A comparative study on the clinical and magnetic resonance imaging features between seronegative and seropositive rheumatoid arthritis

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Abstract

Objective

Seronegative rheumatoid arthritis (SNRA) is less common and less known compared with seropositive rheumatoid arthritis (SPRA). The aim of this study was to characterise the clinical and magnetic resonance imaging (MRI) features of SNRA and investigate the associated factors of structural damage.

Methods

We retrospectively collected newly diagnosed RA patients who had MRI data of the hands at baseline. The clinical and MRI features and treatment responses during the 12-month follow-up were compared between SNRA and SPRA. The associated factors of the erosion rate were analysed.

Results

A total of 310 RA patients were included in this study. Compared with SPRA, SNRA had a higher level of inflammation (p-values were all <0.001), a higher incidence of low bone mineral density (p=0.009), but a lower erosion score (p<0.001) and a lower probability of interstitial lung disease (ILD) (p=0.019). The main eroded bones were different between SNRA (the scaphoid and the lunate) and SPRA (the capitate and the hamate). In the multivariate analysis, synovitis score, the levels of IL-6 and TNF-α, and hyperglobulinaemia were positively associated with the erosion rate of SNRA (p-values were all <0.05). During the 12-month follow-up, the treatment response between the two groups was comparable (p-values were all >0.05).

Conclusion

SNRA had more severe inflammation but milder erosion compared with SPRA. SNRA with severe inflammation or hyperglobulinaemia needs the same powerful therapy of SPRA to prevent erosion progression.

Key words

seronegative, rheumatoid arthritis, magnetic resonance imaging

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Introduction

Rheumatoid arthritis (RA) is a chronic, potentially disabling autoimmune disease characterised by joint inflammation, structural damage, and the presence of autoantibodies (rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies (1, 2). According to the serological status, it can be divided into seropositive RA (SPRA) and seronegative RA (SNRA), and RF and anti-CCP antibodies play an important role in the diagnosis of the disease. Compared with the 1987 criteria, the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA increased the weight of serology and redefined the patient population (3, 4). Less is known about SNRA. It has been suggested that SPRA and SNRA represent distinct diseases (5). Previous studies reported that SPRA had more active disease, more rapid radiographic progression, and increased mortality rates than SNRA (6, 7). By contrast, other studies reported a higher level of inflammation and worse radiographic outcomes in SNRA patients (8, 9). There was also controversy about the response of SPRA and SNRA to treatment (10-12). As SNRA patients lack the presence of RF and anti-CCP antibodies, it is more challenging to diagnose early SNRA patients.

There are many tools available for valuing RA. Radiography (x-ray) can be used to evaluate structural damage, but it is not sensitive to inflammatory lesions and early structural damage. Computed tomography (CT) is more accurate than x-ray as it can detect subtle bone damage in the early stages of the disease. However, CT shares the same limit with radiography as its limited capacity in detecting soft tissue abnormalities. Compared with radiography and CT, magnetic resonance imaging (MRI) can directly detect inflammatory lesions as well as early structural damage (13, 14). Besides, MRI allows a more accurate assessment of synovitis than clinical evaluation and can detect subclinical inflammation (15, 16). Therefore, MRI plays an important role in the diagnosis, evaluation of treatment efficacy, and prognosis of RA.

The aim of this study was to compare the clinical and MRI features of SPRA and SNRA patients and investigate the relative factors of structural damage.

Methods

Patients and clinical assessment

We retrospectively reviewed the medical data of RA patients who were admitted to the in-patient department of Tongji Hospital from January 2012 to November 2022. Patients who fulfilled the 2010 ACR/EULAR classification criteria for RA, were newly diagnosed at baseline, and had MRI scans of hands at baseline were included in this study. Patients with one of the following conditions were excluded: suffered from other rheumatic immune diseases; patients with antinuclear antibody ≥1:320; patients with infectious diseases such as hepatitis B, hepatitis C, tuberculosis, etc.; without MRI of hands at baseline; being pregnant. According to the EULAR recommendations, the indication of MRI for RA patients were: to confirm the diagnosis of RA based on clinical criteria, especially for patients with negative or low titer autoantibodies; to assess inflammation more accurately; to detect joint damage in early RA; to predict the further joint damage; to predict treatment response (13). Patients positive for RF, anti-keratin antibody (AKA) or anti-CCP antibodies were assigned into SPRA group, while the patients negative for the tests of RF, AKA, and anti-CCP antibodies were assigned into SNRA group. Finally, 151 SPRA patients and 159 SNRA patients were included in this study, and 102 of 151 SPRA patients and 108 of 159 SNRA patients were followed up for no less than 12 months.

