Elevated serum uric acid is a predictor of pulmonary artery involvement and subsequent prognosis in patients with Takayasu's arteritis

H. Liao[1], S. Yang[1], N. Zhang[2], J. Du[1], H. Yuan[3], L. Pan[1]

[1]Department of Rheumatology and Immunology, [2]Department of Radiology, [3]Department of Clinical Laboratory, Beijing Anzhen Hospital, Capital Medical University, Beijing, China.

Abstract

Objective

The aim of this study was to investigate the predictive value of uric acid (UA) in prognosis of pulmonary artery involvement (PAI) in patients with Takayasu's arteritis (TAK).

Methods

A total of 166 TAK patients were enrolled in the study, including 76 with PAI and 90 without. Outcomes of 144 TAK patients were followed up and recorded. The possible associations between serum UA levels and incidence of PAI in TAK and PAI-related prognosis of TAK patients were examined using different statistical models.

Results

The serum UA levels were significantly higher in TAK patient with PAI than TAK patients without PAI. Multivariate logistic regression analysis indicated that serum UA level ≥284.5 umol/L was associated with an increasing incidence of PAI in TAK (OR: 2.108, 95% CI: 1.063 to 4.180; p=0.033). Kaplan-Meier survival analysis showed that TAK patients with serum UA level ≥328.1 umol/L had a significantly higher cumulative incidence of PAI-related adverse events compared to TAK patients with serum UA level <328.1 umol/L (p=0.008). Multivariate Cox proportional hazard regression analysis revealed that serum UA level ≥328.1 umol/L (HR: 2.595, 95% CI: 1.198 to 5.622; p=0.016) was a PAI-related prognostic risk factor for TAK.

Conclusion

Elevation of serum UA level was associated with an increasing risk of PAI and PAI-related adverse event in patients with TAK, indicating its potential as a predictor for identification of PAI onset and worsening in TAK patients.

Key words

Takayasu's arteritis, pulmonary artery involvement, uric acid, adverse event

Hua Liao, MD
Shiyu Yang, MM
Nan Zhang, MD
Juan Du, MM
Hui Yuan, PhD
Lili Pan, PhD

Please address correspondence to:
Lili Pan
Department of Rheumatology and Immunology,
Beijing AnZhen Hospital,
Capital Medical University,
Beijing Institute of Heart, Lung and Blood Vessel Diseases,
2 Anzhen Road,
Beijing 100029, China.
E-mail: lilypansxmu@sina.com

and to
Hui Yuan
Department of Clinical Laboratory,
Beijing Anzhen Hospital,
Capital Medical University,
2 Anzhen Road,
Beijing 100029, China.
E-mail: 18911662931@189.cn

Received on March 3, 2024; accepted in revised form on May 13, 2024.

Funding: this research was funded by the National Natural Science Foundation of China, grant number 82270427. The funders had no role in the study design, data collection and analysis, decision to publish or manuscript preparation.

Competing interests: none declared.

Introduction

Takayasu arteritis (TAK) is a chronic, large-vessel vasculitis that primarily affects the aorta and its proximal branches (1). It is an immune-mediated disease (2) with a largely unknown aetiology. Inflammation damages the artery wall, leading to stenosis, occlusion and aneurysm formation (1). TAK mostly affects young people with an age onset peak at 20–30 years (3), is considerably more common among females (3-6). In TAK, pulmonary artery involvement (PAI) is not uncommon with varying incidence in different studies (7-11), ranging from 6.3–66% (7-12), possibly due to differences between study populations and/or methods used for diagnosis (8). Most patients of TAK with PAI were diagnosed only when severe complications like pulmonary embolism, pulmonary hypertension, or hypoxemia arise. By this point, the pulmonary arterial changes have progressed to severe narrowing or occlusion, leading to a poor prognosis. Thus, identifying a screening marker of PAI in TAK that also has a prognostic value is desirable.

Epidemiological studies have commonly indicated a potential link between higher serum uric acid (UA) levels and cardiovascular diseases (CVDs), including coronary heart disease (CHD), stroke, congestive heart failure, and arterial hypertension. In recent years, studies have shown that pulmonary artery hypertension (PAH) affects the level of UA metabolism (13). Elevated serum UA level is a biomarker of PAH (14) and is predictive factor of PAH in systemic sclerosis (SSc) (15) and systemic lupus erythematosus (SLE) (16). But the relationship between TAK-PAI and uric acid is currently under-researched and requires further investigation. Thus, the aim of the present retrospective study was to test the hypothesis that elevated serum UA level could act as a biomarker of PAI in TAK and, if true, to examine its prognostic value.

Patients and methods

Patient population

All TAK patients enrolled in this study fulfilled the criteria of the 1990 American College of Rheumatology (ACR) for TAK (17). And we re-evaluated all TAK patients using the new ACR/EULAR 2022 classification criteria (18, 19). The results showed that all patients met the new criteria. PAI was defined as the presence of thickening, stenosis, occlusion, aneurysm, dilation of pulmonary artery diagnosed by radiologist based on computer tomography pulmonary angiography (CTPA). Patients were enrolled from the inpatient services at Beijing Anzhen Hospital, Capital Medical University, Beijing, China, covering the period from August 2012 to February 2023.

Laboratory parameters and clinical data

Clinical data, laboratory parameters and information on disease activity were obtained from the medical records. Demographics (age and sex) and clinical characteristics (disease duration, personal medical history and medications) were collected by reviewing the medical records of the patients enrolled in the study. The laboratory parameters were obtained by checking the test results of the Beijing Anzhen hospital laboratory. For assessing disease activity, the National Institutes of Health (NIH) criteria (20) and the Indian Takayasu Clinical Activity Score (ITAS 2010 and ITAS.A) (21) were used. The classification of TAK vascular involvement was carried out utilising Numano classification criteria using imaging data (22). The serum uric acid level was assessed upon the patient's initial admission to our hospital, before the commencement of regular treatment.

Imaging data

All patients had data of vascular computed tomography angiography (CTA) and/or magnetic resonance angiography (MRA) of the aorta and of all of its primary branches at presentation. Vascular Doppler data were additionally used to evaluate the involvement of the peripheral arteries, which could not always be visualised with CTA and MRA. The vascular Doppler specialist performed peripheral vascular Doppler examinations. CTA and MRA were interpreted in consensus by two radiologists. PAI was detected by CTPA.

