

Diagnostic Value of Musculoskeletal Ultrasound in Rheumatoid Finger Arthritis

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ABSTRACT

Objective: To determine the value of musculoskeletal ultrasound (MSUS) in evaluating the pathological features and inflammatory lesions of rheumatoid finger arthritis.

Study Design: A comparative study.

Place and Duration of Study: Ningbo No. 6 Hospital, China, from September 2017 to February 2020.

Methodology: Eighty patients with rheumatoid finger arthritis (570 finger joints) were examined by MSUS and MRI. Detection rates of the two methods for diagnosing the pathological features of rheumatoid arthritis, levels of the serum markers rheumatoid factor (RF), etc, were compared.

Results: Detection rate of joint effusion by MSUS was higher than MRI ($p < 0.001$). Spearman's correlation analysis showed that synovial blood flow signal grade was positively correlated with serum RF, anti-CCP, ESR, CRP, IL-6, and IL-33 levels ($r = 0.853$, $p < 0.001$; $r = 0.864$, $p < 0.001$; $r = 0.866$, $p < 0.001$; $r = 0.846$, $p < 0.001$; $r = 0.881$, $p < 0.001$; and $r = 0.873$, $p < 0.001$, respectively). Resistive index value of intra-synovial artery in active patients was lower than in define inactive patients ($p < 0.001$).

Conclusion: Compared to MRI, MSUS has a higher detection rate of joint effusion in RA patients. In the MSUS examination, synovial blood flow signal is positively correlated with RF, Anti-CCP, ESR, CRP, IL-6, and IL-33, and the resistive index of intra-synovial artery is closely related to disease activity.

Key Words: Musculoskeletal ultrasound (MSUS), Rheumatoid arthritis (RA), Synovial hyperplasia, Synovial blood flow signal, Serum markers.

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INTRODUCTION

Rheumatoid arthritis (RA) is a multi-system inflammatory autoimmune disease that primarily affects the lining of the synovial joints, and its typical pathological features include synovial hyperplasia, joint effusion, and bone erosions.^{1,2} Rheumatoid finger arthritis is an early manifestation of RA. Joint pain, fusiform swelling, stiffness, flexion and extension disorder, and other symptoms are usually present in the proximal interphalangeal joints of patients with RA. RA, which is a result of a continuous unbalanced pro- and anti-inflammatory response, can lead to chronic inflammation. After specifically binding to the antigen, rheumatoid factor (RF) forms immune complexes that are deposited in joints, kidney, heart, etc., resulting in impaired organ function.³

Erythrocyte sedimentation rate (ESR) and RF are commonly used in clinic to evaluate the activity level of RA. C-reactive protein (CRP) can more sensitively reflect the presence of inflammation and the activity of rheumatoid disease.⁴ It has been reported that cytokine interleukin 6 (IL-6) is increased in RA patients.⁵ IL-6 is related to RA disease activity, and elevated IL-6 level will further aggravate joint swelling and pain.⁶ Interleukin 33 (IL-33) plays a key role in various inflammations, infections and autoimmune diseases, and its abnormal signal transduction is related to the pathogenesis of RA.⁷⁻⁹ Research by Merola *et al.* confirmed that approximately 80% of patients with RA are positive for RF and CCP antibodies.¹⁰ Anti-cyclic citrullinated peptide (anti-CCP) is a specific antibody used to diagnose RA. Schellekens *et al.* found that anti-CCP antibodies can be tested positive in early stages of RA.¹¹

Quick and accurate evaluation of the pathological features and inflammatory lesions of RA patients is conducive to disease monitoring, clinical treatment, and prognosis evaluation. At present, the widely used imaging tests in academia mainly include X-ray, CT, MRI, etc. However, in long-term clinical practice, these methods are not ideal for evaluating the pathological features and inflammatory lesions of RA. Ultrasound examina-

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tion is a low-cost, non-invasive, simple, and intuitive method that can be repeated in a short period of time. As the resolution of high-frequency ultrasound probes continues to increase, MSUS has become popular in the examination of human soft tissues and bone lesions. However, at present, there are few reports on application of MSUS in evaluating the pathological features and inflammatory lesion degrees of RA.

The purpose of this study was to explore the value of MSUS in evaluating the pathological features and inflammatory lesions of RA.

