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Risk factors of aortic regurgitation progression in Chinese patients with Takayasu's arteritis: a prospective cohort study

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Abstract

Objective: To elucidate the 3-year follow-up outcomes and risk factors associated with aortic regurgitation progression in Takayasu's arteritis (TAK).

Methods: This study was a prospective cohort study conducted among 77 patients with TAK at Zhongshan Hospital, Fudan University, China. All the participants were followed up and assessed with echocardiography for 3 years, and the baseline characteristics and dynamic changes in the aortic valve were recorded and investigated. A multivariable Cox model was used to explore the risk factors for aortic regurgitation progression.

Results: The median onset age was 36.9 (26.0–44.4) years, and 57 patients (74.0%) were females. Fifty patients (64.9%) complained of aortic regurgitation, which was the most common valvular lesion at baseline. During the 3-year follow-up period, the progression of aortic regurgitation was observed in 29 (37.7%) patients with TAK. The progression group had higher baseline erythrocyte sedimentation rate (ESR; $p = 0.013$) and interleukin (IL)-6 ($p = 0.029$) levels and lower early treatment remission rates ($p = 0.024$). According to the Cox model, the elevated baseline IL-6 level [>13 pg/ml, hazard ratio (HR) = 2.4, 95% confidence interval (CI) = 1.0–5.8, $p = 0.042$] and absence of early treatment remission (HR = 3.3, 95% CI = 1.3–8.2, $p = 0.010$) were the independent risk factors for aortic regurgitation deterioration.

Conclusion: About one-third of patients with TAK experienced aortic regurgitation progression within 3 years from first admission. Elevated IL-6 levels at baseline and absence of early treatment remission were the two important risk factors for subsequent aortic regurgitation progression.

Keywords: aortic regurgitation, risk factor, Takayasu's arteritis

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Introduction

Takayasu's arteritis (TAK) is a chronic vasculitis of unknown aetiology, which mainly involves the aorta and its proximal branches.[1] Although TAK usually affects young Asian women, it occurs in both sexes and other racial groups around the world.[2] Vascular inflammation starts from the adventitia and gradually progresses to the intima, finally leading to arterial stenosis, occlusion, or dilation and even aneurysm.[3] Impairments of cardiac structure and function have been frequently reported in TAK, as the aorta is directly connected to the heart. Notably, aortic valve involvement, mainly manifesting as aortic regurgitation (AR), is the most common cardiac involvement in TAK.[4]

The incidence of AR differs among different TAK populations, ranging from 20.0% to 44.8% worldwide.[1,4–6] In addition to systemic and organic ischemic symptoms according to the

involved vessels, patients with TAK and valvular involvement suffer from cardiac symptoms, including chest tightness and dyspnea, which are nonspecific and may result in the delayed diagnosis of AR.[7,8] TAK-related AR is often secondary to ascending aortic dilatation or aneurysm,[9] which can induce heart failure and arrhythmia,[10,11] and TAK with AR showed an increased risk of poor outcomes.[12–14] Soto *et al.*[15] found that AR was an important predictor of death in TAK patients. Therefore, more attention should be paid to the patients with TAK and AR. In addition, cardiac structure and function should be monitored regularly with echocardiography in clinical practice.

Previous studies on TAK-related AR are mostly designed as case reports, case series studies or cross-sectional studies. Prospective observational studies have been rarely conducted on this subject. The outcomes and relative risk factors of AR progression are rarely reported. In addition, the effect of conservative treatment or surgery on patients with TAK-associated AR is unknown. In this study, we aimed to clarify the characteristics and outcomes of aortic valve involvement among patients with TAK of the East Chinese Takayasu's Arteritis (ECTA) cohort. Furthermore, we sought to identify risk factors for AR progression of TAK.

Methods

Study population

This was a prospective cohort study conducted in participants enrolled from the ECTA cohort, Zhongshan Hospital Fudan University, Shanghai, China[16] from January 2012 to December 2017. The diagnosis of TAK was based on the 1990 American College of Rheumatology (ACR) classification criteria.[17] Specifically, vascular images were obtained by angiographic computed tomography (CTA), magnetic resonance angiography (MRA) and/or PET/CT (positron emission tomography/computer tomography), replacing digital subtraction angiography. In the current study, patients with TAK with age $\geqslant$18 years and complete data on baseline and 3-year follow-up were included. Those with potential confounding conditions, including viral myocarditis, rheumatic heart disease or congenital heart disease, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis and other autoimmune diseases, were excluded.

