Predict rheumatoid arthritis conversion from undifferentiated arthritis with dynamic contrast-enhanced MRI and laboratory indexes

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Abstract

Objective

To investigate the clinical value of dynamic contrast-enhanced MRI (DCE-MRI) and laboratory indexes in predicting conversion from undifferentiated arthritis (UA) to rheumatoid arthritis (RA).

Methods

A total 81 DMARD-naive UA patients were studied. 37 cases were ultimately diagnosed as RA, 32 cases were diagnosed as other types of arthritis, and the remaining cases were still UA during the 1-year follow-up. The DCE-MRI and laboratory measures were fed into a logistic regression analysis.

Results

Wash-in rate and anti-cyclic citrullinated peptide (anti-CCP) antibody served as the final variables into the regression equation ($p<0.05$). The area under the ROC curve of wash-in rate was 0.966. With optimal cut-off point 29.84 s^{-1}, wash-in rate achieved a sensitivity of 94.6% and specificity of 88.6% for predicting RA conversion from UA; anti-CCP antibody positive achieved a sensitivity of 37.8% and specificity of 90.9%. The combination of wash-in rate and anti-CCP antibody positive improved specificity (100%) but not sensitivity (27.3%).

Conclusion

The conversion from UA to RA is highly predictable. The wash-in rate of DCE-MRI can be used as an important biomarker to predict UA progression.

Key words

undifferentiated arthritis, rheumatoid arthritis, dynamic enhanced MR, anti-cyclic citrullinated peptide antibody.

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Introduction

Undifferentiated arthritis (UA) is consider as a recent onset arthritis which does not conform to any of the recognised inflammatory arthritis type during the first several weeks or months after symptom onset (1, 2). Spontaneous remission occurs in approximately 40–50%, and conversion to rheumatoid arthritis (RA) in 30%, while developing to other conditions in the rest patients (3, 4). Because the prognosis of patients with UA may vary from spontaneous remission to severe destruction, and RA patients can get the most benefits from treatment if treatment starts at an early stage, it is essential to identify those who will progress to RA in patients with UA before irreversible damage occurs.

RA pathological changes predominantly start with synovitis then followed by pannus development, cartilage destruction and bone erosion. Formation and development of pannus is a key reason for irreversible pathological changes. While development and maintenance of pannus rely on neovascularisation. Evidences have shown that the extent of vascularisation in inflamed synovium is highly associated with disease activity and progression (5, 6).

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a non-invasive MRI technique for evaluating tissue perfusion. In DCE-MRI, T1WI images of affected joint are repeatedly acquisited during a bolus of gadolinium-based chelate injected intravenously. Based on the dynamic changes in signal intensity on T1WI images, parametric maps of specific microvascular biomarkers can then be generated. The DCE-MRI has shown its great potentials in early RA diagnosis, predicting cartilage and bone erosion, and differential diagnosis between psoriatic arthritis and RA (7), therapeutic monitoring of synovitis in patients with inflammatory arthritis (8, 9). At present, there are few studies using DCE-MRI alone (10), and no study using combined DCE-MRI and laboratory tests in predicting RA conversion in UA patients.

The purposes of our study were to investigate the abilities of baseline DCE-MRI alone and its combination with laboratory indexes in predicting RA conversion during 1 year follow-up period in 81 patients with UA.

Materials and methods

Patients

Patients with recent onset pain or swelling in wrists and hands were recruited from the rheumatology outpatient clinic of our hospital between October 2014 and May 2016 (Table I).

The inclusion criteria were: 1) age ≥18 years, 2) first time symptoms onset, presenting with pain or swelling in at least one joint of wrists and hands, symptom duration <12 months, and could not be explained by any diseases, 3) no bone erosion on plain x-ray film, 4) based on the 2010 American College of Rheumatology/European League against Rheumatism classification ACR/EULAR criteria (11), total score <6 at baseline.

The exclusion criteria were: 1) current or previous use of glucocorticoids, methotrexate, or other disease-modifying anti-rheumatic drugs (DMARDs), 2) did not complete clinical, laboratory, or MRI exams, 3) acute trauma, 4) other diseases that can affect bone metabolism, such as acute or chronic infective diseases, haematological diseases, endocrine diseases, and bone tumours.