METHODOLOGY

The comparative study was conducted at Ningbo No. 6 Hospital, China, from September 2017 to February 2020 and approved by the Institutional Ethics Committee of Ningbo No. 6 Hospital. Eighty patients with rheumatoid finger arthritis (570 finger joints) were selected as the research subjects. Inclusion criteria were in accordance with the RA early classification and diagnosis criteria revised by the American College of Rheumatology (ACR) and the European League Against Rheumatism in 2009; the finger joints showed swelling, pain, and limited mobility; no anti-rheumatic drugs treatment was given; organ (such as heart, liver and lung) functions were normal. Exclusion criteria included those with finger joint disability and deformity; history of finger joint surgery; those with arthro-skeletal pain caused by trauma, infection, tumor, blood disease or other autoimmune diseases; severe liver and kidney insufficiency; those with multiple bone erosions; infectious diseases and pregnant or lactating women. All patients (570 finger joints) received MSUS and MRI examinations.

In MSUS examination, a direct scanning method was used. The patients took a sitting position, and their hands were placed on the examination table. After the coupling agent was applied on the joint surface, palmar and dorsal sides of the second to fifth metacarpophalangeal joints. The proximal interphalangeal joints in both hands were examined with transverse and longitudinal scanning. In the MRI examination, multi-channel special coils were used; the sequences were set as: coronal FSE-T1W1, TR/TE = 500/25ms; sagittal FSE-PDW1, TR/TE = 3000/25 ms; fat-suppressed FSE-T2W1, TR/TE = 3650/90ms; T2W1 cross-section scan was added if necessary; the layer thickness was set to 3mm and spacing 3mm.¹²

On the second day after admission, 5 mL fasting cubital venous blood was collected from the patients in the morning, centrifuged, and the serum was separated to detect levels of serum markers (RF, Anti-CCP, ESR, CRP, IL-6, and IL-33). Among them, serum RF and CRP levels were detected by the immunoturbidimetric method, ESR by the ESR analyser, and quantitative levels of anti-CCP antibodies (Anti-CCP), IL-6 and IL-33 by the enzyme-linked immunosorbent assay (ELISA).

The detection rates of typical pathological features (synovial hyperplasia, joint effusion, bone erosions) were recorded and compared between MSUS and MRI. The detection rate was decided with MRI as the gold standard. Synovial hyperplasia

was defined as a thickness $\geq 1\text{mm}$, joint effusion as depth of joint echo-free space $>1\text{mm}$, and bone erosions as local thinning of articular cartilage $\leq 1\text{mm}$.¹²

With reference to the Walther classification standard, MSUS classification of the patient's synovial thickness (grade I, grade II, grade III, and grade IV) was observed.¹³ With reference to the semi-quantitative scores (SQSS), MSUS classification of the patient's synovial blood flow signal (grade 0, grade 1, grade II, and grade III) was observed.

Serum RF, Anti-CCP, ESR, CRP, IL-6, and IL-33 were compared between patients with different grades of synovial thickness and synovial blood flow signal. Pulsed Doppler sampling was performed on the color blood flow under the MSUS examination. The peak velocity of the systolic phase (V_{max}) and the velocity at the end diastolic phase (V_{min}) were measured to calculate resistive index value of the intra-synovial artery. Resistive index of intra-synovial artery = $(V_{\text{max}} - V_{\text{min}}) / V_{\text{max}}$. Resistive index values of intra-synovial artery were compared between active and inactive patients. Those who met any of the following 4 items simultaneously were defined as active patients: (i) moderate pain at rest; (ii) morning stiffness $\geq 1\text{h}$; (iii) swelling in 3 or more joints; (iv) tender joint count ≥ 5 ; (v) ESR $>28\text{mm/h}$.

Data were analysed using SPSS 25 statistical software. Count data were expressed as n (%) and analysed by the Chi-square test. Shapiro-Wilk test was used for evaluation of the normality of quantitative data. Measurement data were expressed as Median (IQR) and Mean \pm S.D. Resistance index values of intra-synovial artery were compared between active and inactive patients using an independent sample t test. RF, Anti-CCP, ESR, CRP, IL-6, and IL-33 levels in patients with different grades of synovial thickness and synovial blood flow signal were compared using Kruskal Wallis test; pairwise correlation analysis was conducted using Spearman's correlation analysis. A p-value less than 0.05 was statistically significant.

RESULTS

Among the 80 patients, 43 were males (53.75%) and 37 were females (46.25%). They were aged 35-70 (63.18 ± 2.45) years; with a disease course of 5-8 (2.76 ± 0.21) years. Among the 570 finger joints, the detection rate of synovial hyperplasia was 72.46% (413) by MSUS, and 75.09% (428) by MRI; the difference was not significant ($\chi^2 = 1.020$, $p = 0.313$). The detection rate of bone erosions was 28.07% (160) by MSUS and 30.53% (174) by MRI; the difference was not significant ($\chi^2 = 0.830$, $p = 0.362$). The detection rate of joint effusion was 57.02% (325) by MSUS and 46.14% (263) by MRI; the former was higher than the latter ($\chi^2 = 13.501$, $p < 0.001$).

