European Review for Medical and Pharmacological Sciences 2020; 24: 9797-9806

A nomogram to predict recurrence of RA patients in clinical remission within one year

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Abstract. – OBJECTIVE: Some patients with rheumatoid arthritis (RA) will recur despite they have achieved clinical remission after treatment. The subclinical synovitis detected by ultrasonography (US) may be one of the main causes of the RA recurrence. The aim of this study is to establish a nomogram for predicting the outcome of RA patients with disease in clinical remission.

PATIENTS AND METHODS: One hundred and sixty-seven RA patients who achieved clinical remission and were willing to receive a 1-year follow-up were included in this study. Their demographic, clinical, and laboratory characteristics were recorded at baseline. 7-joints ultrasound (US7) synovitis score (simplified from US7 score) were evaluated at baseline and at the end of follow-up (or when RA recurrence confirmed). All patients were divided into recurrence group and non-recurrence group after the follow-up. Multivariable regression was applied to link the predictors that were significant at $p < 0.05$ in the univariate analysis and the recurrence of RA patients in clinical remission, which was served as the basis of the nomogram.

RESULTS: Fifty-one RA patients were included in the recurrence group and 116 patients in the non-recurrence group. All US7 synovitis scores in this study showed excellent reproducibility. Multivariable analysis revealed that high-titer positive anti-cyclic citrullinated peptide (anti-CCP), simplified clinical disease activity index (SDAI), baseline grayscale ultrasound (GSUS) score, and baseline power Doppler ultrasound (PDUS) score were the independent predictors for RA recurrence within 1 year. A nomogram incorporating the independent predictors was constructed to predict the risk of RA recurrence. The nomogram showed good discrimination (C-index=0.826) and good calibration.

CONCLUSIONS: The nomogram incorporating anti-CCP, SDAI, and subclinical synovitis helps to achieve complete remission and reduces the risk of short-term recurrence of RA patients.

Key Words:

7 joint ultrasonic score, disease activity score in 28 joints, Rheumatoid arthritis, Clinical remission, Prognosis.

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease with synovitis as the first pathological change. It will result in progressive joint destruction and functional disability[1]. At present, the ideal target of RA treatment is obtaining clinical remission for preventing joint destruction and disability[2]. However, the definition of the remission state is complex[3,4]. Although many definitions have been proposed, no consensus has been reached until now. Currently, disease activity score in 28 joints (DAS28) is commonly used to evaluate the clinical remission[5], but some reports suggest that RA patients will recur despite apparent clinical remission (DAS28 $\leq$ 2.6)[6,7], which indicates the inaccuracy of DAS28 in the evaluation of the disease activity.

It has been proved that subclinical synovitis is one of the main causes of the RA recurrence even after the clinical remission is achieved[8,9]. Subclinical synovitis refers to the synovitis detected under ultrasonography (US) or magnetic resonance imaging (MRI), but no tender or swollen joint is found in physical examination[10,11]. US and MRI are considered superior to physical examination because of their direct, sensitive, and specific visualization of inflammatory lesions and structural damage[12]. Moreover, US is more suitable for the detection of subclinical synovitis during clinical remission since MRI is limited in frequent assessments. Brown et al[13] found persistent inflammation by US and MRI in RA patients who had achieved clinical remission, which might explain

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the discrepancy between clinical remission and outcome in RA. Peluso et al[14] reported that about 47.1% of RA patients would recur after achieving remission and the presence of subclinical synovitis was common in most of them. These studies reveal that the clinical remission evaluated by DAS28 does not seem to sufficiently reflect an absence of inflammation and the subclinical synovitis measured by US may explain the disease progression in clinical remission. However, there are still limited reports about the prediction of RA recurrence after achieving clinical remission *via* the presence of subclinical synovitis.

According to the 7-joints ultrasound (US7) score proposed by Baekhaus et al[15], this investigation simplified and only observed the joint synovitis of RA patients with clinical remission (Tenosynovitis and bone erosion are rare in clinical remission). A nomogram was built to evaluate the recurrence risk of RA patients in clinical remission within one year. The aim of this study is to establish an accurate prediction model to evaluate the outcome of RA patients with disease in remission and try to improve the long-term prognosis by utilizing the model as the treatment target for RA.