A total of 81 patients (16 male, 65 female, age 51.29±11.70 years) with UA (medium disease time 3.2 months, range 7 days – 1 year) who fulfilled the inclusion criteria and completed follow-up during 1 year period were studied in the present study (for flowchart, see Figure 1). Patients underwent follow-up exams at 3 months, 6 months, and 1 year after first visit. RA was ultimately confirmed in 37 patients (male n=7, female n=30; 51.08±13.39 years). The other types of arthritis (connective tissue disease n=9, osteoarthritis n=13, lupus erythematosus n=6, recession n=4) were confirmed in 32 patients (male n=7, female n=25; 51.53±9.58 years). 12 cases were still diagnosed as UA. The RA diagnosis was based on the ACR/EULAR criteria (9). All subjects received general nonsteroidal anti-inflammatory drugs, and no DMARDs were used before RA diagnosis. The study was approved by the local ethics committee. Informed consent was obtained from each patient.

Table I. Demographics and clinical data of subjects.

Group	RA	Non-conversion	*p*
Gender (male/female)	7/30	10/34	0.675
Age (Mean ± SD, years)	51.08 ± 13.39	51.98 ± 9.72	0.729
Disease duration before initial visit (medium, range)	3.0 months 7 days-10 months	3. 5 months 0.5-12 months	0.590
Number of joints involved medium among the 28 joints*	2-18 6	2-20 4	0.036
DSA, mean±SD	4.49 ± 0.84	3.70 ± 1.13	0.001
HAQ score, mean ± SD	2.38 ± 2.99	1.27 ± 1.30	0.218

*The 28 joints of the hands including metacarpophalangeal joints I–V, proximal interphalangeal joints I–V, and distal interphalangeal joints II–V, using the EULAR-OMERACT rheumatoid arthritis MRI atlas (12) as the reference. DAS means Disease Activity Score. HAQ means Health Assessment Questionnaire.

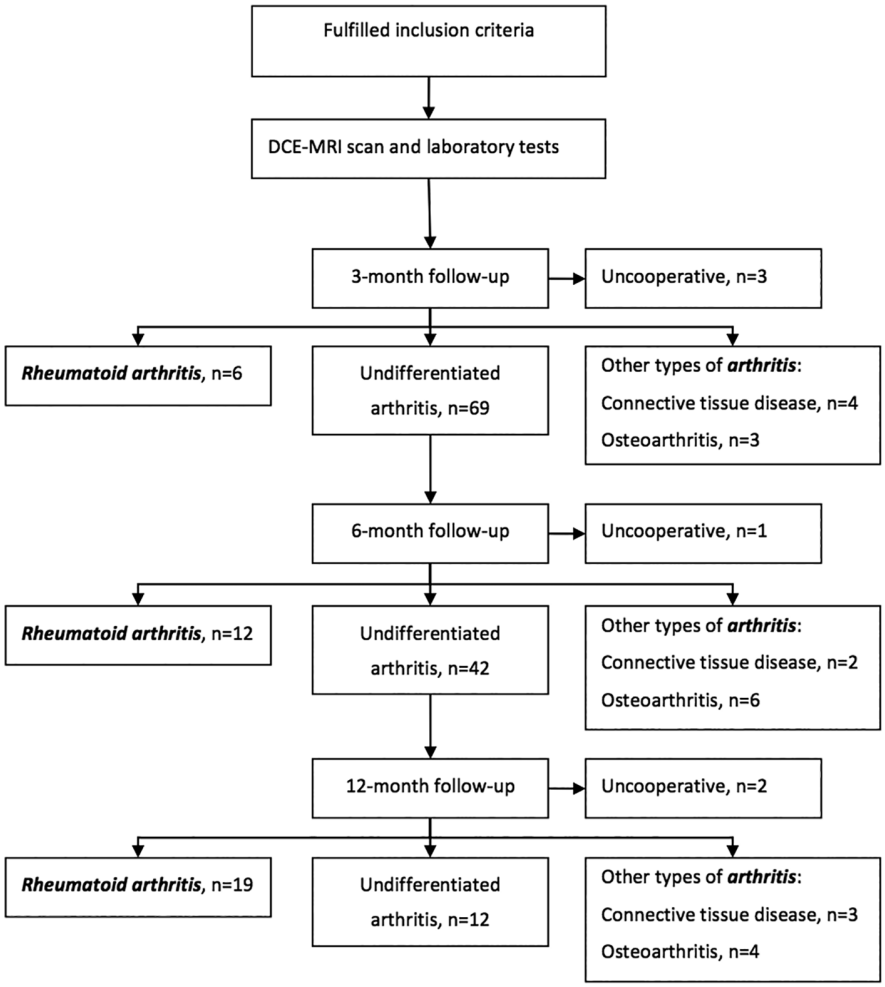

Fig. 1. Flowchart of patient selection.