Outcome and follow-up

All enrolled patients were followed up and the outcomes were recorded, follow-up for a minimum of one year. The outcomes were defined as a cumulative event of exacerbation or new occurrence of PAI or PAI-related adverse events. Exacerbation of PAI was defined as the progression of PAI assessed by CTPA in patients with previous PAI. PAI-related adverse events were defined as exacerbation or new occurrence of PAH or hypoxemia or oppression in chest, new pulmonary infarction, or all-cause death. Exacerbation refers to the increased of pulmonary arterial hypertension, worsening hypoxemia, and heightened oppression in chest resulting from the progression of PAI.

Informed consent was obtained from all participants and/or their legal guardians. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University (no. 2023117X).

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences version 22.0 (SPSS, Chicago, IL, USA) and R language version 4.2.3. A P-value <0.05 was considered statistically significant. Continuous data are expressed as mean ± standard deviation (SD) (normally-distributed data) or median (interquartile range [IQR]) (not-normally-distributed data). For normally-distributed data, the independent-samples *t* test was used for comparing differences between two groups. For not-normally-distributed data, the rank-sum test was used to compare differences between two groups. Categorical variables were expressed as percentages and analysed with the Chi-squared test. Univariate and multivariate logistic regression analyses were carried out for the identification of the predictors of TAK with PAI. The area under the curve (AUC) of receiver operating characteristic (ROC) curve was used for identifying different cut-off values for serum UA level for different scenarios. Associations between UA and cumulative incidence of adverse events were examined using Kaplan-Meier and Cox proportional hazard regression analyses. Analyses of the differences in the predictive ability of different prognosis models (based on multivariate Cox proportional hazard regression analysis) for TAK and TAK with PAI were carried out utilising AUC of ROC curves and method of integrated discrimination improvement (IDI) and net reclassification improvement (NRI).

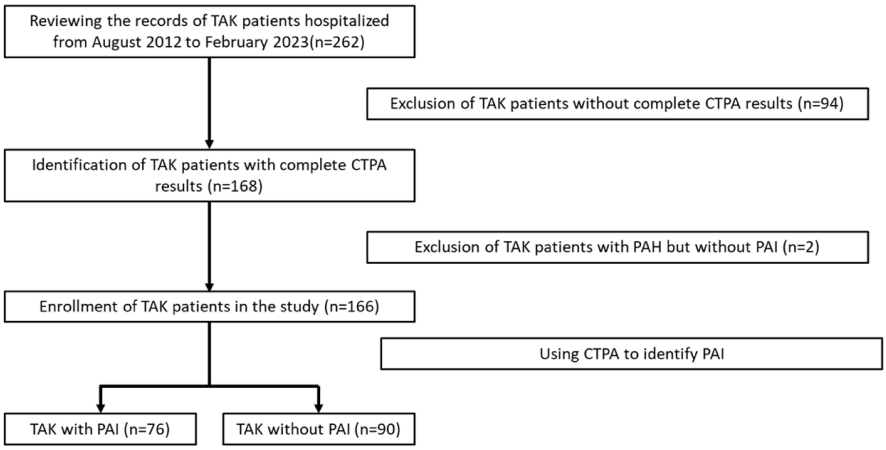

Fig. 1. Consort flow chart of the study.
TAK: Takayasu's arteritis; CTPA: computed tomography pulmonary angiogram; PAH: pulmonary artery hypertension; PAI: pulmonary artery involvement.

Results

Patient characteristics

We reviewed the medical records of 262 patients with TAK from August 2012 to February 2023 from inpatient services in Beijing Anzhen Hospital Capital Medical University, Beijing, China (Fig. 1). Among the 262 TAK patients, 168 had complete CTPA results. Two patients with PAH, but without PAI and ninety-four patients without completing CTPA were excluded. Thus, in total 166 patients with TAK were included, including 76 TAK patients with PAI (age 40±12 years; females 96.1%) and 90 TAK patients without PAI (age 38±12 years; females 92.2%).

The demographics and the clinical characteristics of the TAK patients with and without PAI are presented in Table I. No significant differences were found with respect to demographics (age, sex and body mass index), medical history, the Numano subtypes (I, IIa, IIb, III, IV, and V subtypes), the results of the ultrasound cardiogram characteristics, medications affecting serum uric acid at enrolment and drugs used for the therapy. The following variables were significantly higher in TAK patients with PAI compared to those in TAK patients without PAI: duration of the disease [60 (12, 216) *vs*. 36 (6, 114), respectively; p=0.006], rate of tuberculosis (13.2% *vs*. 4.44%, respectively; p=0.041). The level of serum UA was significantly higher in TAK patients with PAI compared to that in TAK patients without PAI [292 (246, 359) *vs*. 266 (212, 319), respectively; p=0.006] (Table II). There were no significant differences with respect to the levels of other inflammatory markers (including ESR, CRP,), disease activity (including scores of NIH, ITAS2010, and ITAS.A) and the blood biochemistry tests including alanine aminotransferase, serum creatinine, brain natriuretic peptide (BNP), white blood cell (WBC). No correlation between uric acid and disease activity as assessed by NIH score, ITAS2010 score, and ITAS.A score. The difference between the active disease group and the inactive disease group was not statistically significant [277 (233,339) *vs*. 269 (242,295), respectively; p=0.904].

Outcomes of 144 TAK patients were recorded during a median follow-up time of 45 (IQR: 23, 65) months. In the TAK without PAI group 3 patient developed new PAI, which in one patient was accompanied by hypoxemia. In TAK with PAI group, 1 patient died of PAH due to PAI, 8 patients had pulmonary vascular

Table I. The demographic and clinical characteristics of patients with TAK.