Patients and Methods

Patients

This prospective cohort study was approved by the Ethics Committee of the Affiliated Hospital of Guizhou Medical University (No. 2019LSD296). Written informed consents were obtained from all patients. From January 2016 to October 2018, 178 newly diagnosed RA patients (mean age 54.34 ± 10.25 years, disease duration ≤ 2 years, 42 males and 136 females) were included[16]. All patients achieved clinical remission (DAS28 ≤ 2.6)[5] and maintained for 6-9 months after treatment with conventional disease-modifying antirheumatic drugs (cDMARDs) (methotrexate 10 mg qw combined with Iguratimod 25 mg bid or leflunomide 10 mg bid), or biologic disease-modifying antirheumatic drugs (bDMARDs) (adalimumab 40 mg biw in combination with CDMARDs). Patients complicated with other autoimmune diseases, arthrotrauma, infection, or other diseases that could interfere with the protocol were excluded. The general information about the demographic data (age, gender, and disease duration) and data on clinical and quality of life variables, including swollen and tender joint counts, morning stiffness time, pain assessment by visual analog scale, and health assessment questionnaire score were collected. Laboratory assessments included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF) (stratified into negative: <20 U/ml, low-titer positive: 20-200 U/ml, and high-titer positive: >200 U/ml), and anti-cyclic citrullinated peptide (anti-CCP) (stratified into negative:<15 U/ml, low-titer positive: 15-200 U/ml, high-titer positive: >200 U/ml). For each patient, the disease activity was defined by DAS28 (ESR)[17], clinical disease activity index (CDAI)[18], and simplified clinical disease activity index (SDAI)[19], respectively.

Musculoskeletal Ultrasound

Musculoskeletal ultrasonography was performed with LOGIQ E9 US imaging system (GE Healthcare, Milwaukee, Wis., USA). The ultrasound examination and US7 synovitis score (simplified from US7 score[15]) were independently and blindly performed by 2 sonographers with more than 10 years of experience in musculoskeletal ultrasound. The hand and forefoot which were more clinically affected by tenderness or swelling were chosen. The synovial hyperplasia and the pathogenic vascularization can be evaluated by grayscale ultrasound (GSUS) and power Doppler ultrasound (PDUS) (Figure 1). Subclinical synovitis was defined as an abnormally hypoechoic region beneath the joint capsule that is immobile and difficult to compress. The US7 synovitis score was calculated according to the criterion in Table I[15].

Follow-up

All RA patients were followed up for 1 year. DAS28 was evaluated at baseline and at the 3rd, 6th, and 12th month. The definition of RA recurrence is that a DAS28 >2.6 or an increase of DAS28 greater than 0.6 compared to the baseline at one or more follow-up visits was recorded. Ultrasonography was performed and US7 synovitis score was evaluated at baseline and at the end of follow-up (or when RA recurrence confirmed). All patients were divided into recurrence group and non-recurrence group according to the follow-up outcome.

Statistical Analysis

The intraobserver and interobserver reliability of US7 synovitis score was tested by Bland-Altman analysis and intraclass correlation coefficient (ICC) (ICC>0.75 indicates good reliability).