MRI data acquisition

The MR imaging examinations were performed with a 3.0-Tesla MR scanner (Ingenia, Philips Healthcare, Netherlands) by using a quadrature coil to cover bilateral wrists and hands. For all examinations, the patients were placed in a prone position and both hands were fixed in the centre of the coil.

Routine MR sequences were performed as follows: coronal T1-weighted spin-echo (SE) sequence: TR/TE 500 ms/20 ms, slice thickness/gap 2.5 mm/0.25 mm, field of view (FOV) 300 mm × 300 mm, and matrix 500 × 352. Coronal T2-weighted turbo spin-echo (TSE) sequence: TR/TE 2000 ms/50 ms, slice thickness/gap 2.5 mm/0.25 mm, FOV 300 mm × 300 mm, and matrix 500 ×384. Transverse T2-weighted TSE sequence: TR/TE 5800 ms/50 ms, slice thickness/gap 5 mm/1 mm, FOV 100 mm × 78 mm, and matrix 200 ×120.

The DCE-MRI was performed with 3D-fast field echo sequence (TR/TE1/TE2 6.7/1.42/2.7ms, FOV 300 × 300mm, matrix 252 × 250, thickness 1.2mm, and acquisition 30 times). After the second acquisition, gadopentetate (Magnevist, Schering, Berlin, Germany) was intravenously injected at a dose of 0.2 mmol/kg of body weight through the cubital vein at a flow rate of 2.5 ml/s with an automatic injection system, followed by a 10 ml of saline solution.

Image analysis

MRI analyses were performed by a board-certified radiologist (H.L) with 10-year experience on a workstation (IntelliSpace Portal, Philips Healthcare, Netherland). The radiologist was blinded to the clinical and laboratory findings while analysing the MR data. A diagnosis of suspected synovitis of hand or wrist was made if the synovium showed enhancement on DCE-MRI. The inflamed thickened synovium which visually showing the strongest enhancement was chosen from the 14 joints of the hand including metacarpophalangeal joints I–V, proximal interphalangeal joints I–V, and distal interphalangeal joints II–V, using the EULAR-OMERACT rheumatoid arthritis MRI atlas (12) as a reference. A region of interest (ROI) was then manually drawn at centre of the abnormal synovium on the slice. The mean size of the ROIs was 10 mm^2 (range 3–15mm^2). The DCE-MRI derived measures included: Maximum relative enhancement (MaxRelEnh, ratio between signal intensities at maximum (SI_{max}) and before contrast agent arrive (SI_0), $SI_{max}/SI_0 \times 100$), maximum enhancement (MaxEnh, $SI_{max}-SI_0$), relative maximum enhancement [MaxRelEnh, $(SI_{max}-SI_0)/SI_0 \times 100$], time to peak (TTP, time point of SI_{Max}), wash-in rate [$(SI_{max}-SI_0)$/time from SI_0 to SI_{max}], and area under time-intensity curve (AreaCurv) (Fig. 2).

Serological analysis

A blood sample (3 ml) was drawn from

each patient at fasting state, and was centrifuged at 3000 rpm/min for 10 min. The serums were stored at -20°C until use. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and rheumatoid factor (RF) were measured in each patient.

Anti-mutated citrullinated vimentin (anti-MCV) and anti-cyclic citrullinated peptides (anti-CCP) antibodies were determined by Enzyme-Linked Immunosorbent Assay (ELISA). The ELISA kits used to detect Anti-MCV and anti-CCP antibodies were purchased from ORGENTEC (Orgentec Diagnostika, Mainz, Germany) and INOVA (Inova, California, USA), respectively. The assay was performed according to the manufacturer's protocol. A value of >20 U/ml was considered positive for both anti-MCV and anti-CCP antibodies tests. Anti-MCV and anti-CCP antibodies were used as dichotomous variables in all analyses.

Statistical analysis

Univariate test was used to compare the laboratory and imaging measures between the RA and non-RA groups by using IBM SPSS Statistics 17.0 (Armonk, New York, USA). The variables with significant difference in the univariate analysis were then included in a forward step logistic regression test to determine the independent variables for RA conversion. The correlations between DCE-MRI derived parameter and laboratory tests were tested by Pearson correlation coefficient. The sensitivities and specificities of the independent variables in predicting RA conversion were calculated with receiver operating characteristic curve (ROC) analysis. $p<0.05$ was considered statistically significant in all tests.