	TAK without PAI (n=90)	TAK with PAI (n=76)	*p*-value
Clinical data			
Disease duration, median (IQR) (months)	36 (6, 114)	60 (12, 216)	0.006
Female, n (%)	83 (92)	72 (95)	0.493
Age, mean±SD (years)	38 ± 12	40 ± 12	0.083
Age at disease onset, mean±SD (years)	30 ± 11	31 ± 12	0.815
Body Mass Index, mean±SD	21.8 ± 2.8	22.8 ± 3.9	0.165
hypertension, n (%)	32 (36)	24 (32)	0.631
Diabetes, n (%)	5 (6)	4 (5)	1.000
Hyperlipidaemia, n (%)	15 (17)	7 (9)	0.168
Coronary heart disease, n (%)	6 (7)	11 (14)	0.092
Stroke, n (%)	9 (10)	2 (3)	0.060
Tuberculosis, n (%)	4 (4)	10 (13)	0.041
History of smoking, n (%)	8 (9)	4 (5)	0.381
Drinking history, n (%)	5 6)	1 (1)	0.305
Numano subtype			
Type I, n (%)	11 (12)	5 (7)	0.220
Type IIa, n (%)	7 (8)	5 (7)	0.766
Type IIb, n (%)	18 (20)	15 (20)	0.966
Type III, n (%)	5 (6)	1 (1)	0.298
Type IV, n (%)	5 (6)	0 (0)	0.103
Type V, n (%)	45 (50)	48 (63)	0.089
Ultrasound cardiogram			
E/A<1, median (IQR)	0 (0,1)	0 (0,1)	0.505
Left ventricular ejection fraction, median (IQR) (%)	64 (60, 68)	64 (58, 67)	0.177
Main pulmonary artery diameter, mean±SD	22.3 ± 2.6	23.0 ± 4.0	0.113
Interventricular septal thickness, median (IQR)	9 (8, 10)	10 (8, 11)	0.731
Medications affecting serum uric acid at enrolment			
uretic, n (%)	2 (2)	6 (8)	0.085
Aspirin, n (%)	13 (14)	9 (12)	0.622
Drugs used for the therapy			
Glucocorticoids, n (%)	70 (78)	58 (76)	0.823
Hydroxychloroquine, n (%)	7 (8)	8 (11)	0.538
Methotrexate, n (%)	32 (35)	37 (49)	0.087
Cyclophosphamide, n (%)	25 (28)	22 (29)	0.868
Leflunomide, n (%)	5 (6)	3 (4)	0.906
Tacrolimus, n (%)	1 (1)	1 (1)	1.000
Mycophenolate mofetil, n (%)	23 (26)	13 (17)	0.188
Tumour necrosis factor-α inhibitors, n (%)	3 (3)	0 (0)	0.307
Tocilizumab, n (%)	22 (24)	24 (32)	0.306
Azathioprine, n (%)	1 (1)	2 (3)	0.882
Tofacitinib, n (%)	1 (1)	2 (3)	0.882

TAK: Takayasu's arteritis; PAI: pulmonary artery involvement.

Table II. The levels of inflammatory markers, scores of disease activity and blood biochemistry of patients with TAK.

	TAK without PAI (90)	TAK with PAI (76)	*p*-value
Inflammatory markers, and disease activity			
ESR, median (IQR) (mm/1h)	17 (8, 30)	14 (8, 34)	0.811
CRP, median (IQR) (mg/L)	3.64 (0.63, 11.44)	4.11 (0.91, 10.86)	0.526
NIH, median (IQR)	2 (2, 3)	2 (2, 3)	0.727
ITAS2010, median (IQR)	6 (3, 9)	7 (3, 10)	0.367
ITAS.A, median (IQR)	7 (4, 11)	8 (6, 11)	0.272
disease activity, n (%)	81 (90)	70 (92)	0.637
Blood biochemistry			
white blood cell count, mean±SD (109/L)	7.11 ± 2.4	7.08 ± 2.42	0.926
Alanine aminotransferase, median (IQR) (U/L)	12 (8, 16)	11 (8, 17)	0.843
Serum creatinine, median (IQR) (umol/L)	53 (46, 65)	53 (47, 61)	0.799
Serum UA, median (IQR) (umol/L)	266 (212, 319)	292 (246, 359)	0.006
BNP, median (IQR)	50 (30, 106)	132 (36, 551)	0.124

TAK: Takayasu's arteritis; PAI: pulmonary artery involvement; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NIH: National Institutes of Health; ITAS: Indian Takayasu Clinical Activity score; BNP: brain natriuretic peptide.

aggravation, 4 patients had pulmonary arterial pressure aggravation, and 12 patients had hypoxemia aggravation, two of which were accompanied by chest pain aggravation.

Serum uric acid level as a predictor of risk of PAI in TAK patients

ROC curve analysis showed that the best cut-off value for serum UA level for the incidence of TAK with PAI was 284.5 umol/L with sensitivity of 57.9% and specificity of 63.3%, where the AUC was 0.625 (Fig 2A). The cut-off sensitivity of uric acid levels to assess pulmonary artery involvement is the maximum predictive capability. For identifying the risk factors associated with TAK with PAI, univariate and multivariate logistic regression analyses were performed (Table III). In univariate analysis, the following were found to have significant associations with PAI in TAK: disease duration [odds ratio (OR): 1.004, 95% confidence interval (CI): 1.001 to 1.006; p=0.014] and serum UA level ≥284.5 umol/L (OR: 2.375, 95% CI: 1.271 to 4.439; p=0.007). Multivariate analysis was performed, which revealed that serum UA level ≥284.5 umol/L (OR: 2.108, 95% CI: 1.063 to 4.180; p=0.033) was a predictor of TAK with PAI.

Serum uric acid level as a marker of prognosis for PAI in TAK patients

Analysis of AUC of ROC curve showed that the best cut-off value for serum UA level for the incidence of adverse events in TAK was 328.1 umol/L with sensitivity of 48.4% and specificity of 75.2% (Fig. 2B). Kaplan-Meier survival analysis was performed for analysing the cumulative incidence of adverse events in TAK patients with serum UA level ≥328.1 umol/L and serum UA level <328.1 umol/L (Fig. 2C). Thus, it was found that TAK patients with serum UA level ≥328.1 umol/L had a significantly higher cumulative incidence of adverse events compared to TAK patients with serum UA level <328.1 umol/L (p=0.008).