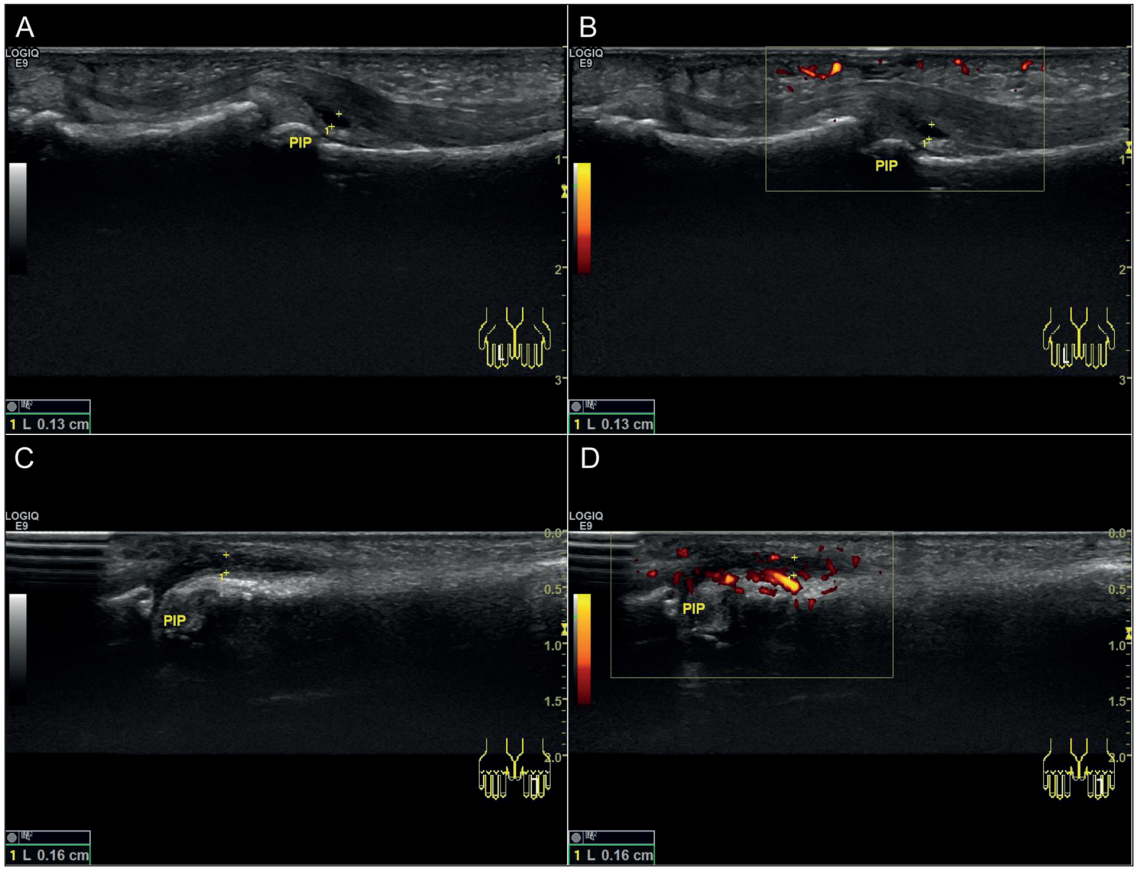

Figure 1. Ultrasonic characteristics of subclinical synovitis in RA patients with disease in clinical remission. Synovitis is present in 2 different PIP joints. One shows mild synovitis with no power Doppler signal (GSUS=1, PDUS=0, Figure A and B) and the other shows moderate synovitis with hypervascularized signal (GSUS=1, PDUS=1, Figure C and D). RA: Rheumatoid arthritis, GSUS: grayscale ultrasound, PDUS: Power Doppler ultrasound, PIP: proximal interphalangeal.

Kaplan-Meier survival analysis was performed for the RA recurrence. The comparison was performed between the recurrence group and non-recurrence group for univariate analysis (independent sample *t*-test for normally distributed continuous data, Mann-Whitney U test for nonnormally distributed continuous data, and chi-square test for categorical data). Multivariable Cox regression was used to link the predictors that were significant at $p < 0.05$ in the univariate analysis and the

Table I. Criterion of US7 synovitis score.

Score	Wrist	MCP II and III	PIP II and III	MTP II and V
GSUS (0-27)	Dorsal view 0-3 Ventral view 0-3 Lateral view 0-3	Ventral view 0-3	Ventral view 0-3	Dorsal view 0-3
PDUS (0-39)	Dorsal view 0-3 Ventral view 0-3 Lateral view 0-3	Dorsal view 0-3 Ventral view 0-3	Dorsal view 0-3 Ventral view 0-3	Dorsal view 0-3

qRT-PCR, quantitative a MCP: metacarpophalangeal; PIP: proximal interphalangeal; MTP: metatarsophalangeal; GSUS: Grayscale ultrasound; PDUS: Power Doppler ultrasonography. US7: 7-joints ultrasound GSUS on a scale of 0-3, 0=absence; 1=a small hypoechoic/anechoic line beneath the joint capsule; 2=joint capsule elevated parallel to the joint area; 3=a strong distension of the joint capsule. PDUS on a scale of 0-3, 0=no intraarticular color signal; 1=up to 3 color signals or 2 single and 1 confluent signal in the intraarticular area; 2=<50% of the intraarticular area filled with color signals; 3=≥50% of the intraarticular area filled with color signals.-Transcription Polymerase Chain Reaction.

recurrence during follow-up, which was served as the basis of the nomogram. The performance of the nomogram was assessed by Harrell's concordance index (C-index)[20]. Bootstrap resampling (1,000 times) was used for internal validation[21]. Calibration plots for the incidence of recurrence were plotted to compare the predicted and observed incidence after the bias correction of bootstrap resampling. All analyses were performed with SPSS (version 22.0; SPSS Inc., Chicago, IL, USA), Medcalc software (version 11.0, Ostend, Belgium), and R package version 3.6.2.