Results

The MaxRelEnh, MaxEnh, wash-in rate, AreaCurv, ESR, CRP, anti-CCP antibody, and anti-MCV antibody significantly differed between RA and non-RA groups, but not for TTP and RF (Table II). In the logistic regression analysis, the wash-in rate and anti-CCP antibody were the independent variables in predicting RA conversion ($p\leq0.015$) (Table III).

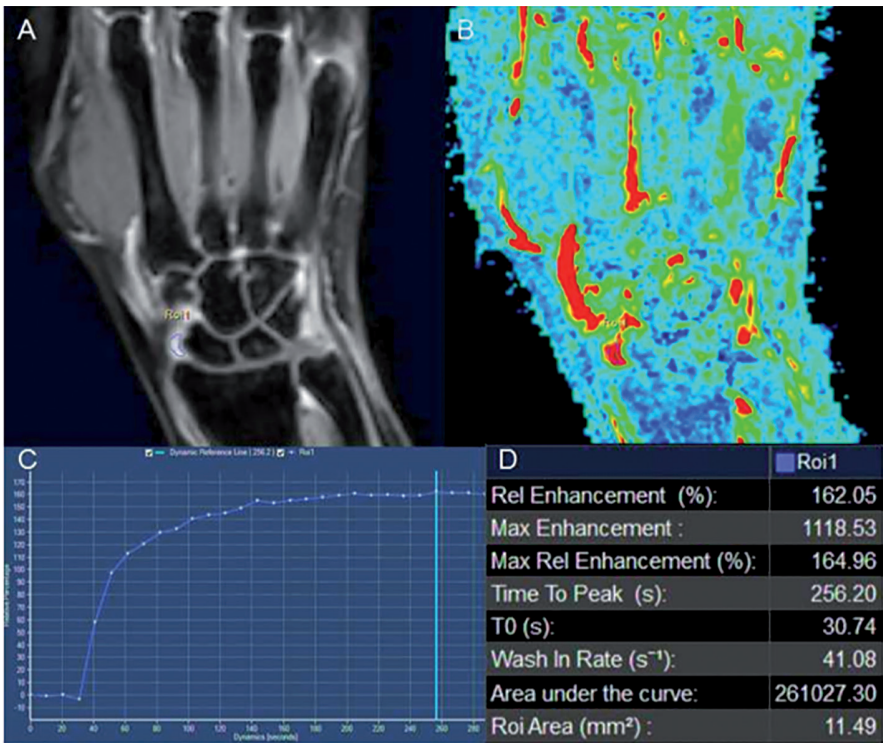

Fig. 2. A 56-year-old female complained pain in bilateral wrists for 2 months. Baseline laboratory tests showed erythrocyte sedimentation rate 31.0 mm/hr, C-reactive protein 68.0 mg/L, rheumatoid factor negative, anti-mutated citrullinated vimentin positive, and anti-cyclic citrullinated peptides antibody positive. Rheumatoid arthritis was confirmed at 6-month follow-up. The region of interest (ROI) was first draw on inflamed thickened synovium of wrist which showing the most strong enhancement on coronal gadolinium-enhanced fat suppressed T1-weighted MRI (**A**), then the ROI was copied to the corresponding color-coded image of dynamic contrast enhanced MRI (**B**). In the time-intensity curve (**C**), the X-axial indicates the time after contrast agent injection (sec), while the Y-axial indicates signal intensity. The signal intensity (SI_0) started to increase when contrast agent arriving at 30.74 sec (T0), and reached the peak of signal intensity (SI_{max}) at 256.20 sec (Time to peak) (**D**).

Table II. DCE-MRI and laboratory measures in RA and non-RA groups.