In univariate Cox proportional hazard regression analysis, serum UA level ≥328.1 umol/L [hazard ratio (HR): 2.503, 95% CI: 1.234 to 5.078;

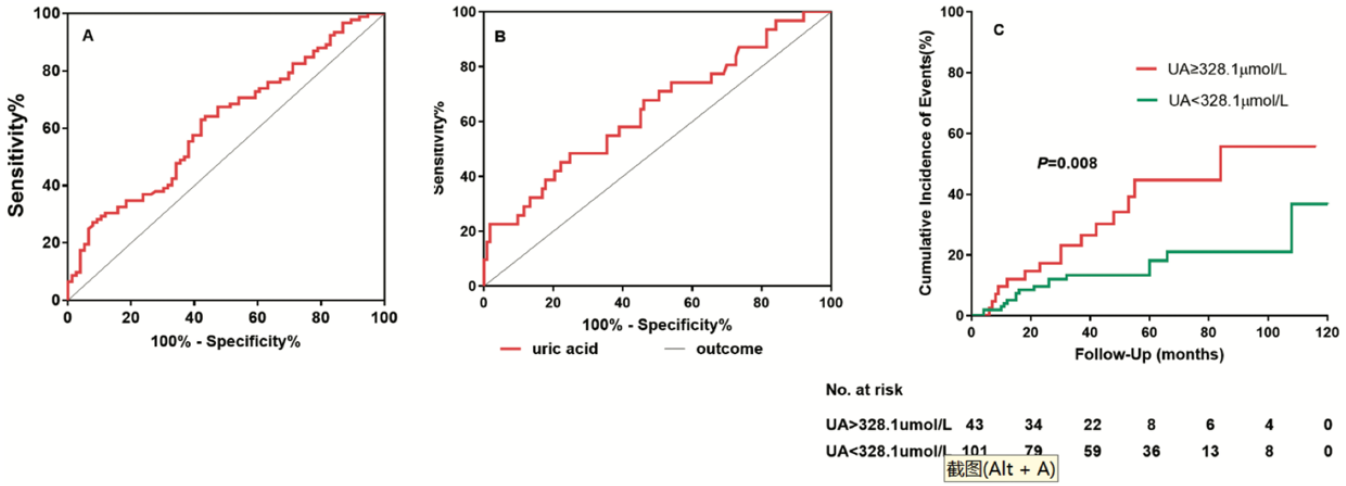

Fig. 2. Prognostic value of serum uric acid levels in patients with TAK.
A: Receiver-operating characteristic (ROC) curve for the serum uric acid levels in TAK (incidence of PAI was the standard in this analysis). For the serum uric acid levels, the area under the curve (AUC) was 0.625 (95% CI: 0.539 to 0.708, p=0.006). The best cut-off value was 284.5 umol/L, with sensitivity and specificity of 57.9% and 63.3%, respectively.
B: Receiver-operating characteristic (ROC) curve for the serum uric acid levels in TAK (incidence of adverse events was the standard in this analysis). For the serum uric acid levels, the area under the curve (AUC) was 0.642 (95% CI: 0.528 to 0.755, p=0.016). The best cut-off value was 328.1 umol/L, with sensitivity and specificity of 48.4% and 75.2%, respectively.
C: Kaplan-Meier survival analysis for TAK patients with serum uric acid ≥328.1 umol/L showed significantly more cumulative incidence of adverse events than TAK patients with serum uric acid <328.1 umol/L (p=0.008).

Table III. Results of logistic regression analyses for the identification of the predictors of PAI in patients with TAK.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age (years)	1.025	0.998 – 1.052	0.710	1.003	0.971 – 1.036	0.846
Sex	2.052	0.512 – 8.228	0.310	2.501	0.553 – 11.301	0.234
Disease duration (months)	1.004	1.001 – 1.006	0.014	1.003	0.999 – 1.006	0.129
Tuberculosis	3.308	0.993 – 11.02	0.051	3.082	0.845 – 11.244	0.088
Serum UA level ≥284.5 umol/L	2.375	1.271 – 4.439	0.007	2.108	1.063 – 4.180	0.033
Uretic	3.771	0.738 – 19.264	0.111	3.515	0.622 – 19.854	0.155
Aspirin	0.796	0.320 – 1.978	0.623	0.944	0.352 – 2.528	0.908

TAK: Takayasu's arteritis; PAI: pulmonary artery involvement; UA: uric acid.

Table IV. COX regression analysis for the cumulative incidence of PAI related adverse events in patients with TAK.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (years)	1.011	0.982 – 1.040	0.468	1.000	0.965 – 1.037	0.989
Sex	0.764	0.231 – 2.522	0.658	0.937	0.270 – 3.251	0.918
Disease duration (months)	1.002	0.999 – 1.004	0.197	1.001	0.998 – 1.005	0.494
Tuberculosis	1.775	0.674 – 4.675	0.246	2.196	0.771 – 6.253	0.141
Serum UA level ≥328.1 umol/L	2.503	1.234 – 5.078	0.011	2.595	1.198 – 5.622	0.016

TAK: Takayasu's arteritis; UA: uric acid.

p=0.011] was found to be significantly associated with cumulative incidence of adverse events in TAK. Thus, multivariate Cox proportional hazard regression analysis showed that serum UA level≥328.1 umol/L (HR: 2.595, 95% CI: 1.198 to 5.622; p=0.016) was a PAI-related prognostic risk factor for TAK (Table IV).

The prognostic ability of the model based on the multivariate Cox proportional hazard regression analysis was evaluated using analyses of AUC of ROC curves and IDI. For this purpose, first a prognostic baseline risk model based on multivariate Cox proportional hazard regression analysis was constructed using age, sex, disease duration and tuberculosis. Afterwards, serum UA level ≥328.1 umol/L was added as a risk factor to the baseline model and the change in the prognostic ability of the revised prognostic model was evaluated using analyses of AUC of ROC curves and IDI. In analysis of AUC of ROC curve, the AUC of the baseline model was AUC = 0.608