Results

Intraobserver and Interobserver Reliability of US7 Synovitis Score

The interobserver agreements of the two sonographers were excellent for US7 synovitis score at baseline (ICC = 0.94) and at the end of follow-up (ICC = 0.90). The US7 synovitis scores evaluated by sonographer-1 and sonographer-2 showed excellent intraobserver agreement (sonographer-1: ICC = 0.97, 0.96; sonographer-2: ICC = 0.98, 0.97). All US7 synovitis scores in this study showed excellent reproducibility. Visual assessment of Bland Altman plots did not reveal any systematic intra- and interobserver bias (Figure 2).

Recurrence of RA Patients With Disease in Remission

Of the 178 RA patients, 11 of them were lost to follow-up and the 167 patients who completed the follow-up were included in this study. Totally 51 RA patients suffered recurrence (recurrence rate 30.5%) were included in the recurrence group, and the remaining 116 patients were included in the non-recurrence group (Figure 3).

Baseline Information of RA Patients Between Two Groups

The baseline demographic, clinical, and laboratory characteristics between the two groups are shown in Table II. The proportion of high-titer anti-CCP positive expression, SDAI in the recurrence group were greater than those in the non-recurrence group ($p<0.05$).

Comparison of US7 Synovitis Score Between the Two Groups

AT baseline, the GSUS score, PDUS score, and US7 synovitis score in the recurrence group were greater than those in the non-recurrence group

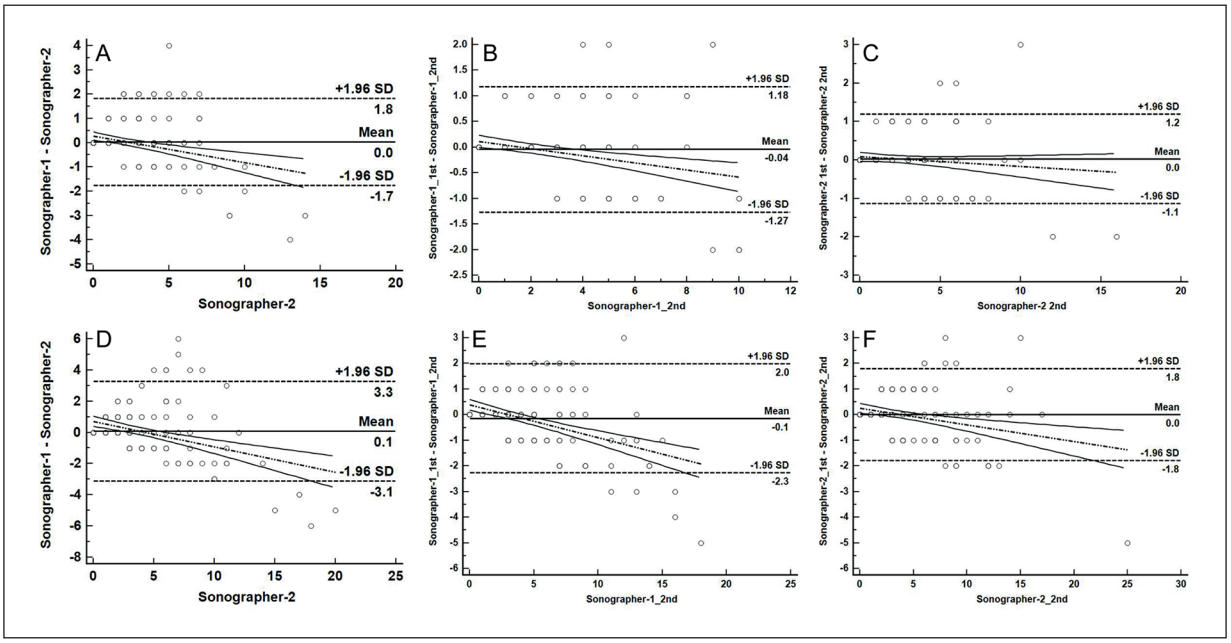

Figure 2. Bland-altman analysis of US7 synovitis score at baseline and at the end of follow-up. At baseline, the interobserver agreement is shown in (**A**), and the intraobserver agreements are showed in (**B**) for sonographer-1 and (**C**) for sonographer-2. At the end of follow-up, the interobserver agreement is shown in (**D**), and the intraobserver agreements are showed in (**E**) for sonographer-1 and (**F**) for sonographer-2. US7: 7-joints ultrasound.