Measures	RA n=37	Non-RA n=44	*p*-value
MaxRelEnh (%)	145 ± 49	70 ± 48	<0.001
MaxEnh	1467 ± 465	622 ± 457	<0.001
TTP (s)	284 ± 60	289 ± 65	0.707
Wash-in rate (s^{-1})	48 ± 18	16 ± 10	<0.001
AreaCurv	376516 ± 1	133052 ± 1	<0.001
ESR (mm/hr)	28.8 ± 14.7	17.8 ± 12.7	<0.001
CRP (mg/L)	23.5 ± 29.3	7.2 ± 11.3	0.006
RF (positive/negative)	9/28	6/38	0.217
anti-CCP (positive/negative)	14/23	4/40	0.002
Anti-MCV (positive/negative)	14/23	7/37	0.025

Relative enhancement at time point of maxium enhancement (MaxRelEnh), maximum enhancement (MaxEnh), time to peak (TTP), area under time-intensity curve (AreaCurv), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-mutated citrullinated vimentin (anti-MCV), and anti-cyclic citrullinated peptides (anti-CCP).

The wash-in rate was significantly correlated with ESR and CRP in all subjects (r=0.451, $p<0.001$; r=0.494, $p<0.001$, respectively) and in the RA group (r=0.405, $p=0.013$; r=0.391, $p=0.017$, respectively), but not in the non-RA group (r=0.068, $p=0.660$; r=0.289, $p=0.057$, respectively) (Fig. 3).

For the wash-in rate, the area under ROC curve was 0.966. By using the optimal cut-off value 29.84 s^{-1}, it achieved a sensitivity of 94.6% and a specificity of 88.6% in predicting RA conversion (Fig. 4A). For the anti-CCP antibody positive, the area under ROC curve was 0.644, anti-CCP antibody positive achieved a

Table III. WASHIN and anti-CCP antibody positive are independent variables in predicting RA conversion in logistic regression analysis.

Independent variables	Wald	OR	95% CI	*p*-value
Wash-in rate (s^{-1})	11.954	0.741	0.625-0.878	0.001
anti-CCP	5.903	0.033	0.002-0.518	0.015

Among the relative enhancement, maximum enhancement, area under time-intensity curve, erythrocyte sedimentation rate, C-reactive protein, anti-mutated citrullinated vimentin, anti-cyclic citrullinated peptides (anti-CCP), and wash-in rate, the anti-CCP and wash-in rate were the only independent variables in predicting RA conversion.