Tender joint number in the 28 joints (TJC28) and swollen joints number in the 28 joints (SJC28), pain score, patient's global assessment (PGA), physician's global assessment (PhGA), health assessment questionnaire-disability Index (HAQ-DI), disease activities (including disease activity score-28 (DAS28), simplified disease activity index (SDAI) and clinical disease activity index (CDAI)) were assessed at

baseline, 1 month, 3 months, 6 months and 12 months. Inflammatory biomarkers (serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) of each follow-up visit were collected. Low disease activity (LDA) was defined as DAS28CRP ≤3.2.

This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College of Huazhong University of Science & Technology (project identification code: TJ-IRB20210823). The clinical trial registration ID number is ChiCTR2200056320.

MRI assessment

MRI plain scans of the hands of RA patients were collected from the electronic medical record system. Structural damage scores (erosion and joint space narrowing) were assessed on T1-weighted sequences and inflammation scores (synovitis, tenosynovitis, and bone marrow oedema) were assessed on short tau inversion recovery (STIR) sequences. The sites included for erosion and bone marrow oedema scoring were the wrists (the distal radius, the distal ulnar, the carpals, the base of metacarpals), the metacarpophalangeal (MCP) joints (the head of metacarpals, the base of proximal phalanges), the proximal interphalangeal (PIP) joints (the head of proximal phalanges, the base of middle phalanges) and the interphalangeal joint of the thumb (the head of proximal phalange, the base of distal phalange) (35 sites for erosion scoring and bone marrow oedema scoring); for joint space narrowing scoring were the sites included in the OMERACT Rheumatoid Arthritis MRI Scoring System (RAMRIS) plus the PIP joints and the interphalangeal joint of the thumb (a total of 27 sites for joint space narrowing scoring) (17); for synovitis scoring were the sites included in the RAMRIS plus the carpometacarpal (CMC) joints, the PIP joints and the interphalangeal joint of the thumb (a total of 18 sites for synovitis scoring) (18); for tenosynovitis scoring were the sites included in the RAMRIS (a total of 14 sites for tenosynovitis scoring) (19). The scale of synovitis, tenosynovitis, bone marrow oedema, and joint space narrowing was 0-1 based on the presence of the lesion or not (0: no lesion; 1: visible lesion) for each site. We adopted the scoring method of RAMRIS for erosion scoring: each bone was scored separately and the scale of erosion was 0–10 according to the proportion of eroded bone in the "assessed bone volume" (0: no erosion; 1: 1–10%; 2: 11–20%, etc.). For the carpal bones, "the assessed volume" was the whole bone. While in the long bones, it was from the articular surface to a depth of 1 cm (18). The total score for synovitis, tenosynovitis, bone marrow oedema, erosion, and joint space narrowing was 18, 14, 35, 350, and 27, respectively. MRI was assessed by two experienced readers who were blind to patients' formation. The average scores from the two readers were used as the final score. The erosion rate was calculated by dividing the erosion score by symptom duration.

Data collection and statistical analysis

The baseline data of patients regarding gender, age, smoking (ever vs. never), symptom duration, type of joints first involved, presence of interstitial lung disease (ILD), comorbidity (hypertension, coronary heart disease, diabetes, and low bone mineral density) and MRI images of the hands were collected. The baseline levels of interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), CRP, ESR, RF, and anti-CCP antibodies were assessed. IL-6 and TNF-α were detected by flow cytometry, CRP and RF were evaluated by turbidimetric inhibition immunoassay, ESR was measured by Westergren method, and anti-CCP antibodies were assessed by chemiluminescence. The positivity of AKA was determined by immunofluorescence. Clinical assessments (including PGA, PhGA, DAS28, SDAI, and CDAI), and laboratory parameters (including CRP and ESR) were collected at every follow-up visit. Numeric data were presented as median [IQR] and categorical data were presented as percentages. Mann-Whitney U-test was used to compare the continuous variables and the Chi-square test was used to compare the categorical data. Associations between erosion rate and clinical or MRI factors were determined by simple linear regression. Those factors with p-values <0.05 in the simple linear regression analysis were included in the multiple linear regression and presented as a beta estimate with 95% confidence intervals (CI). p-values <0.05 were considered statistically significant.

