博士論文の要約

博士の専攻分野の名称：博士（保健科学）　　氏名：房 宛萱

学位論文題名

Deep Learning-Based Automated Quantitative Analysis and Clinical Application of Synovitis and Joint Space Changes in Rheumatoid Arthritis

（深層学習に基づく関節リウマチの滑膜炎および関節間隙変化の自動定量解析と臨床応用研究）

1. Fully Automatic Quantification for Hand Synovitis in Rheumatoid Arthritis Using Pixel-Classification-based Segmentation Network in DCE-MRI

- Wanxuan Fang, Yijun Mao, Haolin Wang, Hiroyuki Sugimori, Shinji Kiuch, Kenneth Sutherland, Tamotsu Kamishima, Jpn J Radiol 42, 1187–1197 (2024).

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial joint inflammation, leading to joint damage and disability [1，2]. Imaging techniques, particularly magnetic resonance imaging (MRI), play a crucial role in assessing RA disease activity [3]. Among them, dynamic contrast-enhanced MRI (DCE-MRI) enables quantitative evaluation of synovitis based on perfusion dynamics

[4]. Time-intensity curve (TIC) shape analysis in DCE-MRI has been proposed to aid in synovitis assessment [5-8]. However, existing TIC-based methods [5,6] have limitations, including difficulty in differentiating synovitis from arteries and the time-consuming nature of manual contouring. Deep learning (DL) approaches, particularly one-dimensional convolutional neural networks (1D-CNNs), have shown promise in time-series signal analysis and medical imaging segmentation [9-11]. This study aims to develop a DL-based method to automatically segment and quantify synovitis in RA patients using TICs from DCE-MRI, comparing its performance with manual segmentation.

Materials and Methods

This retrospective study analyzed DCE-MRI scans of 28 RA patients (six males, mean age 53.7 years), with ground truth annotations provided by an experienced musculoskeletal (MSK) radiologist. Data preprocessing included noise reduction, motion correction, contrast enhancement, and intensity normalization. The proposed DL model was a 1D CNN incorporating dilated causal convolution and the scaled exponential linear unit (SELU) activation function for TIC-based pixel classification into muscle, bone, and synovitis categories. The network was trained and tested using leave-one-out cross-validation. Statistical analysis included Pearson's correlation analysis to assess agreement between DL-based and manual quantifications at pixel- and patient-based levels, as well as Bland–Altman analysis for systematic bias evaluation.

Results

The dataset comprised 27,255 pixels with corresponding TICs (muscle: 11,413, bone: 8502, synovitis: 7340). Manual segmentation identified synovitis in 129 joint bounding boxes, including 74 finger joints and 55 wrist joints. Illustrative examples of pixelwise segmentation of synovitis cases in finger and wrist joints using the software are presented in Fig. 1. The DL model achieved high segmentation performance with an average sensitivity of 85%, specificity of 98%, accuracy of 99%, and precision of 84%, achieving a Dice score of 0.73. The false-positive rate for cases without synovitis was 0.8%. Strong correlations were observed between DL-measured and manually delineated synovial volumes at both pixel-based ($r = 0.87$, $p < 0.001$) and patient-based levels ($r = 0.84$, $p < 0.001$). Bland-Altman analysis indicated a slight overestimation by the DL model, with mean differences of -9.46 mm^3 at the pixel level and -50.87 mm^3 at the patient level. The DL-based segmentation required only 1 second per bounding box, compared to several minutes for manual contouring.

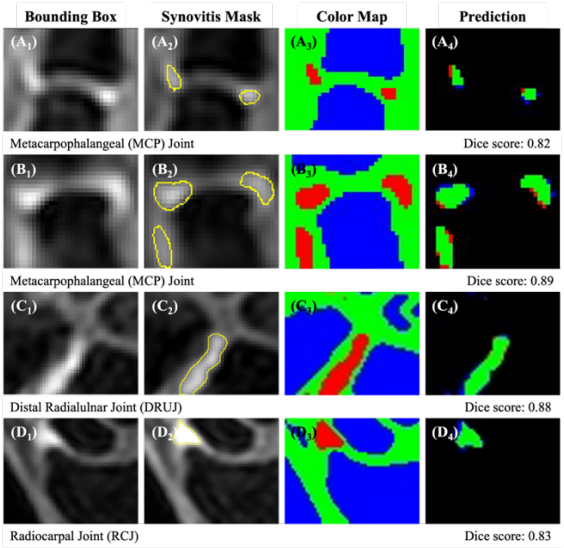

Fig. 1 Examples of the proposed segmentation network on the time-intensity curve characteristic curve. A1-B 4 Cases of Metacarpophalangeal (MCP) Joint, C1-4 One

case of Distal Radioulnar Joint (DRUJ), D1-4 One case of Radiocarpal Joint (RCJ). Bounding box: Native dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) images of selected regions of interest, synovitis mask: ground truth from manual segmentation, Color Map: Enhancing pannus segmentation obtained from the network, Prediction: Overlapping regions of manual and automated segmentation. In prediction, red pixels represent manually segmented areas, blue pixels represent areas segmented automatically by the network, and green pixels represent regions where manual and automatic segmentation overlap

Discussion

This study demonstrated that a DL-based approach could accurately and efficiently segment and quantify synovitis in RA patients from DCE-MRI data. Compared to existing semi-quantitative and manual delineation methods, the proposed model offered enhanced objectivity, speed, and reproducibility while reducing radiologists' workload. The results suggested that deep learning could provide a viable alternative to manual segmentation, potentially facilitating automated synovitis quantification in clinical settings. Future research should focus on refining model accuracy, expanding the dataset, and validating performance across different imaging centers.