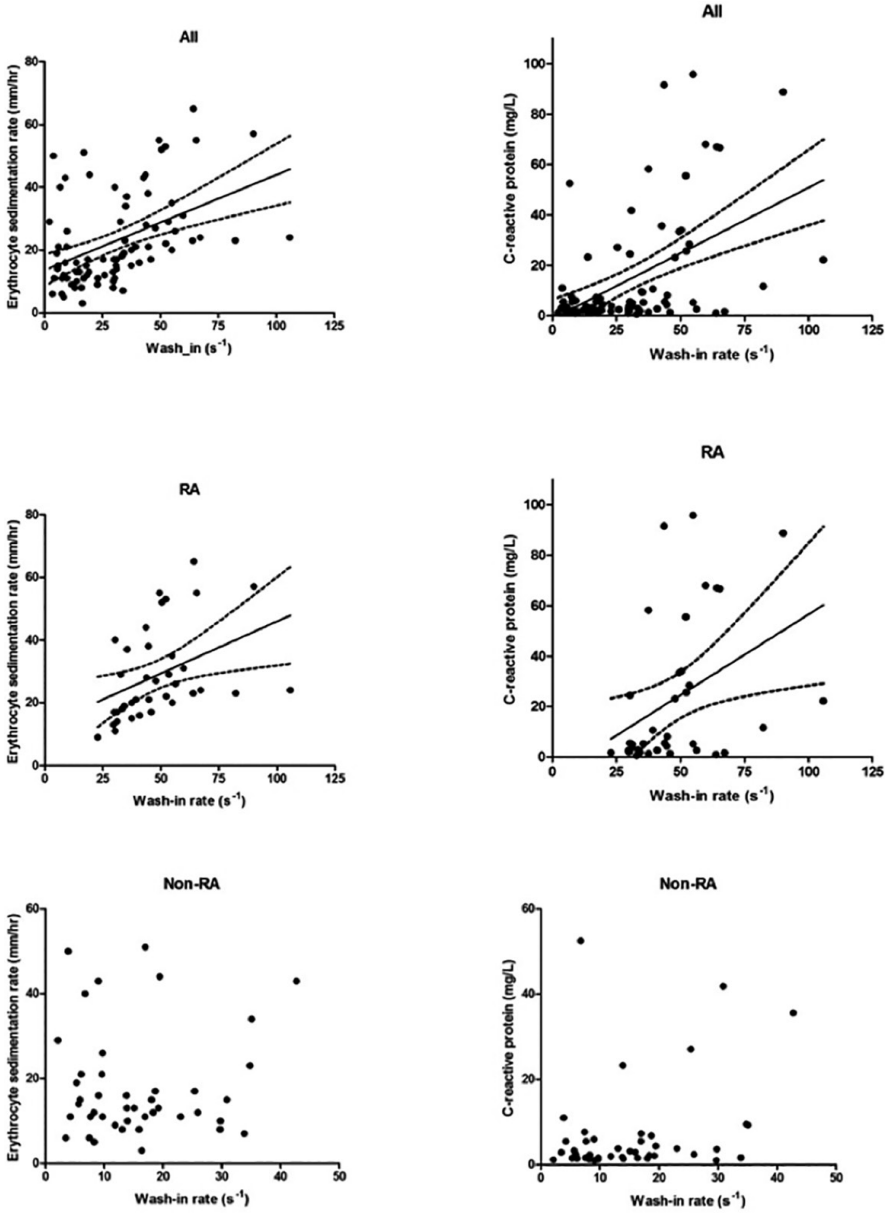

Fig. 3. The wash-in rate was significantly correlated with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in all subjects (first row) and RA group (second row), but not in the non-RA group (third row). The fitted line and its 95% confidence interval are presented.

sensitivity of 37.8% (14/37) and specificity of 90.9% (40/44) (Fig. 4B). Among the 81 UA patients, 18 patients (22.2%) presented anti-CCP antibody positive at the baseline visit. Combination of wash-in rate >29.84 s^{-1} and anti-CCP antibody positive achieved a sensitivity of 27.3% (12/44) and specificity of 100% (32/32).

Discussion

In the present study we found the wash-in rate on DCE-MRI could achieve high sensitivities and specificities in predicting RA conversion from UA, and the conventional laboratory tests, such as RF, ESR, CRP, even the anti-MVA were excluded from the logistic regression analysis, indicating the potential of DCE-MRI in early RA diagnosis.

Accurately predicting RA conversion from UA is essential. Even though prompt and aggressive treatment with DMARDs is advocated in UA patients to prevent or minimise the risk of occurrence of the irreversible damage. However, as showed in the literature, it is estimated that around 40–50% of the UA patients may experience spontaneous remission (3, 4), overtreatment could cause potential damage in those patients. Efforts have been made to establish RA prediction rule among UA patients (13–16). All these prediction rules focus on patient's age, gender, number of joints affected, duration of morning stiffness, CRP, RF, anti-CCP antibody, and/or synovitis and oedema of bone marrow on contrast-enhanced MRI.

In the present study among the laboratory tests, the RF, ESR, and CRP were excluded in the forward step logistic regression analysis, the anti-CCP antibody was the only variable predicting RA conversion. RF is considered as the first biomarker of RA. Evidences have shown RF is positive in about 80% of people with RA. However, RF can be positive in other inflammatory diseases, such as in autoimmune diseases, infectious diseases, liver diseases, endocarditis, and leukaemia (17). The sensitivity of RF for established rheumatoid arthritis is 60–70% with a specificity of 78% (18). ESR and CRP level are biomarkers of inflammation, but a high ESR or CRP is not specific to RA. A positive anti-CCP antibody test is a stronger clue to RA. A positive anti-CCP antibody test could achieve sensitivity from 39–92%, and specificity from 65–100% for diagnosis of RA (19). In the present study, the anti-CCP antibody positive achieved a sensitivity of 37.8% (14/37) and specificity of 90.9% (40/44). The lower sensitivity in the present study compared to the previous studies might