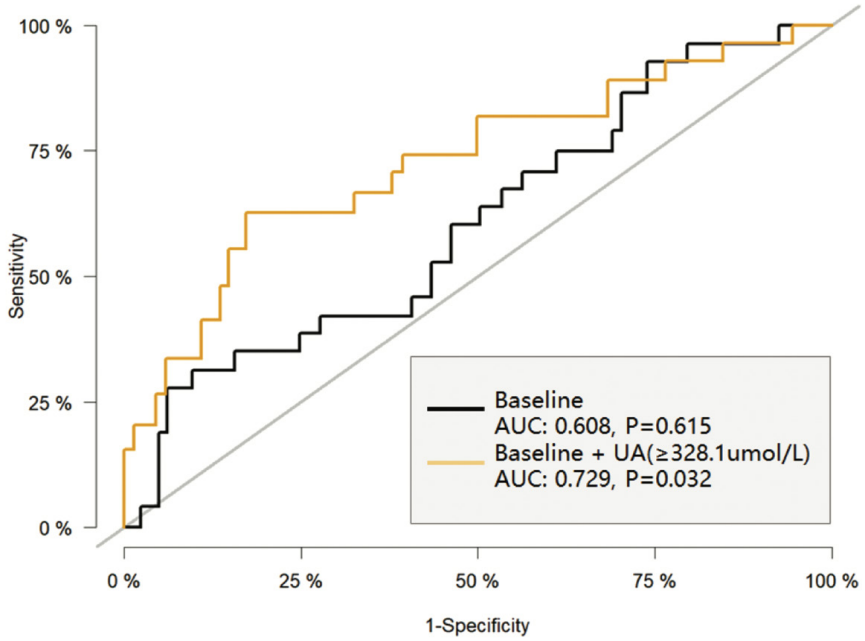

Fig. 3. Enhanced prognostic model for TAK with serum uric acid as a risk factor.
The prognostic ability of the model based on the multivariate Cox proportional hazard regression analysis for TAK was evaluated using analysis of the area under the curve (AUC) of receiver-operating characteristic (ROC) curves. The baseline risk model was constructed using age, sex, disease duration and tuberculosis (AUC = 0.608, p=0.615). In the next step, serum UA level ≥328.1 umol/L was added to the model as a risk factor (AUC = 0.729, p=0.032), which was accompanied with an increased AUC.

Table V. Results of analysis for evaluating the prognostic value of different risk factors.

Baseline / baseline + serum UA level ≥328.1 umol/L

	Index	95% CI	p-value
IDI	0.048	0.001 – 0.220	0.033
NRI category	0.034	0.003 – 0.166	0.033
NRI continue	0.389	0.003 – 0.715	0.047

IDI: integrated discrimination improvement; NRI: net reclassification improvement; CI: confidence interval. Baseline model included sex, age, disease duration and tuberculosis.

(p=0.615) (Fig. 3). Inclusion of serum UA level ≥328.1 umol/L as a risk factor to the baseline model enhanced the predictive ability of the baseline model by increasing the value of AUC to 0.729 (p=0.032) (Fig. 3). Furthermore, IDI analysis, NRI category, NRI continue also indicated a significant improvement in the prognostic ability of the baseline model upon inclusion of serum UA level ≥328.1 umol/L by showing a significantly increased index (IDI index = 0.048, p=0.033; NRI category index = 0.034, p=0.033; NRI continue = 0.389, p = 0.047) (Table V).

Discussion

To the best of our knowledge, this study was the larger study that explored the relationship between PAI and serum uric acid levels in patients with TAK. The main findings of this study are: elevated serum UA level has been identified as a risk factor for the incidence of PAI in TAK (UA level ≥284.5 umol/L) and the PAI-related adverse event prognosis of TAK (UA level ≥328.1 umol/L).

Currently, there are no predictive factors indicating the presence of pulmonary artery involvement in patients with TAK. There were no significant differences in Numano subtypes, ESR, CRP and other inflammatory factors between TAK patients with PAI and without PAI. Thus, distinguishing patients with PAI from those without PAI was difficult unless CTPA was used. The finding in this study that TAK with PAI in Takayasu's arteritis have a longer disease duration. Tuberculosis was significantly higher in TAK patients with PAI compared to those in TAK patients without PAI. These results are consistent with previous studies (11, 23, 24). But these differences are of poor specificity. In univariate analysis and multivariate analysis, the disease duration and tuberculosis were not found to have significant associations with PAI in TAK. However, in the present study it was found that there was a significant difference in serum UA level between TAK with PAI and TAK without PAI, which has not been reported before. This is the study showing that elevated serum UA level has been identified as a risk factor for the incidence of PAI in TAK and the PAI-related adverse event prognosis of TAK. This means that clinicians should be vigilant when serum UA level is elevated in female TAK patients, because PAI worsens the prognosis of TAK through inducing PAH (7, 8, 25) and by showing increased incidences of serious infection, respiratory infection, and nontuberculous mycobacteria infection (12) and poor prognosis (26). Needless to say, the effects of in TAK with PAI is not limited to PAH. For example, in Figure 4 we present CTA images of a 24-year-old female patient with PAI who had an elevated serum UA level and showed pulmonary artery occlusion and concurrent pulmonary infarction.

A previous study has shown that patients with idiopathic pulmonary hypertension (IPAH) have elevated serum UA level (27). Furthermore, other studies have investigated the role of UA in the pathogenesis of PAH by examining cultured pulmonary artery smooth muscle cells (PA-SMCs) derived from IPAH patients (28) and human pulmonary artery endothelial cells (PA-ECs) (29) together with studying animal models of severe PAH. The irreversible remodelling of the pulmonary vasculature in PAH is governed by elevated proliferation, migration and survival of pulmonary vascular cells within the PA wall, including of PA-SMCs and PA-ECs (30). Thus, *in vitro* tests demonstrated that increased UA concentrations induced a mild increase in the cell growth of cultured PA-SMCs