Results

Baseline clinical characteristics

A total of 310 newly diagnosed RA patients were included in this study, 151 SPRA patients, and 159 SNRA patients. The baseline characteristics of the two groups, including age, the symptom duration, the percentage of female, the percentage of smoking and the percentage of patients with morning stiffness ≥60 minutes were similar. Patients with small joints or small joints plus large joints first affected were comparable between the two groups. However, more SNRA patients only had large joints involved at the onset of the disease (11.3% *vs*. 22.6%, p=0.010). It is worth noting that SNRA patients had longer symptom duration (7.0 [5.0, 11.0] *vs*. 12.0 [8.0, 16.0], p<0.001), which indicated that SNRA patients experienced a longer time from disease onset to diagnosis than SPRA patients. TJC28, STC28, pain score, PhGA, HAD-DI, SDAI, CDAI, DAS28CRP, and DAS28ESR were significantly higher in SNRA patients, when compared with SPRA patients. Consistent with disease activities and symptoms, SNRA patients had much higher levels of inflammatory biomarkers, including TNF-α, IL-6, ESR, and CRP than the SPRA patients. Besides, SNRA patients had a higher occurrence rate of low bone mineral density (27.0% *vs*. 45.7%, p=0.009). However, more SPRA patients developed ILD than SNRA patients (20.5% *vs*. 10.7%, p=0.019). There was no significant difference in the occurrence rate of hypertension, coronary heart disease, diabetes, and hyperglobulinaemia between the two groups (Table I).

MRI score

All the patients included in this study had MRI scans of their hands at baseline. The erosion score of SPRA pa-

Table I. Comparison of clinical features between SPRA and SNRA at baseline.

	SPRA (n=151)	SNRA (n=159)	*p* value
Female, n (%)	101 (66.9)	105 (66.0)	0.905
Age, years	52.0 [43.0, 60.0]	53.0 [44.0, 61.0]	0.759
Symptom duration, months	7.0 [5.0, 11.0]	12.0 [8.0, 16.0]	<0.001
Smoking, n (%)	50 (33.1)	40 (25.2)	0.134
Location start of symptoms, n (%)			
Small joints	86 (57.0)	79 (49.7)	0.212
Large joints	17 (11.3)	36 (22.6)	0.010
Both	48 (31.8)	43 (27.0)	0.384
Anti-CCP positive, n (%)	125 (82.8)	0 (0.0)	<0.001
RF positive, n (%)	121 (80.1)	0 (0.0)	<0.001
AKA positive, n (%)	81 (53.6)	0 (0.0)	<0.001
TJC28	6.0 [5.0, 8.0]	12.0 [11.0, 14.0]	<0.001
SJC28	4.0 [3.0, 6.0]	7.0 [6.0, 9.0]	<0.001
Pain VAS (mm)	50.0 [40.0, 60.0]	60.0 [50.0, 65.0]	<0.001
PGA VAS (mm)	50.0 [40.0, 60.0]	60.0 [50.0, 65.0]	<0.001
PhGA VAS (mm)	50.0 [40.0, 60.0]	60.0 [50.0, 70.0]	<0.001
Morning stiffness ≥60 minutes, n (%)	43 (28.5)	49 (30.9)	0.710
HAQ-DI	0.9 [0.5, 1.3]	1.0 [0.8, 1.4]	0.005
SDAI	22.8 [19.3, 28.9]	33.6 [30.0, 39.3]	<0.001
CDAI	21.0 [18.0, 25.5]	30.0 [27.0, 35.0]	<0.001
DAS28CRP	4.6 [4.2, 5.1]	5.7 [5.4, 6.0]	<0.001
DAS28ESR	5.2 [4.8, 5.7]	6.3 [5.9, 6.7]	<0.001
CRP (mg/l)	15.4 [10.5, 26.3]	25.8 [16.6, 43.0]	<0.001
ESR (mm/h)	37.0 [31.0, 53.0]	49.0 [38.0, 72.0]	<0.001
TNF-α	14.7 [2.8, 32.5]	34.2 [25.2, 55.2]	<0.001
IL-6	13.4 [5.5, 26.9]	22.6 [14.7, 34.2]	<0.001
Hyperglobulinaemia	61 (40.4)	57 (35.8)	0.905
ILD, n (%)	31 (20.5)	17 (10.7)	0.019
Hypertension, n (%)	21 (13.9)	25 (15.7)	0.750
Coronary heart disease, n (%)	3 (2.0)	3 (1.9)	1.000
Diabetes, n (%)	14 (9.3)	12 (7.5)	0.683
	SPRA (89)	SNRA (94)	
Low bone mineral density, n (%)	24 (27.0)	43 (45.7)	0.009

Values are presented as median [IQR], unless otherwise indicated.
SPRA: seropositive rheumatoid arthritis; SNRA: seronegative rheumatoid arthritis; CCP: cyclic citrullinated peptide; RF: rheumatoid factor; AKA: anti-keratin antibody; TJC28: tender joint count in 28 joints; SJC28: swollen joint count in 28 joints; TJC28: tender joint count in 28 joints; VAS: visual analogue scale; PGA: patient's global assessment; PhGA: physician's global assessment; HAQ-DI: Health Assessment Questionnaire-Disability Index; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; DAS: disease activity score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; TNF: tumour necrosis factor; IL: interleukin; ILD: interstitial lung disease.

