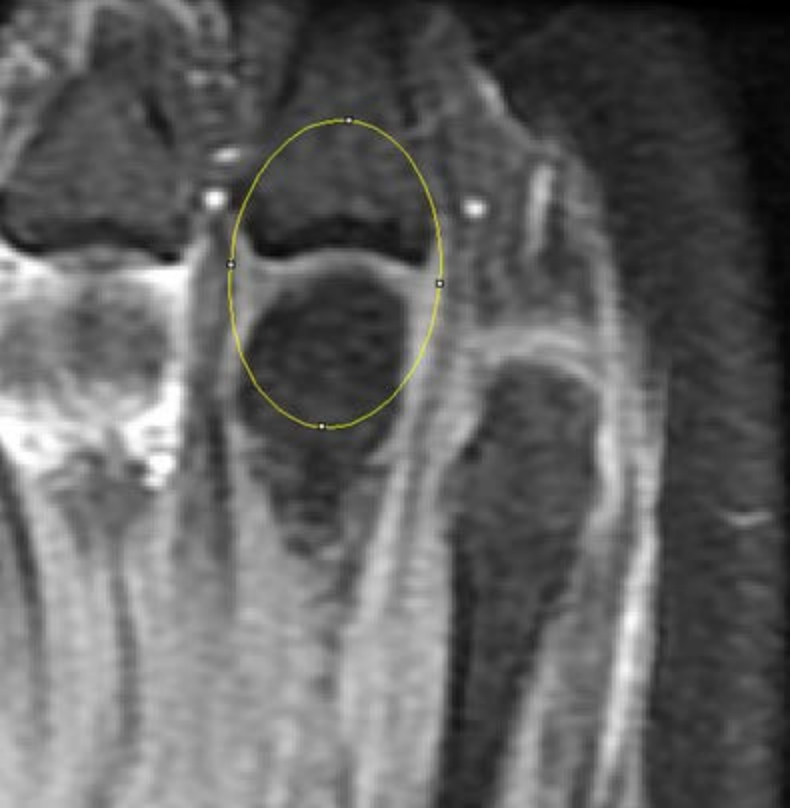
(a) Type 1 (dark blue): no enhancement. Type 2 (blue): slow enhancement. Type 3 (light blue): slight change of signal after fast enhancement. Type 4 (light green): washout after fast initial enhancement; Type 5 (orange): quick enhancement and a slow constant enhancement; Type 6 (red): rapid enhancement and a sharp signal drop; Type 7 (burgundy): all others. (b) The classification algorithm was applied using MATLAB software.

Figure 3. The number of Type 4 pixels plotted against synovitis score

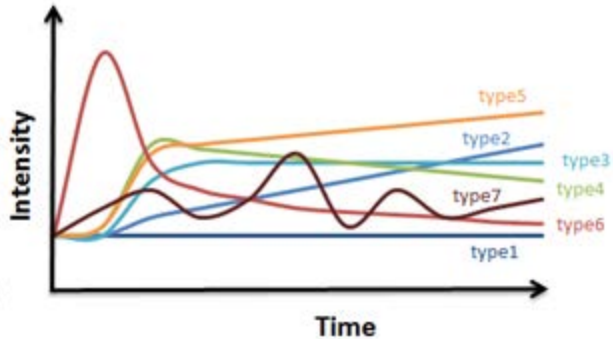
There was excellent correlation between Type 4 curve shape and synovitis score in MP joints (R-squared value = 0.6549).

Figure 4. Coronal images outlining the area of enhancing pannus (AEP) in the rheumatoid hand via different segmentation techniques

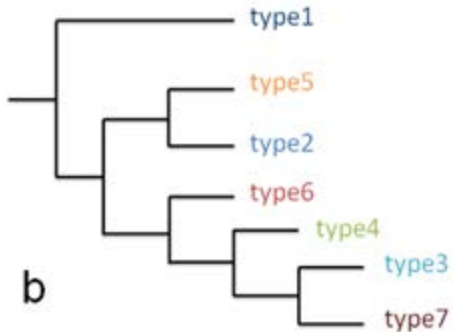
(a) On the post-gadolinium-DTPA image, the area of enhancing synovial pannus has been manually outlined (light green outline). (b) The automated threshold segmentation image is shown as a binary image. The pixels fulfilling the pre-set criteria appeared white and were calculated as the area of enhancing pannus. (c) On the Pixel-by-pixel TIC analysis image, each TIC of every pixel is classified into one of seven predefined TIC shape categories. Type 4 (light green pixels) indicates pannus formation.

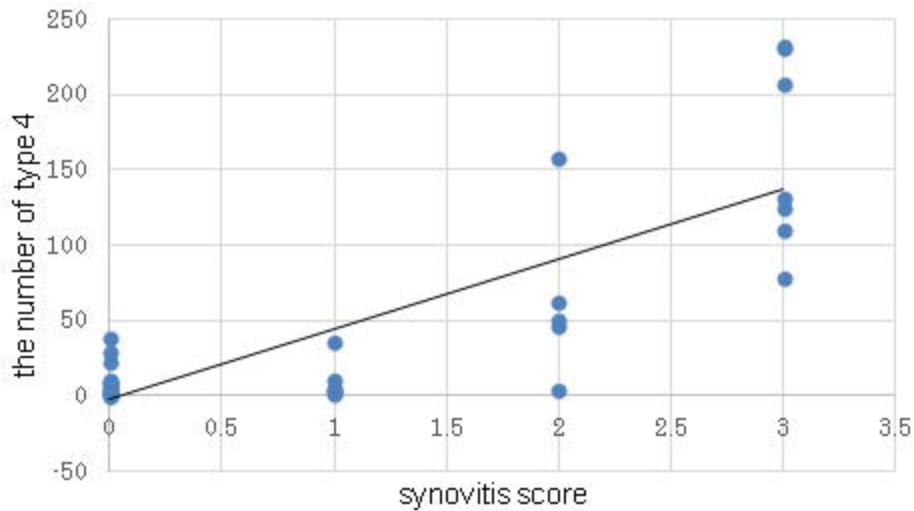


a

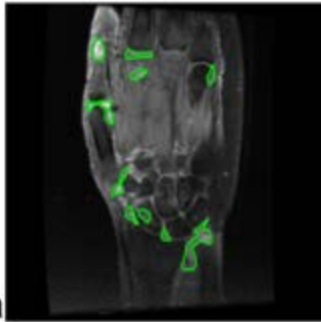


b





a



b



c