According to MSUS, 41 patients (51.25%) had synovial thickness in grades I-II, 29 patients (36.25%) in grade III, and 10 patients (12.50%) in grade IV, respectively. There were no significant differences in serum RF, Anti-CCP, ESR, CRP, IL-6, and IL-33 levels between patients with synovial thickness of grades I-II, III, and IV ($p = 0.883, 0.276, 0.263, 0.932, 0.944, \text{ and } 0.533$, respectively, Table I).

Table I: Comparison of serum marker levels in patients with different grades of synovial thickness.

Serum markers	Grades I-II synovial thickness (n=41)	Grade III synovial thickness (n=29)	Grade IV synovial thickness (n=10)	p-value
RF(IU/mL)	19.67 (19.04-20.94)	19.90 (19.29-20.51)	19.90 (19.30-20.81)	0.883
Anti-CCP (RU/mL)	296.79 (287.21-315.88)	293.67 (284.67-302.60)	300.19 (291.14-313.84)	0.276
ESR (mm/h)	30.73 (29.74-32.70)	31.58 (30.62-32.55)	31.39 (30.44-32.82)	0.263
CRP (mg/L)	8.04 (7.78-8.56)	8.11 (7.86-8.36)	8.12 (7.88-8.48)	0.932
IL-6 (pg/mL)	36.00 (34.84-38.31)	36.11 (35.00-37.21)	36.12 (35.03-37.77)	0.944
IL-33 (pg/mL)	300.21 (290.52-319.52)	298.18 (289.04-307.25)	301.85 (292.75-315.58)	0.533

Table II: Comparison of serum marker levels in patients with different grades of synovial blood flow signal.

Serum markers	Grades 0-I synovial blood flow signals (n=37)	Grade II synovial blood flow signals (n=30)	Grade III synovial blood flow signals (n=13)	p-value
RF (IU/mL)	18.14 (17.56-19.01)	20.09 (19.55-20.57)	22.16 (21.92-23.42)	<0.001
Anti-CCP (RU/mL)	285.93 (280.48-290.58)	303.23 (297.15-307.37)	319.65 (317.99-323.43)	<0.001
ESR (mm/h)	28.08 (27.49-28.53)	31.68 (30.75-32.86)	34.32 (34.04-35.18)	<0.001
CRP (mg/L)	7.69 (7.46-7.94)	8.29 (7.83-8.92)	8.83 (8.51-9.67)	<0.001
IL-6 (pg/mL)	35.02 (33.99-35.46)	37.05 (36.83-37.80)	38.56 (38.26-39.04)	<0.001
IL-33 (pg/mL)	294.52 (290.56-298.01)	305.10 (303.21-306.96)	316.80 (310.96-320.74)	<0.001

Table III: Correlation between serum markers and different grades of synovial thickness and synovial blood flow signal.

Serum markers	Grade of synovial thickness		Grade of synovial blood flow signal	
	r	p-value	r	p-value
RF	0.053	0.644	0.853	<0.001
Anti-CCP	0.040	0.724	0.864	<0.001
ESR	0.111	0.328	0.866	<0.001
CRP	0.132	0.243	0.846	<0.001
IL-6	0.050	0.659	0.881	<0.001
IL-33	0.018	0.876	0.873	<0.001

According to MSUS, 37 patients (46.25%) had synovial blood flow signals in grade 0-I, 30 patients (37.5%) in grade II, and 13 patients (16.25%) in grade III, respectively. Levels of serum RF, Anti-CCP, ESR, CRP, IL-6, and IL-33 were statistically different between patients with grade 0-I, II, and III synovial blood flow signals (all $p < 0.001$, Table II), and serum RF, Anti-CCP, ESR, CRP, IL-6, and IL-33 levels increased with the increase of the patient's synovial blood flow signal grade.

Spearman's correlation analysis showed that the synovial thickness was not correlated with serum RF, Anti-CCP, ESR, CRP, IL-6, and IL-33 levels ($r = 0.053$, $p = 0.644$; $r = 0.040$, $p = 0.724$; $r = 0.111$, $p = 0.328$; $r = 0.132$, $p = 0.243$; $r = 0.050$, $p = 0.659$; $r = 0.018$, and $p = 0.876$, respectively, Table III). Spearman's correlation analysis showed that the synovial

blood flow signal grade was positively correlated with serum RF, Anti-CCP, ESR, CRP, IL-6, and IL-33 levels ($r = 0.853$, $p < 0.001$; $r = 0.864$, $p < 0.001$; $r = 0.866$, $p < 0.001$; $r = 0.846$, $p < 0.001$; $r = 0.881$, $p < 0.001$; and $r = 0.873$, $p < 0.001$, respectively, Table III).