Table II. Comparison of MRI scores between SPRA and SNRA at baseline.

	SPRA (n=151)	SNRA (n=159)	*p*-value
Erosion	5.0 [3.0, 10.0]	3.0 [1.0, 7.0]	<0.001
Bone marrow oedema	5.0 [2.0, 8.0]	5.0 [2.0, 8.0]	0.873
Joint space narrowing	3.0 [0.0, 4.0]	3.0 [1.0, 4.0]	0.171
Synovitis	6.0 [4.0, 7.0]	8.0 [6.0, 9.0]	<0.001
Tenosynovitis	2.0 [1.0, 3.0]	2.0 [1.0, 3.0]	0.623

Values are presented as median [IQR].
SPRA: seropositive rheumatoid arthritis; SNRA: seronegative rheumatoid arthritis.

tients was significantly higher than that of SNRA patients (5.0 [3.0, 10.0] *vs*. 3.0 [1.0, 7.0], $p<0.001$), while the synovitis score of SPRA patients was significantly lower than that of SNRA patients (6.0 [4.0, 7.0] *vs*. 8.0 [6.0, 9.0], $p<0.001$], which was consistent with the clinical assessments. There was no difference in the bone marrow oedema score (5.0 [2.0, 8.0] *vs*. 5.0 [2.0, 8.0], $p=0.873$), the joint space narrowing score (3.0 [0.0, 4.0] *vs*. 3.0 [1.0, 4.0], $p=0.171$) and the tenosynovitis score (2.0 [1.0, 3.0] *vs*. 2.0 [1.0, 3.0], $p=0.623$) between SPRA patients and SNRA patients (Table II).

Then, we further analysed the distribution of erosion and synovitis involvement. A total of 484 bones were affected by erosion in 151 SPRA patients and 330 bones in 159 SNRA patients, and we calculated the proportion of each bone involved in all bones with erosion in each group. In both SPRA and SNRA, the most susceptible bones to erosion were the carpal bones. In SPRA, the capitate and the hamate were the most commonly involved, followed by the scaphoid, the lunate, the triquetrum, and the trapezoid. While in the SNRA, the most commonly involved bones were the scaphoid and the lunate, followed by the trapezium, the trapezoid, the capitate, the triquetrum, and the hamate. The least affected bones in both groups were the pisiform and the bones at either end of the interphalangeal joint of the thumb and the MCP joint of the thumb (Fig. 1A-B). As for the distribution of synovitis, a total of 874 joints had synovitis in 151 SPRA patients and 1232 joints in 159 SNRA patients. The joint most prone to synovitis was the midcarpal joint both in SPRA and SNRA patients. In SPRA patients, the midcarpal joint, the third CMC joint, and the second to fourth MCP joints were most susceptible to synovitis. While in SNRA patients, the most common sites for synovitis were the midcarpal joint and the radiocarpal joint (Fig. 1C-D).

The risk factors of erosion

There was a significant difference in bone erosion between SNRA and SPRA, so we investigated the factors associated with the erosion rate in RA patients. The erosion rate was calculated by dividing the erosion score by symptom duration. Firstly, we used the simple linear regression analysis to screen the factors associated with the erosion rate, then factors with p values <0.05 were included in the multiple linear regression analysis. The synovitis score ($\beta=0.229$, $p<0.001$) and smoking ($\beta=0.397$, $p<0.001$) were positively associated with the erosion rate in the SPRA group. The synovitis score ($\beta=0.040$, $p<0.001$), the levels of TNF-α ($\beta=0.004$, $p<0.001$) and IL-6 ($\beta=0.002$, $p=0.004$) and hyperglobulinaemia ($\beta=0.071$, $p=0.002$) were posi-