References

1. Dakkak YJ, Jansen FP, DeRuiter MC, Reijnierse M, van der Helm-van Mil AHM. Rheumatoid Arthritis and Tenosynovitis at the Metatarsophalangeal Joints: An Anatomic and MRI Study of the Forefoot Tendon Sheaths. Radiology. 2020;295(1):146-54.

2. Micu MC, Fodor D. Concepts in monitoring the treatment in rheumatoid arthritis-

the role of musculoskeletal ultrasound. Part I: synovitis. Med Ultrason. 2015;17(3):367-76.

3. Burke CJ, Alizai H, Beltran LS, Regatte RR. MRI of synovitis and joint fluid. J Magn Reson Imaging. 2019;49(6):1512-27.

4. Ostergaard M, Boesen M. Imaging in rheumatoid arthritis: the role of magnetic resonance imaging and computed tomography. Radiol Med. 2019;124(11):1128-41.

5. Kobayashi Y, Kamishima T, Sugimori H, Ichikawa S, Noguchi A, Kono M, et al. Quantification of hand synovitis in rheumatoid arthritis: Arterial mask subtraction reinforced with mutual information can improve accuracy of pixel-by-pixel time-intensity curve shape analysis in dynamic MRI. J Magn Reson Imaging. 2018.

6. Sakashita T, Kamishima T, Kobayashi Y, Sugimori H, Tang M, Sutherland K, et al. Accurate quantitative assessment of synovitis in rheumatoid arthritis using pixel-by-pixel, time-intensity curve shape analysis. Br J Radiol. 2016;89(1061):20151000.

7. van de Sande MG, van der Leij C, Lavini C, Wijbrandts CA, Maas M, Tak PP. Characteristics of synovial inflammation in early arthritis analysed by pixel-by-pixel time-intensity curve shape analysis. Rheumatology (Oxford). 2012;51(7):1240-5.

8. Lavini C, de Jonge MC, van de Sande MG, Tak PP, Nederveen AJ, Maas M. Pixel-by-pixel analysis of DCE MRI curve patterns and an illustration of its application to the imaging of the musculoskeletal system. Magn Reson Imaging. 2007;25(5):604-12.

9. Liang H, Lu Y, Liu Q, Fu X. Fully Automatic Classification of Cardiotocographic Signals with 1D-CNN and Bi-directional GRU. Annu Int Conf IEEE Eng Med Biol Soc. 2022;2022:4590-4.

10. Hassan F, Hussain SF, Qaisar SM. Epileptic Seizure Detection Using a Hybrid 1D CNN-Machine Learning Approach from EEG Data. J Healthc Eng. 2022;2022:9579422.

11. Hsieh CH, Li YS, Hwang BJ, Hsiao CH. Detection of Atrial Fibrillation Using 1D Convolutional Neural Network. Sensors (Basel). 2020;20(7).

2. Deep Registration Method for Finger Joint Space Width Changes: A Comparative Study with HR-pQCT

- Wanxuan Fang, Haolin Wang, Bingqing Lu, Sze Lok Lau, Isaac Cheng, Masayuki Ikebe, Lai Shan Tam, James F Griffith, Tamotsu Kamishima (manuscript in prepration)

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation and progressive joint destruction, with joint space narrowing (JSN) being a key radiographic indicator of disease progression [1-2]. Early detection of subtle changes in joint space width (JSW) is crucial for assessing disease activity and treatment response [3]. Traditional radiographic scoring methods, such as the van der Heijde modification of the Sharp (VdH-S) score, are widely used but are subjective, time-consuming, and have limited sensitivity to minor JSW changes [4]. High-resolution peripheral quantitative computed tomography (HR-pQCT) has emerged as a gold standard for precise JSW quantification due to its high spatial resolution [5], but its high cost and limited availability hinder widespread clinical adoption.

Recent advancements in deep learning-based image registration methods offer promising alternatives for automated and precise JSW assessment in standard X-ray images. Unlike conventional bone edge detection methods [6-8] that operate at the pixel level, deep registration-based approaches can detect sub-pixel changes in JSW by aligning sequential X-ray images over time. This study aims to validate a deep learning method for quantitatively measuring JSW changes of finger joints in patients with RA using X-rays and to compare its performance with morphological parameters related to JSW changes measured by the gold standard HR-pQCT.