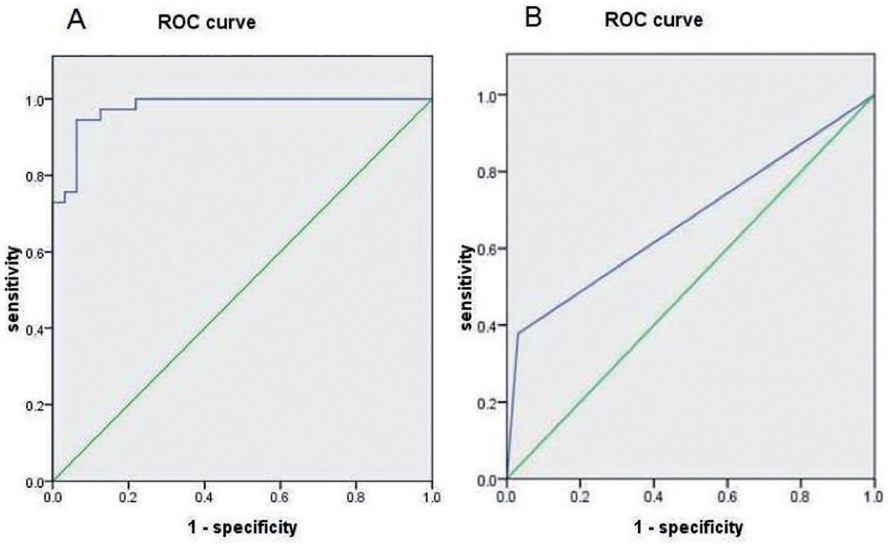

Fig. 4. Receiver operating characteristic curve (ROC) of wash-in rate and anti-CCP antibody positive in predicting rheumatoid arthritis conversion from undifferentiated arthritis. For wash-in rate, the area under ROC curve was 0.966. By using the optimal cut-off value 29.84 s-1, it achieved a sensitivity of 94.6% and specificity of 88.6% (**A**). For the anti-CCP antibody positive (>20 U/ml), the area under ROC curve was 0.644, and anti-CCP antibody positive achieved a sensitivity of 37.8% and specificity of 90.9% (**B**).

relate to the differences in the phase of the disease, disease duration, test methods, cut-points, severity and other clinical characteristics.

The extent of vascularisation in inflamed synovium is highly associated with RA activity and progression (5, 6). Conventional contrast enhanced-MRI (CE-MRI) has been considered as the gold standard to evaluate synovitis in RA (20) and provides imaging evidence of hypervascular synovial tissue according to the ACR/EULAR criteria (12, 20-23). The inflamed synovium appears as bright signal enhancement on CE-MRI. However, synovium enhancement can also be detected in other types of arthritis (24). Thus, early identification of RA-related vascularisation in UA is essential for accurate prediction.

DCE-MRI is considered as a quantitative tool in evaluating vascularisation, and DCE-MRI derived semi-quantitative parameters show broad correlations with underlying physiology, and increased vascular density and/or vascular permeability (25). Semi-quantitative parameters have been used to differentiate malignant tumour from benign lesions based on neovascularisation, and to assess the effect of anti-vascular drugs in cancer management (26). DCE-MRI has also been used in differentiating vascular pannus from fibrous pannus. However, the technique was mainly applied in RA patients (13, 27), and scarcely be used in UA patients (10). In a recent study in which 5 RA conversion and 21 non-RA were confirmed during a 2-year follow-up in 28 DMARD-naive UA patients, the baseline DCE-MRI shows distinct pattern of time-intensity curve in RA (10), which is line with our findings. In the present study, the wash-in rate was the only MRI measure was left in the regression analysis, and was the most accurate measure among the laboratory tests and DCE-MRI measures in predicting RA conversion. The wash-in rate represents the slope between signal intensities at arrival time of contrast inflow and time of peak enhancement on the time intensity curve. Animal models have shown the wash-in rate is highly related to increased vascular density and/or vascular permeability (28). Clinically, wash-in rate has been shown great potential for prostate cancer detection and localisation (29). With the optimal cut-off value of 29.84 s^{-1} it achieved sensitivity 94.6% and specificity 88.6%. This parameter likely reflects the density of neovascularisation of inflamed synovium, and could be used in RA diagnosis and prediction of RA conversion from UA.

Our study has certain limitations. The wash-in rate [$(SI_{max}-SI_0)$/time from SI_0 to SI_{max}] has dimension of arbitrary machine unit (SI), and is difficult to be standardised. The SI is dependent on the scanner parameters and field strength, *i.e.* the wash-in rate varies between pulse sequences and between scanners. Moreover $(SI_{max}-SI_0)$ is related in a complex non-linear way to contrast agent concentration, implying that each radiologist might need to separately determine his or her wash-in rate cut-off values for predicting conversion from UA to RA. A potential solution is to use physiology-related quantitative parameters that are obtained by means of pharmacokinetic models (30, 31).

Conclusion

Currently, studies on prediction of UA conversion using DCE-MRI are rare, our findings highlight the importance of DCE-MRI in early RA diagnosis. The conversion from UA to RA is highly predictable. The wash-in rate of DCE-MRI can be used as an important biomarker to predict the RA progression.

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