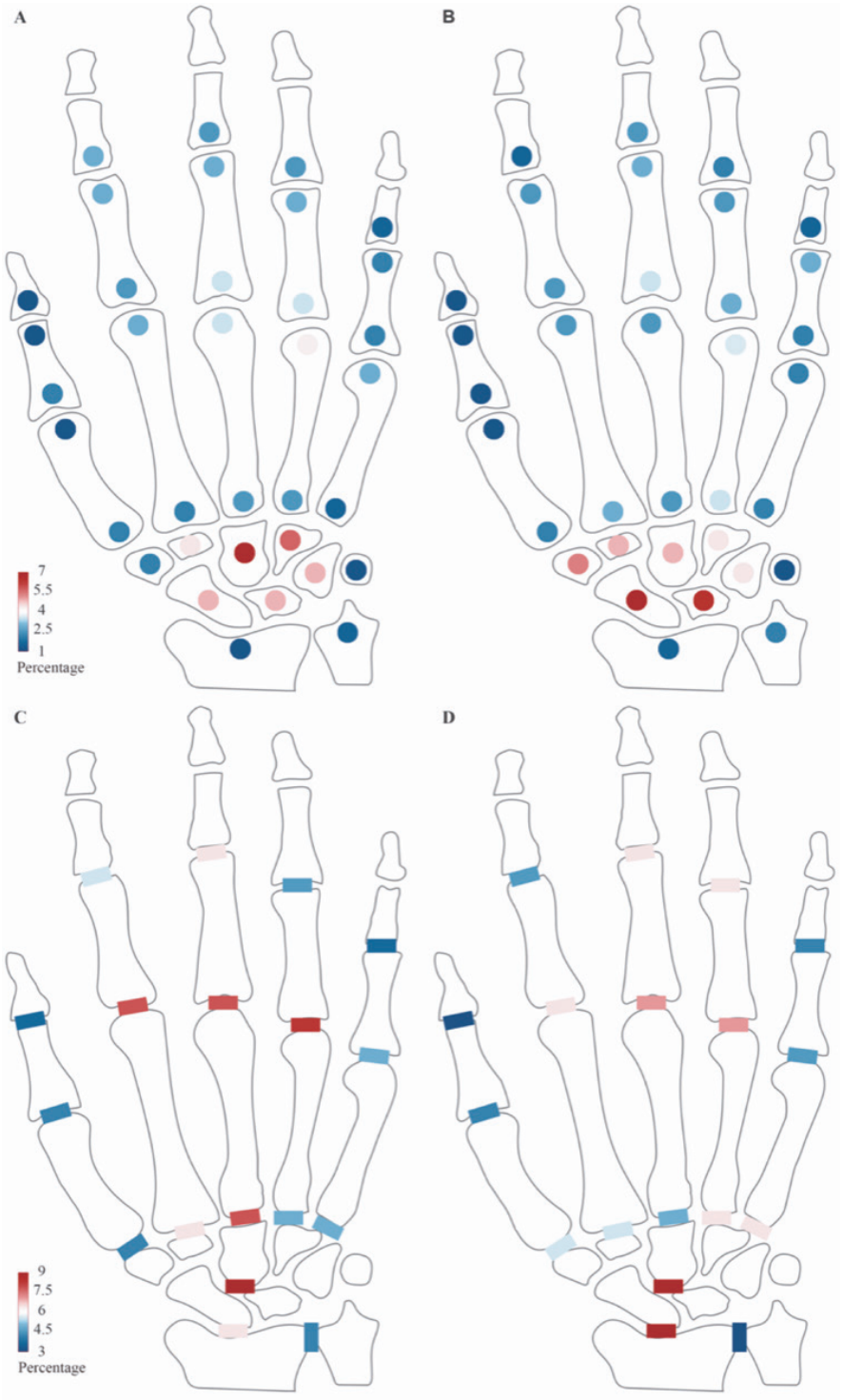

Fig. 1. The distribution of erosion and synovitis involvement of the hands in SPRA and SNRA. There were 35 bones to be assessed for erosion and 18 joints to be assessed for synovitis in each patients. The different colors represent the percentage of the bones or joints involved in the total involved bones or joints.
A: In all SPRA patients, a total of 484 bones had erosion.
B: In all SNRA patients, a total of 330 bones had erosion.
C: In all SPRA patients, a total of 874 joints had synovitis.
D: In all SNRA patients, a total of 1232 joints had synovitis.

tively associated with SNRA patients' erosion rate. Other factors, including age, gender, morning stiffness, ESR, CRP, SJC28, TJC28, PGA, and PhGA were not associated with the erosion rate (Fig. 2A-B).