Materials and Methods

This a secondary analysis of a prospective study included 170 posteroanterior (PA) hand X-ray images and 173 HR-pQCT images from 58 RA patients, involving 510 and 513 finger joints, respectively. The second to fourth metacarpophalangeal (MCP2, MCP3, MCP4) joints were analyzed. HR-pQCT was used to measure five JSW-related morphometric parameters: joint space volume (JSV), mean JSW (JSW.mean), maximum JSW (JSW.max), minimum JSW (JSW.min), and asymmetry (JSW.AS).

A deep learning-based registration method was developed to measure JSW changes in X-ray images. The pipeline involved joint segmentation using a U-Net++ network, followed by an unsupervised ResNet-based deep registration model to quantify vertical displacement between follow-up and baseline images, representing JSW changes.

For statistical analysis, Spearman's correlation was used to assess relationships

between JSW changes measured by deep registration and HR-pQCT-derived morphometric parameters. Repeated measures ANOVA was performed to evaluate significant differences in JSW parameters over time, followed by post-hoc testing.

Results

A total of 58 patients (mean age 58 ± 10 years; 37 females) were analyzed, with 510 MCP 2-4 joints assessed on X-ray and 513 on HR-pQCT. In MCP2, significant correlations were observed during the M12-M24 interval between deep registration-derived JSW changes and HR-pQCT-measured JSW.min ($r = 0.415$, $p < .01$) and JSW.AS ($r = -0.3442$, $p < .05$). However, no significant correlations were found in MCP3 or MCP4, nor in other time intervals.

JSW changes measured by deep registration showed partial correlations with HR-pQCT parameters. Between the baseline-to-12-month and baseline-to-24-month intervals, JSW changes measured via deep registration on X-rays significantly correlated with MCP2 ($r = 0.3269$, $p < .05$), MCP3 ($r = 0.2968$, $p < .05$), and MCP4 ($r = 0.478$, $p < .01$). Repeated measures ANOVA showed significant differences in JSW.mean for MCP2 between baseline and 12 months ($F (1.918, 97.82) = 3.733$, $P = 0.0197$) and MCP3 ($F (1.621, 79.44) = 5.056$, $P = 0.0291$), as well as JSW.AS for MCP2 between baseline and 24 months, as well as between 12 and 24 months ($F (1.011, 38.41) = 6.473$, $P = 0.0125$ and $P = 0.018$, respectively).

Discussion

This study demonstrated the feasibility of using a deep learning-based registration

method to detect sub-pixel JSW changes in RA patients from X-ray images. Significant correlations were observed between deep registration-derived JSW changes and HR-pQCT parameters, particularly JSW.min and JSW.AS in MCP2. Compared to manual radiographic assessment, this method offered greater efficiency, objectivity, and reproducibility. While HR-pQCT remains the gold standard, its high cost and limited availability restrict its use. Deep registration-based X-ray analysis could provide a practical alternative, especially in settings where HR-pQCT is inaccessible.

In conclusion, the deep learning-based registration method enabled precise, automated JSW measurement in RA patients using X-ray images. With its ability to detect sub-pixel changes, it could support early disease monitoring and treatment assessment, complementing HR-pQCT in clinical and research applications.

References

1. van der Heijde D. Erosions versus joint space narrowing in rheumatoid arthritis: what do we know? Ann Rheum Dis 2011;70 Suppl 1:i116-118.

2. Ding Q, Hu W, Wang R, Yang Q, Zhu M, Li M, et al. Signaling pathways in rheumatoid arthritis: implications for targeted therapy. Signal Transduct Target Ther 2023;8(1):68.

3. Mandl P, Supp G, Baksa G, Radner H, Studenic P, Gyebnar J, et al. Relationship between radiographic joint space narrowing, sonographic cartilage thickness and anatomy in rheumatoid arthritis and control joints. Ann Rheum Dis 2015;74(11):2022-2027.

4. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 2000;27(1):261-263.

5. Demehri S, Baffour FI, Klein JG, Ghotbi E, Ibad HA, Moradi K, et al. Musculoskeletal CT Imaging: State-of-the-Art Advancements and Future Directions. Radiology 2023;308(2):e230344.

6. Sharp JT, Angwin J, Boers M, Duryea J, von Ingersleben G, Hall JR, et al. Computer based methods for measurement of joint space width: update of an ongoing OMERACT project. J Rheumatol 2007;34(4):874-883.

7. Huo Y, Vincken KL, Viergever MA, Lafeber FP. Automatic joint detection in rheumatoid arthritis hand radiographs. 2013 IEEE 10th International Symposium on Biomedical Imaging2013; p. 125-128.

8. Huo Y, Vincken KL, Heijde Dvd, Hair MJHD, Lafeber FP, Viergever MA. Automatic Quantification of Radiographic Finger Joint Space Width of Patients With Early Rheumatoid Arthritis. IEEE Transactions on Biomedical Engineering 2016;63(10):2177-2186.