Among the 80 patients, there were 46 active patients (57.50%) and 34 inactive patients (42.50%). The resistive index value of intra-synovial artery was 0.62 ± 0.09 in active patients and 0.83 ± 0.11 in inactive patients; the former was lower than the latter ($t = -9.526$, $p < 0.001$).

DISCUSSION

MRI has the advantages of high-contrast resolution in tissue, no interference from bone artifacts, multi-directional

imaging, and the ability to obtain TWI, TW2 and PWI that are conducive to the contrast analysis of imaging. However, the expensive and time-consuming MRI examination is not suitable as a routine tool for clinical diagnosis. MSUS enjoys the advantages of multiplane imaging and flexible scanning, realisation of combined dynamic and static imaging, real-time dynamic evaluation of tissue lesions, and high resolution of fine structures like muscles and ligaments.¹⁴

However, MSUS imposes high requirements for the machine and the operator alike. It was found in this study that MSUS and MRI show no significant difference in the detection rates of synovial hyperplasia and bone erosions; however, MSUS has a higher detection rate of joint effusion than MRI. It suggests that MSUS is the optimal method to examine joint effusion. In clinical practice, the author has found that MSUS can detect at least about 1 mL joint effusion. Seifeldein *et al.* also confirm that MSUS shows a strong diagnostic value for joint effusion, synovitis, tenosynovitis and bone erosions in early RA.¹⁵

Some studies suggest that ultrasound Doppler technology can not only sensitively detect blood flow signals of early joint lesions, but also detect the presence or absence of inflammatory blood flow signals of chronic synovial hyperplasia in RA patients.¹⁶ Since the hyperplastic synovial vessels are mostly microvessels, and the flow rate is very low, color Doppler is insensitive in this aspect. Energy Doppler can make up for this shortcoming, clearly observe the blood supply of the synovium, and grade according to the richness of the blood flow for a semi-quantitative study. Being able to detect the blood flow signals of microvessels even in small joints like the metacarpophalangeal joint and the proximal interphalangeal joint, it indirectly reflects the degree of synovial inflammation and is more accurate to assess joint inflammation and changes in joint structure.

CRP, IL-6, and IL-33 are important markers of the body's inflammatory response. ESR is an important indicator of the degree of synovial inflammation. RF is proportional to the severity of the inflammatory response. CRP is important for disease progression in patients with early RA.¹⁷ Najafizadeh *et al.* observed that the physiologic correlation between leptin and CRP and BMI and CRP was not present in RA patients.¹⁸ IL-6 is closely related to both the classical humoral disease activity and the HPA axis in RA.¹⁹ It has been shown that serum IL-33 is positively correlated with RF; IL-33 may be partly involved in bone erosions in RA.²⁰ In this study, MSUS examination results show that the synovial thickness is not related to RF, Anti-CCP, ESR, CRP, IL-6, or IL-33; however, the synovial blood flow signal is positively correlated to RF, Anti-CCP, ESR, CRP, IL-6, and IL-33. It suggests that the inflammatory level of RA lesions cannot be evaluated solely on synovial thickness under MSUS examination, but should be comprehensively evaluated in combination with blood flow signals.

The inflammatory activity of RA is closely related to the patient's condition, treatment, prognosis and outcome. In this study, the resistive index of intra-synovial artery is a parameter to observe the inflammatory activity of RA. The results showed that the resistive index value of the intra-synovial artery in active patients was lower than that in inactive patients. Karami *et al.* also found ultrasonography was an appropriate method in detecting active RA patients.²¹ It suggests that the resistive index value of intra-synovial artery in MSUS examination can be used as an objective indicator to reflect the activity of synovial inflammation in RA clinically.

CONCLUSION

Compared to MRI, MSUS has a higher detection rate of joint effusion in RA patients. In the MSUS examination, synovial blood flow signal is positively correlated with RF, Anti-CCP, ESR, CRP, IL-6, and IL-33, and the resistive index of intra-synovial artery is closely related to disease activity. MSUS has an important application value for diagnosing pathological features and inflammatory lesions in rheumatoid finger arthritis.

ETHICAL APPROVAL:

This study has been approved by the Ethics Committee of Ningbo No. 6 Hospital, China.

PATIENTS' CONSENT:

Informed consents were obtained from all participants.

CONFLICT OF INTEREST:

Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

XW: Contributed to design articles, collected and analysed data, and wrote the manuscript.

GQ: Revised the manuscript, helped perform the analysis with constructive discussions.

HD: Contributed to design articles, collected and analysed data, and approved the final manuscript.

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