The response to treatment

There were 102 SPRA patients and 108 SNRA patients who were followed up for 12 months. We further investigated whether there was the difference in treatment response between SPRA and SNRA. The proportion of SPRA patients who reached LDA at 1 month, 3 months, 6 months, and 12 months were 7.8%, 41.2%, 62.7%, and 60.8%, respectively. And those of SNRA patients were 8.3%, 32.4%, 62.0%, and 63.0%, respectively. The treatment response of SPRA and SNRA during the 12-month follow-up was comparable (*p*-values were all >0.05) (Fig. 3A). Then we further compared the treatment response to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) or target/biologic DMARDs (t/bDMARDs) between SPRA and SNRA patients. There was no significant difference between the two groups in treatment response to csDMARDs or t/bDMARDs at 3 months or 12 months (Fig. 3B).

Discussion

In this clinical study, the symptom duration of SNRA patients was much longer than that of SPRA patients. Besides, we found that SNRA patients had higher disease activity and milder structural damage, assessed by both clinically and MRI, than SPRA patients, despite comparable demographic characteristics. The distribution of erosion and synovitis and the risk factors of the erosion rate for SPRA and SNRA were different. Despite these differences above, the treatment response to csDMARDs or t/bDMARDs was comparable between the two groups.

The 2010 ACR/EULAR criteria emphasise the status of RF and anti-CCP antibodies. Only one affected joint is sufficient to fulfill the criteria for SPRA patients, while more than 10 affected joints are needed for SNRA patients to fulfill the same criteria. This could be the reason for SNRA patients experiencing a longer time from symptom onset to diagnosis which was observed in our study as the patients included in our study were all newly diagnosed at baseline. Besides, as more SNRA patients only had large joints involved at the on-

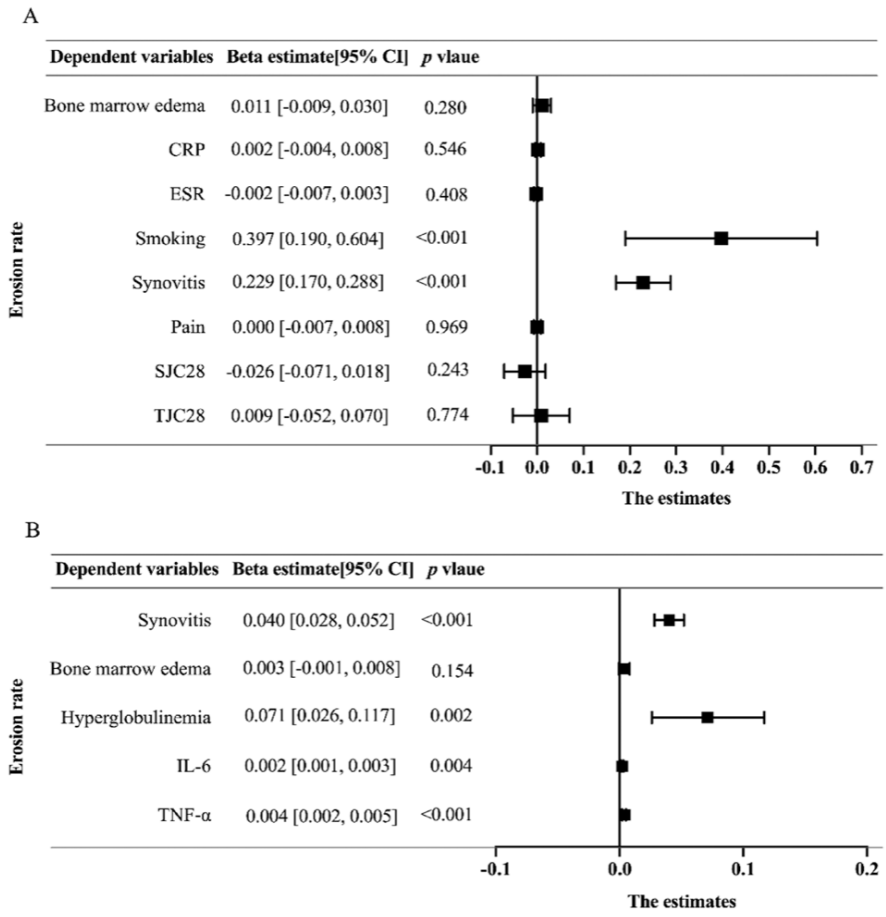

Fig. 2. Forest plot of multiple linear regression analysis of the erosion rate for SPRA (**A**) and SNRA (**B**). The erosion rate was calculated by dividing the erosion score by symptom duration. Independent variables were selected by simple linear regression, those variables with $p<0.05$ were included in multiple linear regression.
IL: interleukin; TNF: tumour necrosis factor; ESR: erythrocyte sedimentation rate; SJC28: swollen joint count in 28 joints; TJC: tender joint count in 28 joints.