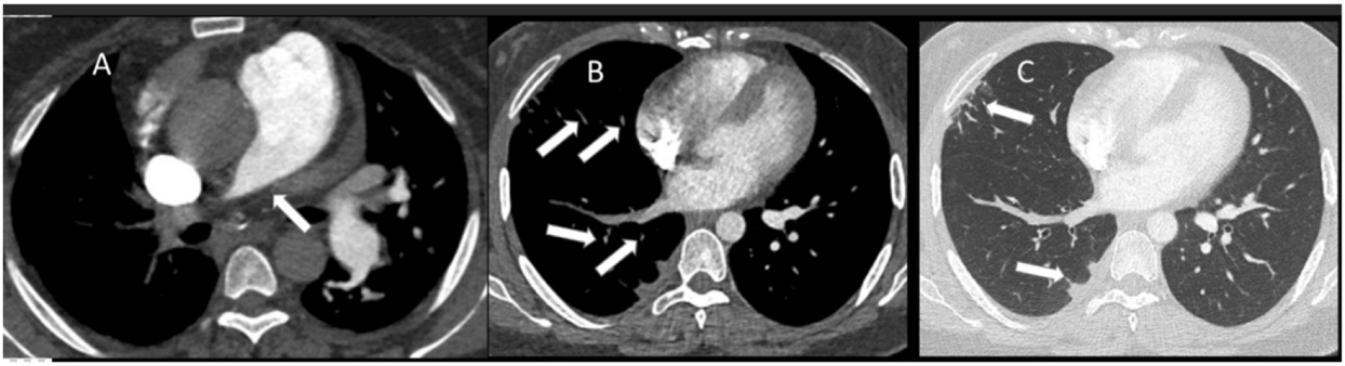

Fig. 4. Imaging findings of pulmonary artery involvement in patients with TAK.
A: Computed tomography angiography (CTA) images of a 39-year-old female with TAK showed pulmonary artery occlusion (white arrows mark) and pulmonary hypertension. Her serum uric acid level was 921 umol/L.
B: A 24-year-old female patient with TAK showed PAI. She had a history of hyperuricaemia for many years. The white arrows mark pulmonary artery occlusion in the images.
C: The 24-year-old female with TAK had multiple pulmonary infarctions (white arrows mark) and her serum uric acid level was 387.1 umol/L

derived from IPAH patients (but not in PA-SMCs derived from controls) (28). UA production is accompanied by an increase in the activity of the enzyme xanthine oxidase (XO), which is one of the key origins of oxygen free radicals (31). Hence, examination of the lungs of patients with IPAH and those of two animal models with a severe form of PAH revealed the upregulation of the protein expression of XO and URATv1 (voltage-driven urate transporter 1; an influx transporter of urate (32) in the wall of remodelled PAs, thus showing a disturbance in the production and metabolism of UA (28). Also, chronic treatment of PAH rats with benzbromarone (an inhibitor of URATv1) induced a mild reduction in pulmonary vascular remodelling (30). Consistent with these results, the expression of messenger RNA (mRNA) was identified for URATv1 and MCT9 (monocarboxylic acid transporter 9; an influx transporter of urate (33)) in UA-cultured human PA-ECs and for URATv1 in the lungs of a rat model with severe PAH (29). Furthermore, upon inducing hyperuricaemia in PAH rats by feeding them with 2% oxonic acid (an inhibitor of the hepatic enzyme uricase that degrades UA in rodents), their lung UA level was increased, which was accompanied with a higher elevation of right ventricular systolic pressure with exacerbation of occlusive neointimal lesions in small PAs, compared with non-hyperuricaemic PAH rats. Moreover, administering benzbromarone to hyperuriacemic PAH rats resulted in a significant decrease in lung UA levels and reducaed right ventricular systolic pressure increase and occlusive lesion development (29).

UA is the final product of exogenous purines and endogenous purine metabolisms (31) and is elevated in hypoxic states, *e.g.*, in obstructive pulmonary disease (34). Under hypoxia and/or ischaemia, UA production via degradation of adenine nucleotides increases due to the depletion of adenosine triphosphate (ATP) resultant from the impairment in the cellular capability of ATP synthesis (35). Hypoxia affects inflammatory responses related to the structure and function of PA (36). Thus, elevated serum UA level has been found to be a biomarker of PAH (14). Elevated serum UA level has also been identified in rheumatic diseases (37) including lupus nephritis (38) and SSc (39). In the present study we found that elevated serum UA level was predictive of adverse events due to PAI in TAK and was a biomarker of poor prognosis. The adverse events considered were exacerbation or new occurrence of PAI (changes in PAs related to increased wall thickening, stenosis, occlusion and dilatation as assessed by CTPA) and exacerbation or new occurrence of PAI leading to disease progression events (exacerbation or new occurrence of PAH, exacerbation or new onset of hypoxemia, new pulmonary infarction, exacerbation or new onset of oppression in chest, and death). Zhao *et al*. research serum UA levels in active TAK patients were significantly higher than in inactive TAK patients (40). In our study the active disease group showed a slight increase in serum uric acid levels compared to the inactive disease group. However, the results of this study revealed no correlation between uric acid and disease activity. This could be due to the limited number of TAK patients in the inactive disease group in our study. Previous studies have shown that elevated serum UA level is positively associated with disease severity and/or poor prognosis in patients suffering from PAH of different aetiologies (41, 42), connective tissue disease (CTD)-associated PAH (43, 44) [including PAH in SLE (16) and PAH secondary to SSc (45)], and IPAH (27). In particular, baseline elevated serum UA level has been found to be associated with a lower survival in patients with IPAH (a 2.6-fold increased risk of 5-year death) (27) and PAH secondary to CTD (43, 44). Moreover, serum UA level is negatively correlated with functional status in patients with PAH due to SSc (46) and is positively correlated with pulmonary vascular resistance in patients with PAH secondary to CTD (43). Furthermore, baseline serum UA level >357 umol/L was found to have significant association with PAH (OR=9.7) in SLE patients (16) and elevated baseline UA was associated with significantly increased odds of PAH diagnosis at right heart catheterisation (OR=4.1) in SSc patients (45).

A first limitation is that this is a retrospective study, and it is subject to research bias due to the limitations in research methods and the restricted number of participants included. Secondly, a notable limitation of this study lies in its small sample size, which may impact the generalisability of the findings. A prospective cohort study with a larger number of TAK patients is required to confirm the usefulness of elevated serum UA level as a biomarker of PAI in TAK and its prognostic value for TAK with PAI.

Conclusion

In conclusion, our research underscores the significant association between elevated serum uric acid (UA) levels (≥284.5 umol/L) and an increased incidence PAI in TAK patients. Notably, TAK patients with serum UA levels ≥328.1 umol/L exhibited twice the incidence of adverse events related to PAI compared to those with lower UA levels. This underscores the prognostic significance of elevated serum UA levels as a risk factor for PAI-related outcomes in TAK. Consequently, indicating serum UA level potential as a predictor for identification of PAI onset and worsening in TAK patients.