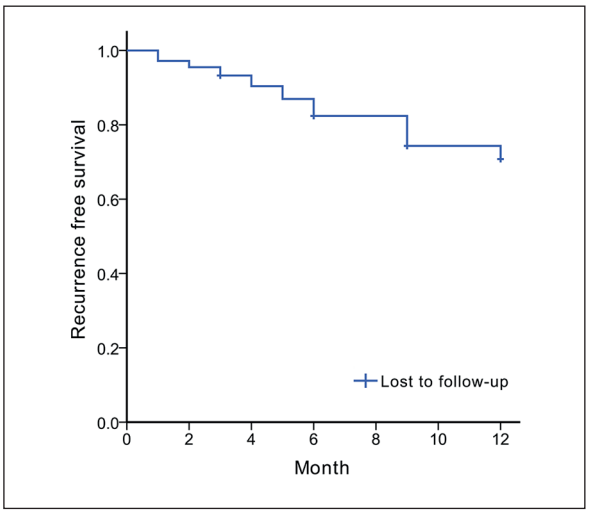

Figure 3. Kaplan-Meier analysis of the outcome of RA patients with disease in remission. The recurrence rate within one year was 30.5%. RA: rheumatoid arthritis.

(p<0.05). The proportion of imaging remission in the recurrence group was lower than that in the non-recurrence group (p<0.05). At the end of follow-up, the GSUS score, PDUS score, and US7 synovitis score were higher than those at baseline. The differences in US7 synovitis score related variables between the two groups were more significant (p<0.05) (Table III).

Multivariate analysis for the Alternative Predictors Associated with the RA Recurrence within 1 Year

The results of the univariate analysis indicated that high-titer positive anti-CCP, SDAI, baseline GSUS score, and baseline PDUS score were associated with the risk of RA recurrence within 1 year (Table II and Table III). Multivariate analysis further revealed that these variables were the independent predictors for RA recurrence (Figure 4). A nomogram incorporating the independent predictors was constructed to predict the risk of RA recurrence within 1 year (Figure 5).

Validation of the Nomogram

The nomogram had a bias-corrected C-index of 0.826, which indicated a good discrimination (> 0.75) (Figure 6). No significant difference was observed between the predicted and the observed probabilities of RA recurrence within 1 year, which demonstrated a good calibration between the prediction by nomogram and the actual observation (Figure 7).

Table II. Comparison of the baseline demographic, clinical, and laboratory characteristics between the two groups.

Variables		Recurrence group (n = 51)	Non-recurrence group (n = 116)	p
Gender (Male/Female)	11/40	26/90	0.904*	
Age (years)	53.25 ± 10.48	54.03 ± 10.93	0.671#	
Stage	Low-activity	0 (0%)	13 (11.20%)	0.418*
	Moderate-activity	26 (50.98%)	52 (44.83%)	
	Severe-activity	25 (49.02%)	51 (43.97%)	
RA duration (months)	10 (9, 14)	10 (8, 12.75)	0.122$	
Duration of remission (months)	7 (7, 9)	8 (6, 9)	0.877$	
RF	negative	12 (23.5%)	23 (19.8%)	0.769*
	Low-titer positive	20 (39.2%)	52 (44.8%)	
	High-titer positive	19 (37.3%)	41 (35.4%)	
Anti-CCP	Negative	3 (5.9%)	21 (18.1%)	0.013*
	Low-titer positive	13 (25.5%)	34 (29.3%)	
	High-titer positive	35 (68.6%)	61 (52.6%)	
DAS28	1.5 (1.0, 2.1)	1.6 (1.2, 2.0)	0.630$	
CDAI	2.8 (2.2, 4.1)	3.1 (2.0, 3.8)	0.729$	
SDAI	3.1 (2.0, 4.1)	2.6 (1.8, 3.7)	0.025$	
Treatment	cDMARDs	40 (78.4%)	97 (83.6%)	0.421
	bDMARDs	11 (21.6%)	19 (16.4%)	

RA: Rheumatoid arthritis, RF: rheumatoid factor, Anti-CCP: anti-cyclic citrullinated peptide, DAS28: disease activity score in 28 joints, CDAI: clinical disease activity index, SDAI: simplified clinical disease activity index. CDMARDs: conventional disease-modifying antirheumatic drugs (methotrexate 10 mg qw combined with Iguratimod 25 mg bid or leflunomide 10 mg bid), bDMARDs: biologic disease-modifying antirheumatic drugs (adalimumab 40 mg biw in combination with CDMARDs). *for chi-square test; #for independent sample t-test; $for Mann-Whitney U test.