set of the disease, which suggests that the joints first affected of SPRA and SNRA patients were not similar and a new method to diagnose SNRA alone may be needed. Synovitis and erosion are the characteristic features of MRI of RA patients, and our study found that the scaphoid and the lunate were most prone to erosion, followed by other carpals, and the midcarpal joint and the radiocarpal joint were most prone to synovitis in SNRA. In the future, we should pay more attention to the wrist to help us diagnose SNRA. SNRA patients had more involved joints and higher disease activity compared with SPRA patients, which is consistent with the results of two previous studies (8, 20). This may be caused by delayed diagnosis and treatment. Other seasons related to this result need more experiments to find out.

The prevalence of ILD varies from 7.7% to 67% among RA patients and the exact pathogenesis of RA-associated ILD is still elusive (21-24). In our study, the rate of ILD in SPRA patients was significantly higher than in SNRA patients. The previous study had also reported that ACPA was associated with lung involvement in early RA patients and higher ACPA titer was related to the increasing rate of ILD (25, 26). It has been proposed that the immune

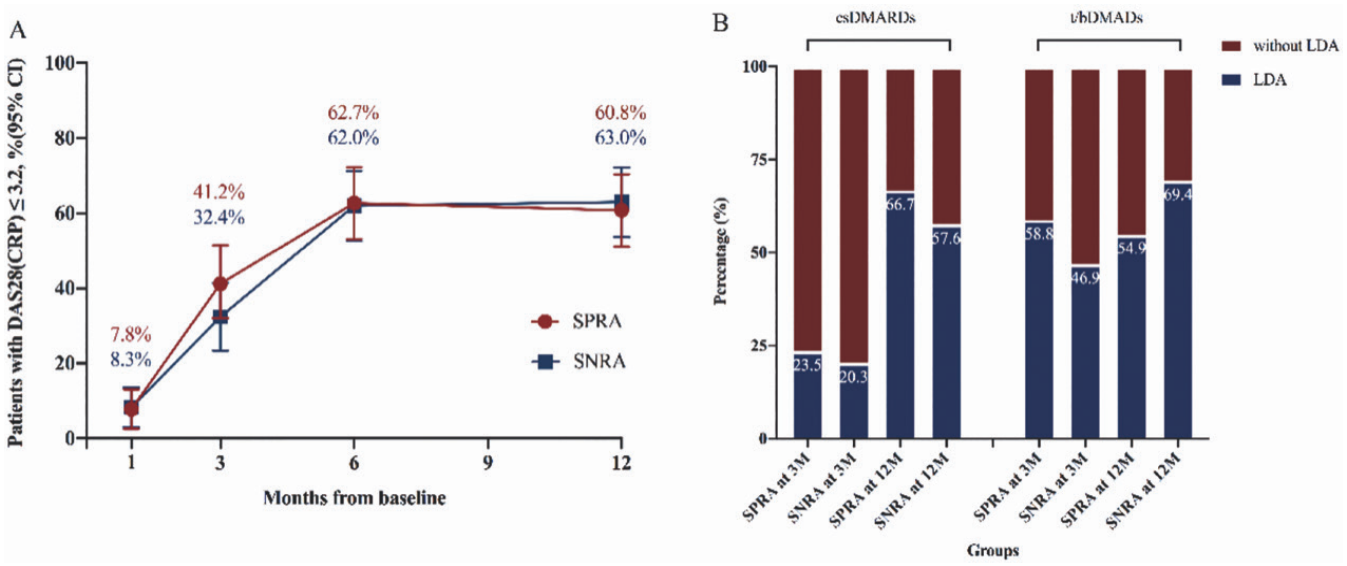

Fig. 3. Comparison of the treatment response during 12-month follow-up between SPRA and SNRA.
A: The rate achieving low disease activity (DAS28CRP ≤3.2) at 1 month, 3 months, 6 months, 9 months and 12 months between SPRA and SNRA was similar.
B: The treatment response to csDMARDs or t/bDMARDs at 3 months or 12 months between SPRA and SNRA was similar.

response against citrullinated peptides not only takes place in joints, but also in the lungs, resulting in interstitial lung inflammation and a higher prevalence of ILD in SPRA patients (27).