References

1. NUMANO F, OKAWARA M, INOMATA H, KOBAYASHI Y: Takayasu's arteritis. *Lancet* 2000; 356(9234): 1023-25. https://doi.org/10.1016/S0140-6736(00)02701-x
2. TERAO C: Revisited HLA and non-HLA genetics of Takayasu arteritis--where are we? *J Hum Genet* 2016; 61(1): 27-32. https://doi.org/10.1038/jhg.2015.87
3. ONEN F, AKKOC N: Epidemiology of Takayasu arteritis. *Presse Med* 2017; 46(7-8 Pt 2): e197-203. https://doi.org/10.1016/j.lpm.2017.05.034
4. ZHANG Z, WANG W, ZHOU M, LU P, LI Y, CHEN Y: An Observational study of sex differences in Takayasu arteritis in China: implications for worldwide regional differences. *Ann Vasc Surg* 2020; 66: 309-17. https://doi.org/10.1016/j.avsg.2019.12.007
5. JANG SY, SEO SR, PARK SW, KIM DK: Prevalence of Takayasu's arteritis in Korea. *Clin Exp Rheumatol* 2018; 36 (Suppl. 111): S163-64
6. SARITAS F, DONMEZ S, DIRESKENELI H, PAMUK ON: The epidemiology of Takayasu arteritis: a hospital-based study from northwestern part of Turkey. *Rheumatol Int* 2016; 36(7): 911-16. https://doi.org/10.1007/s00296-016-3445-z
7. HE Y, LV N, DANG A, CHENG N: Pulmonary artery involvement in patients with Takayasu Arteritis. *J Rheumatol* 2020; 47(2): 264-72. https://doi.org/10.3899/jrheum.190045
8. YANG J, PENG M, SHI J, ZHENG W, YU X: Pulmonary artery involvement in Takayasu's arteritis: diagnosis before pulmonary hypertension. *BMC Pulm Med* 2019; 19(1): 225. https://doi.org/10.1186/s12890-019-0983-7
9. BICAKCIGIL M, AKSU K, KAMALI S *et al*.: Takayasu's arteritis in Turkey - clinical and angiographic features of 248 patients. *Clin Exp Rheumatol* 2009; 27 (Suppl. 52): S59-64.
10. LEE GY, JANG SY, KO SM *et al*.: Cardiovascular manifestations of Takayasu arteritis and their relationship to the disease activity: analysis of 204 Korean patients at a single center. *Int J Cardiol* 2012; 159(1): 14-20. https://doi.org/10.1016/j.ijcard.2011.01.094
11. LIAO H, ZHANG N, PAN L, DU J, LIU J, ZHENG Y: Predictors for pulmonary artery involvement in Takayasu arteritis and its cluster analysis. *Arthritis Res Ther* 2023; 25(1): 9. https://doi.org/10.1186/s13075-022-02987-4
12. MUKOYAMA H, SHIRAKASHI M, TANAKA N *et al*.: The clinical features of pulmonary artery involvement in Takayasu arteritis and its relationship with ischemic heart diseases and infection. *Arthritis Res Ther* 2021; 23(1): 293. https://doi.org/10.1186/s13075-021-02675-9
13. ZHOU Y, CHEN M, ZHENG J *et al*.: Insights into the relationship between serum uric acid and pulmonary hypertension (Review). *Mol Med Rep* 2024; 29(1). https://doi.org/10.3892/mmr.2023.13133
14. SMITS AJ, BOTROS L, MOL M *et al*.: A systematic review with meta-analysis of biomarkers for detection of pulmonary arterial hypertension. ERJ *Open Res* 2022; 8(2). https://doi.org/10.1183/23120541.00009-2022
15. COGHLAN JG, DENTON CP, GRUNIG E *et al*.: Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. *Ann Rheum Dis* 2014; 73(7): 1340-49. https://doi.org/10.1136/annrheumdis-2013-203301
16. HUANG C, LI M, LIU Y *et al*.: Baseline characteristics and risk factors of pulmonary arterial hypertension in systemic lupus erythematosus patients. *Medicine* 2016; 95(10): e2761. https://doi.org/10.1097/md.0000000000002761
17. AREND WP, MICHEL BA, BLOCH DA *et al*.: The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. *Arthritis Rheum* 1990; 33(8): 1129-34. https://doi.org/10.1002/art.1780330811
18. GRAYSON PC, PONTE C, SUPPIAH R *et al*.: 2022 American College of Rheumatology/EULAR classification criteria for Takayasu arteritis. *Ann Rheum Dis* 2022; 81(12): 1654-60. https://doi.org/10.1136/ard-2022-223482
19. MORETTI M, TREPPO E, MONTI S *et al*.: Systemic vasculitis: one year in review 2023. *Clin Exp Rheumatol* 2023; 41(4): 765-73. https://doi.org/10.55563/clinexprheumatol/zf4daj
20. KERR GS, HALLAHAN CW, GIORDANO J *et al*.: Takayasu arteritis. *Ann Intern Med* 1994; 120(11): 919-29. https://doi.org/10.7326/0003-4819-120-11-199406010-00004
21. MISRA R, DANDA D, RAJAPPA SM *et al*.: Development and initial validation of the Indian Takayasu Clinical Activity Score (ITAS2010). *Rheumatology* 2013; 52(10): 1795-801. https://doi.org/10.1093/rheumatology/ket128
22. HATA A, NODA M, MORIWAKI R, NUMANO F: Angiographic findings of Takayasu arteritis: new classification. *Int J Cardiol* 1996; 54 Suppl: S155-63. https://doi.org/10.1016/s0167-5273(96)02813-6
23. KONG X, MA L, LV P *et al*.: Involvement of the pulmonary arteries in patients with Takayasu arteritis: a prospective study from a single centre in China. *Arthritis Res Ther* 2020; 22(1). https://doi.org/10.1186/s13075-020-02203-1
24. XI X, DU J, LIU J, ZHU G, QI G, PAN L: Pulmonary artery involvement in Takayasu arteritis: a retrospective study in Chinese population. *Clin Rheumatol* 2021; 40(2): 635-44. https://doi.org/10.1007/s10067-020-05271-5
25. TOLEDANO K, GURALNIK L, LORBER A *et al*.: Pulmonary arteries involvement in Takayasu's arteritis: two cases and literature review. *Semin Arthritis Rheum* 2011; 41(3): 461-70. https://doi.org/10.1016/j.semarthrit.2011.06.001
26. HUANG Z, GAO D, LIU Z, LIU X, LIANG Y: Long-term outcomes and prognostic predictors of patients with Takayasu's arteritis along with pulmonary artery involvement. *Clin Exp Rheumatol* 2022; 40(4): 765-71. https://doi.org/10.55563/clinexprheumatol/mbs830
27. YAN L, HUANG Z, ZHAO Z *et al*.: The prognostic impact of serum uric acid on disease severity and 5-year mortality in patients with idiopathic pulmonary artery hypertension. *Front Med* (Lausanne) 2022; 9. https://doi.org/10.3389/fmed.2022.805415
28. SAVALE L, AKAGI S, TU L *et al*.: Serum and pulmonary uric acid in pulmonary arterial hypertension. *Eur Respir J* 2021; 58(2). https://doi.org/10.1183/13993003.00332-2020
29. WATANABE T, ISHIKAWA M, ABE K *et al*.: Increased lung uric acid deteriorates pulmonary arterial hypertension. *J Am Heart Assoc* 2021; 10(23): e22712. https://doi.org/10.1161/jaha.121.022712
30. HUMBERT M, GUIGNABERT C, BONNET S *et al*.: Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. *Eur Respir J* 2019; 53(1). https://doi.org/10.1183/13993003.01887-2018
31. LI K, LI K, YAO Q *et al*.: The potential relationship of coronary artery disease and hyperuricemia: A cardiometabolic risk factor. *Heliyon* 2023; 9(5): e16097. https://doi.org/10.1016/j.heliyon.2023.e16097
32. NAKANISHI T, OHYA K, SHIMADA S, ANZAI N, TAMAI I: Functional cooperation of URAT1 (SLC22A12) and URATv1 (SLC2A9) in renal reabsorption of urate. *Nephrol Dial Transpl* 2013; 28(3): 603-11. https://doi.org/10.1093/ndt/gfs574
33. OTANI N, KURATA Y, MAHARANI N *et al*.: Evidence for urate uptake through monocarboxylate transporter 9 expressed in mammalian cells and its enhancement by heat shock. *Circ Rep* 2020; 2(8): 425-32. https://doi.org/10.1253/circrep.cr-20-0016