Table III. Comparison of US7 synovitis score of RA patients between two groups.

Variables		Recurrence group (n = 51)	Non-recurrence group (n = 116)	p
Baseline	Number with GSUS-positive	2 (1, 4)	1 (0, 2)	0.000$
	GSUS score	4 (2,5)	2 (0, 2)	0.000$
	Number with PDUS-positive	1 (0, 1)	0 (0, 1)	0.000$
	PDUS score	1 (0, 2)	0 (0, 1)	0.000$
	US7 synovitis score	5 (2, 7)	2 (0, 3)	0.000$
	Number(%) with imaging remission) (GSUS score+ PDUS score=0	11 (21.6%)	57 (49.1%)	0.000*
End of follow-up	Number with GSUS-positive	4 (3, 5)	1 (0.25, 2)	0.000$
	GSUS score	5 (3, 8)	2 (0.25, 2)	0.000$
	Number with PDUS-positive	1 (1, 2)	0 (0, 1)	0.000$
	PDUS score	2 (1, 3)	0 (0, 1)	0.000$
	US7 synovitis score	7 (4, 10)	2 (0.25, 3)	0.000$
	Number(%) with imaging remission (GSUS score+ PDUS score=0)	0 (0%)	29 (25.0%)	0.000*

RA: Rheumatoid arthritis, RF: rheumatoid factor, Anti-CCP: anti-cyclic citrullinated peptide, DAS28: disease activity score in 28 joints, CDAI: clinical disease activity index, SDAI: simplified clinical disease activity index. GSUS: grayscale ultrasound, PDUS: power Doppler ultrasound.*for chi-square test; $for Mann-Whitney U test.

Utility of the Nomogram

The nomogram could be utilized to calculate the scores corresponding to each independent predictor of RA recurrence, and the predicted probability corresponding to the sum of the scores was the risk of RA patients in clinical remission suffering recurrence within 1 year. It could help select the patients with a high risk of recurrence and develop preventive treatment strategies. So, when a RA patient in clinical remission with high-titer anti-CCP positive expression, 4 in SDAI, 4 in baseline GSUS score, and 2 in baseline PDUS score, the total score was about 180. It indicated that the probability of recurrence was about 62%. Clinicians could choose some appropriate treatments according to the result to avoid the recurrence.

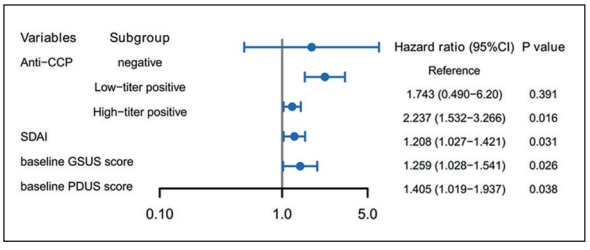

Figure 4. Forest plot of the multivariate COX regression analysis for independent predictors of RA recurrence within 1 year. Anti-CCP: anti-cyclic citrullinated peptide, SDAI: simplified clinical disease activity index. GSUS: grayscale ultrasound, PDUS: power Doppler ultrasound, 95% CI: 95% confidence interval.

Discussion

Our study demonstrated that US7 synovitis score is feasible in the evaluation of subclinical synovitis for RA patients with disease in clinical remission. According to the multivariate analysis, we found that high-titer positive anti-CCP, SDAI, baseline GSUS score, and baseline PDUS score were predictive for the recurrence of RA patients in clinical remission within 1 year. The nomogram constructed in this research showed good discrimination and calibration and could

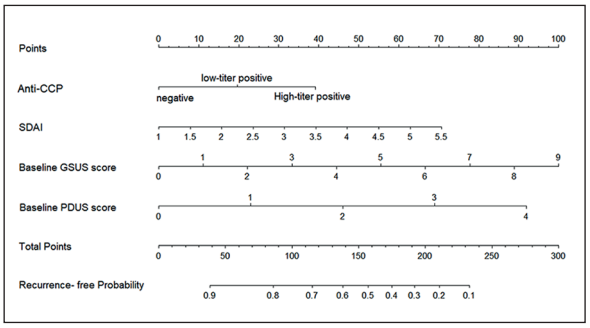

Figure 5. The nomogram incorporating the risk factors of Anti-CCP, SDAI, baseline GSUS score, and baseline PDUS score to predict the RA recurrence within 1 year. The nomogram can be used to obtain the probability of RA recurrence by adding up the points identified on the point scale for each variable. Anti-CCP: anti-cyclic citrullinated peptide, SDAI: simplified clinical disease activity index. GSUS: grayscale ultrasound, PDUS: power Doppler ultrasound.