RA patients complicated with systemic bone loss can be related to many risk factors, such as menopause, inflammation, and glucocorticoid (28). Our data showed that the incidence of low bone mineral density was higher in SNRA patients than in SPRA patients (45.7% *vs*. 27.0%, p=0.009). It has been reported that periarticular bone loss of RA patients was correlated with local overexpression of IL-6 (29). Inflammation-related bone loss in juvenile collagen-induced arthritis rats was reduced by tocilizumab (an antibody that binds the IL-6 receptor) (30). Palmqvist *et al*. proved that IL-6 or soluble IL-6 receptor-induced osteoblasts to produce more receptor activators of nuclear factor ϰB ligand (RANKL), resulting in osteoclast formation and bone resorption in neonatal mouse calvaria (31). Besides, several studies had showed that disease activity contributed to periarticular bone loss or osteoporotic fractures (32, 33). In our study, SNRA patients had much higher levels of TNF-α and IL-6, as well as a higher occurrence of low bone mineral density. All the above evidence suggests a negative effect of IL-6 and TNF-α on bone mass and SNRA patients were more susceptible to low bone mineral density. So in the management of SNRA, the test of bone mineral density should be considered in the routine exam.

Compared with SNRA patients, SPRA patients had more severe bone erosion and the distribution of erosion involvement was different between the two groups. However, erosion damage predominantly occurred in the wrist both in SNRA and SPRA, which was consistent with the study by Gadeholt (34). Several studies had proved that SNRA patients had less structural damage and less radiographic progression assessed by x-ray, and the presence of ACPA was recognised as one of the best clinical predictors of radiological progression (7, 34-36). So we analysed the risk factors of erosion rate for SPRA and SNRA separately. In our multivariate analysis, synovitis was the risk factor of the erosion rate both in SPRA and SNRA which suggested that patients with severe inflammation need a more strict strategy to prevent disease progression. Previous studies have reported that smoking was a risk factor for ACPA positivity and symptom development, and the positivity of ACPA was associated with radiographic progression (7, 37). Therefore, in SPRA, smoking may accelerate the erosion progression by promoting the production of ACPA. The hyperglobulinaemia were the risk factors for SNRA, so more attention should be paid to SNRA patients with hyperglobulinaemia.

As hyperglobulinaemia was the risk factor only for SNRA patients in our study, it may suggest that SNRA patients with hyperglobulinaemia were not real seronegative but existed other undetected autoantibodies. But some researchers have proposed that SNRA may be a different type of disease from SPRA. A recently published article on single-cell sequencing of ACPA- and ACPA+ RA patients had shown that the expression of cytotoxic and exhaustion-related genes in the synovial tissues of ACPA-RA patients were lower, suggesting the cellular and molecular pathways involved in the pathogenesis of SNRA and SPRA were different (38). Besides, the specific risk factors, the pre-clinical history, and the treatment response to methotrexate or drugs targeting adaptive immunity were different between SNRA and SPRA (39). More studies are needed to clarify why there are so many differences between SPRA and SNRA.

Although the clinical characteristics were obviously different between SPRA and SNRA patients, the response to csDMARDs or t/bDMARDs between SPRA and SNRA patients during 12-month follow-up was comparable. Similarly, in the study of Nordberg LB, SNRA and SPRA patients were treated with csDMARDs or t/bDMARDs and the treatment response was similar across groups (10). Conversely, other studies had showed that SPRA patients responded better than SNRA patients to rituximab, abatacept and non-TNF inhibitors (TNFi) bDMARDs (12, 40, 41). We just compared the overall treatment response rather than one specific treatment regimen and this may be the reason for the inconsistence of results between ours and other studies.

There are some limitations to be considered for this study. Firstly, the relatively small sample size of each group, the nature of patients included in this study, and the nature of single-centre study may cause potential bias. Prospective multicentre cohort studies with a larger sample size are needed to further confirm the generalisability of our findings. Secondly, MRI of RA patients we used was not contrast-enhanced MRI, so we cannot use the methods of RAMRIS to assess synovitis, tenosynovitis, bone marrow oedema and joint space narrowing. However, MRI plain scan is more available and had lower risk (for example, allergic reaction). It is necessary to develop a new simplified score system based on MRI plain scan and our study provides a referable assessment method. Our study firstly investigated the use of MRI plain scan on RA patients and analysed the clinical, laboratory and imaging characteristics of SNRA and SPRA, as well as the risk factors associated with the erosion rate, providing referable information for clinical physicians to recognise early seronegative RA patients or make a more appropriate decision.

In conclusion, this clinical study showed that SNRA patients had a higher level of inflammation both in clinical and MRI assessments but less severe erosion compared with SPRA patients. SNRA patients with severe inflammation or hyperglobulinaemia need the same powerful therapeutic regimens of SPRA to prevent structural damage progression.

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