34. BRAGHIROLI A, SACCO C, ERBETTA M, RUGA V, DONNER CF: Overnight urinary uric acid: creatinine ratio for detection of sleep hypoxemia. Validation study in chronic obstructive pulmonary disease and obstructive sleep apnea before and after treatment with nasal continuous positive airway pressure. *Am Rev Respir Dis* 1993; 148(1): 173-78. https://doi.org/10.1164/ajrccm/148.1.173
35. MANY A, HUBEL CA, ROBERTS JM: Hyperuricemia and xanthine oxidase in preeclampsia, revisited. *Am J Obstet Gynecol* 1996; 174(1 Pt 1): 288-91. https://doi.org/10.1016/s0002-9378(96)70410-6
36. THOMPSON M, BRITT RJ, PABELICK CM, PRAKASH YS: Hypoxia and local inflammation in pulmonary artery structure and function. *Adv Exp Med Biol* 2017; 967: 325-34. https://doi.org/10.1007/978-3-319-63245-2_20
37. SARI I, AKAR S, PAKOZ B *et al*.: Hyperuricemia and its related factors in an urban population, Izmir, Turkey. *Rheumatol Int* 2009; 29(8): 869-74. https://doi.org/10.1007/s00296-008-0806-2
38. YANG Z, LIANG Y, XI W, ZHU Y, LI C, ZHONG R: Association of serum uric acid with lupus nephritis in systemic lupus erythematosus. *Rheumatol Int* 2011; 31(6): 743-48. https://doi.org/10.1007/s00296-010-1373-x
39. DE LEONARDIS F, GOVONI M, COLINA M, BRUSCHI M, TROTTA F: Elderly-onset gout: a review. *Rheumatol Int* 2007; 28(1): 1-6. https://doi.org/10.1007/s00296-007-0421-7
40. ZHAO J-M, LI X-H, ZHANG Z-X: The clinical significance of serum uric acid in patients with Takayasu arteritis. *Int J Clin Exp Med* 2017; 10(5): 8276-81.
41. VOELKEL MA, WYNNE KM, BADESCH DB, GROVES BM, VOELKEL NF: Hyperuricemia in severe pulmonary hypertension. *Chest* 2000; 117(1): 19-24. https://doi.org/10.1378/chest.117.1.19
42. NAGAYA N, UEMATSU M, SATOH T *et al*.: Serum uric acid levels correlate with the severity and the mortality of primary pulmonary hypertension. *Am J Resp Crit Care* 1999; 160(2): 487-92. https://doi.org/10.1164/ajrccm.160.2.9812078
43. WANG J, WANG Y, LI X *et al*.: Serum uric acid is associated with disease severity and may predict clinical outcome in patients of pulmonary arterial hypertension secondary to connective tissue disease in Chinese: a single-center retrospective study. *BMC Pulm Med* 2020; 20(1): 272. https://doi.org/10.1186/s12890-020-01309-1
44. NJAMAN W, IESAKI T, IWAMA Y, TAKASAKI Y, DAIDA H: Serum uric Acid as a prognostic predictor in pulmonary arterial hypertension with connective tissue disease. *Int Heart J* 2007; 48(4): 523-32. https://doi.org/10.1536/ihj.48.523
45. SIMPSON CE, DAMICO RL, HUMMERS L *et al*.: Serum uric acid as a marker of disease risk, severity, and survival in systemic sclerosis-related pulmonary arterial hypertension. *Pulm Circ* 2019; 9(3). https://doi.org/10.1177/2045894019859477
46. DIMITROULAS T, GIANNAKOULAS G, DIMITROULA *et al*.: Significance of serum uric acid in pulmonary hypertension due to systemic sclerosis: a pilot study. *Rheumatol Int* 2011; 31(2): 263-67. https://doi.org/10.1007/s00296-010-1557-4