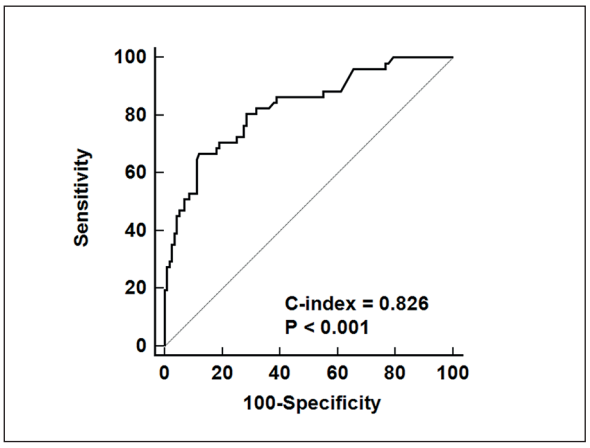

Figure 6. The receiver operating characteristic curve for the discrimination of the nomogram to predict RA recurrence within 1 year. The C-index is 0.826 (95% CI: 0.760 - 0.881). RA: Rheumatoid arthritis

be utilized to calculate the probability of RA recurrence within 1 year.

Recurrence of RA Patients in Clinical Remission

In this study, 30.5% of RA patients in clinical remission suffered recurrence within 1 year, which was similar to the report of Foltz et al[22]. It indicates that "clinical remission" as defined by DAS28<2.6 seems not be used as a criterion of remission to prevent joint destruction. It may be an inaccurate measurement of the subclinical inflammation since it may allow the presence of tender or swollen joints. It has been reported that subclinical synovitis develops in patients with

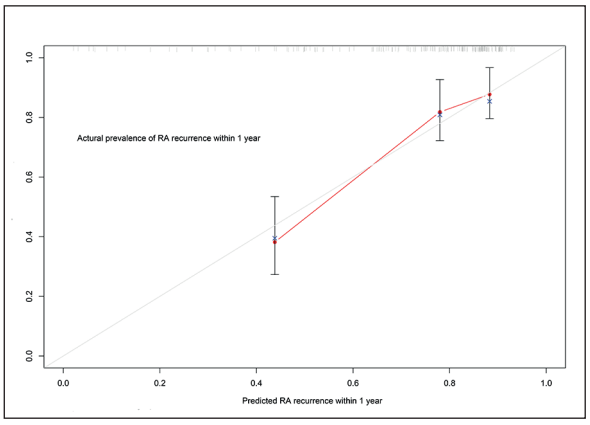

Figure 7. Calibration curve for predicting RA recurrence within 1 year. The red line along the dashed line indicates that the predicted prevalence is close to the actual prevalence. RA: Rheumatoid arthritis.

clinical remission according to "DAS28<2.6"[9], which may be missed in physical examination. Subclinical synovitis has been proven to be an important factor for the recurrence in RA patients.

Advantage of US7 Synovitis Score

High-frequency musculoskeletal ultrasonography is capable of directly visualizing and objectively quantifying subclinical synovitis. It is reported to be more accurate and reliable in the measure of RA disease activity than physical examination and may be more useful for the early diagnosis, efficacy evaluation, and long-term prediction of recurrence during clinical remission[23,24]. In addition, the radiographic characteristics of patients with the same disease activity may be different, so ultrasonographic evaluation is more suitable for individualized treatment. At present, there are many kinds of ultrasound examination methods for RA but no consensus is reached. The scoring methods, such as US22, US28, and US78 involve many joints, resulting in a long duration of examination. Based on the US7 score proposed by Backhaus et al[15], we only evaluated the synovitis score in 7 joints and removed the bone erosion and tenosynovitis score, which are weakly related to the RA patients in clinical remission. The duration of examination for each patient was 10-15 min, which is feasible in the daily efficacy evaluation. The US7 synovitis scores in this study showed excellent intra- and interobserver, which indicated good repeatability and could be widely used in the clinical setting. Our study found that 99 RA patients (59.3%) with subclinical synovitis were detected by US7 synovitis score, which was consistent with the detection rate of Hurnakova et al[25] (58% by US7), and Geng et al[26] (51.4% by US22). It implied that the US7 synovitis score was accurate in the detection of subclinical synovitis as well compared with other multi-joint scores. Meanwhile, it is more efficient and easier to apply.

Predictors for the Recurrence of RA Patients in Clinical Remission

The proportion of high-titer positive anti-CCP, SDAI, baseline GSUS score, and baseline PDUS score in the recurrence group were significantly higher than those in the non-recurrence group. Multivariate analysis suggested that anti-CCP, SDAI, baseline GSUS score, and baseline PDUS score can independently predict the recurrence of RA. It suggested that besides baseline US7 syno-

vitis score, anti-CCP and SDAI were predictive for the short-term recurrence of RA patients in clinical remission as well.

Anti-CCP is an antibody mainly based on IgG type, which has important significance in the clinical diagnosis of RA[27]. Du et al[28] reported that anti-CCP is feasible in the prediction of the RA prognosis. Patients with high-titer positive anti-CCP are more likely to develop joint destruction. Nevertheless, the relationship between anti-CCP and disease activity is still controversial. The results of our study found that the number of subclinical synovitis joints increased in patients with high-titer positive anti-CCP, and the proportion of recurrence was higher, suggesting that high-titer positive anti-CCP may be related to the increase in the number of subclinical synovitis joints. Therefore, musculoskeletal ultrasonography should be performed for patients with high-titer positive anti-CCP to further evaluate the subclinical synovitis of RA patients.

SDAI and CDAI are two new scores for the evaluation of RA disease activity[29]. They have not been developed to replace DAS28, but rather to provide physicians and patients with simple and more comprehensible instruments. Sfriso et al[30] found that 35.8% of RA patients achieved clinical remission if DAS28 was used as the evaluation standard. However, when SDAI and CDAI were used as criteria, only 14.7% and 17.9% of RA patients achieved clinical remission, which indicated that SDAI and CDAI were relatively stricter than DAS28. In this study, SDAI was an independent predictor of RA recurrence (not CDAI). This suggested that SDAI might be more effective than CDAI in evaluating the prognosis of RA.

Nomogram as a Convenient Tool for Predicting the RA Recurrence

The nomogram built on the multiple independent predictors has been identified as a useful and convenient tool for disease prediction. Therefore, we plotted and verified a nomogram to overcome the shortage of DAS28 as a means of RA outcome prediction and treatment guidance for RA patients. The present nomogram incorporating high-titer positive anti-CCP, SDAI, and baseline US7 synovitis score was capable of identifying the patients in clinical remission who may suffer recurrence within 1 year. Moreover, the plotted nomogram showed good discrimination (0.826 in C-index), and the calibration plot implied a good fit. When a patient in clinical remission is ready to receive maintenance therapy. It is useful to consult this nomogram whether the patient has the risk of recurrence within 1 year. By using this nomogram, the decision-making regarding the management of patients in clinical remission is hoped to be improved.

Limitation

Due to the limitation of the sample size, the nomogram has not been externally verified in different populations. Besides, this is an observational study and only RA patients with disease duration ≤ 2 years and maintained clinical remission for 6-9 months were included to minimize the selective bias. Larger-scale randomized controlled trials are needed to confirm our present findings, which will be forthcoming in a subsequent report.

Conclusions

We demonstrated that the US7 synovitis score was efficient to detect subclinical synovitis in daily efficacy evaluation. To our knowledge, this is the first nomogram incorporating baseline US7 synovitis score to predict the recurrence of RA patients with clinical remission. We believe that it will help to achieve complete remission and reduce the short-term recurrence risk of RA patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

The authors wish to thank all the study participants, research staff and students who participated in this work.

Availability of Data and Materials

The datasets during the current study are available from the corresponding author on reasonable request.

Funding

This study was supported by Science and technology plan project of Guizhou Province (LH20177207).

Ethical Approval

Ethical approval for the study was obtained from Ethics Committee of the Affiliated Hospital of Guingzhou Medical University.

Informed Consent
Written informed consent was obtained from all patients.

Authors' Contribution
Study design: Xiao-li Hu, Ying Gu and Xia Chen. Data collection and analysis: Xiao-li Hu, Da-lang Wu and Zhen-xia Lin. Supervision: Xiao-li Hu, Ying Gu and Xia Chen. Statistics: Ying Gu, Da-lang Wu and Zhen-xia Lin. Manuscript writing: Xiao-li Hu and Ying Gu. Manuscript revision: Xiao-li Hu, Ying Gu and Xia Chen. Approval of the manuscript: all authors.

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