Clinical assessment and follow-up

The first clinical evaluation at our centre was considered as the baseline timepoint in the current study. Follow-up assessments were performed once a month in the active disease phase and once every 3 months in the remission disease phase. Each patient's clinical data at baseline and during follow-up were collected and recorded in a database. The data included information regarding sex, onset age, duration of disease, cardiovascular risk factors [smoking, hypertension (systolic blood pressure $>$140 mmHg and/or diastolic blood pressure $>$90 mmHg), hypercholesterolemia (low-density lipoprotein cholesterol $>$3.4 mmol/L), overweight (body mass index $>$24 kg/m^2), diabetes mellitus and other risk factors], clinical manifestations, inflammatory markers [erythrocyte sedimentation rate (ESR), high-sensitivity C-reactive protein (hsCRP), serum cytokines (tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6))], arterial imaging, detailed surgical and medical treatment, and echocardiography. All the laboratory results were obtained in the clinical laboratory of Zhongshan Hospital through standard operation. Furthermore, ESR was measured by the Westergren method; hsCRP was tested using an automated biochemical analyser; and cytokines such as TNF-α and IL-6 were tested by chemiluminescence. Arterial imaging follow-up including MRA or CTA or PET/CT was performed at baseline and every 6 months. The vascular lesions were classified according to the 1996 Numano classification,[18] and disease activity was assessed by the Kerr score proposed by the National Institutes of Health (NIH).[1]

Aortic valve assessment

Echocardiography (Philips iE33, Philips Medical Systems, Bothell, WA, USA) was performed at baseline and routinely retested at an interval of 6 months. However, once a patient reported heart problems during any of the 3-year follow-up periods, echocardiography was performed promptly. The echocardiographic images of the aortic valve were evaluated by an echocardiography expert, who was blinded to the symptoms and treatment of patients with TAK. The severity of AR was graded to be mild (vena contracta width $<$0.3 cm), moderate (0.3–0.6 cm) or severe ($>$0.6 cm) according to the guidelines of the American Society of Echocardiography.[19] AR progression

during follow-up was defined by an upgradation of the AR degree (from normal to AR, mild to moderate or severe, moderate to severe) or by an increase of 0.1 cm in the vena contracta width in patients with severe AR.[20] Furthermore, progression in cardiac function was defined as an increase in New York Heart Association (NYHA) functional grade, as opposed to improvement in heart function. Aortic valve and cardiac function outcomes were reviewed and determined by a multidisciplinary team, comprising rheumatologists and cardiologists.

Treatment and remission

TAK treatment includes induction and stable phases. Glucocorticoid is the first-line drug for TAK. The initial dose of oral prednisone or its equivalents was 0.8–1.0 mg/kg per day, which was tapered to 0.3–0.4 mg/kg per day in about 3 months. A combination of immunosuppressants [such as cyclophosphamide (CTX), leflunomide (LEF) and myocophenolate mofetil (MMF), methotrexate (MTX)] and biological preparations [TNF-α antibody (adalimumab) and IL-6 antibody (tocilizumab)] were administered, as directed by the rheumatologists. The major immunosuppressive treatments in the induction period included intravenous CTX 0.4–0.5 g/m^2 per month, oral LEF 10–20 mg per day, oral MTX 10–15 mg per week and oral MMF 1.0–1.5 g per day. After patients achieved clinical remission, intravenous CTX was always replaced by LEF, MTX or MMF in the stable phase, while the drugs used for oral induction were maintained but their doses were reduced according to the disease condition. The criteria of treatment remission were defined as follows according to previous reports:[21,22] (1) no new or worsened systemic symptoms; (2) no new or worsened vascular symptoms; (3) ESR $\leqslant$40 mm/h; and (4) glucocorticoid dose $\leqslant$15 mg/d. Early treatment remission was defined, if the criteria were satisfied after 3 months of treatment. In addition, cardiac valvular surgeries, including aortic valve replacement (AVR) and composite graft repair (CGR), were recorded during the 3 years of follow-up.

Statistical analysis

Data were summarized as frequencies and percentages for categorical variables. Quantitative variables with non-normal contribution were expressed as medians and interquartile ranges (IQR). Differences between participants with and without AR progression were tested with either the Mann–Whitney *U* test or chi-square test. The receiver-operating characteristic (ROC) curve was used to determine the cut-off value of each continuous parameter, and these variables were converted into dichotomous ones. The association between clinical characteristics and AR progression was assessed with the Cox proportional hazard model. The proportional hazards assumption for the Cox regression model fit was fulfilled. Hazard ratios (HRs) and their 95% confidence intervals (CIs) are presented as a measure of association. All factors with a p-value <0.1 in the univariate analysis and statistically significant differences between two groups ($p<0.05$) were included in a multiple Cox regression model. Given the important effect of age and hypertension on AR in previous reports,[23,24] these two factors were included in the final multiple Cox model. Survival curves were reported using the Kaplan–Meier method. All tests were two-sided at the 0.05 significance level. All statistical analyses were performed with the SPSS software (version 25.0, Chicago, IL, USA). Graphs were generated using Prism GraphPad 8.0 (San Diego, CA, USA) and R software (Murray Hill, NJ, USA).

Results

Baseline characteristics of patients with TAK

Seventy-seven patients with TAK were enrolled in our study; 57 (74.0%) patients were females (Table 1). The median age of onset was 36.9 (26.0–44.4) years, and the median disease duration was 12.2 (2.2–49.3) months. Among the participants, 34 (44.2%), 5 (6.5%) and 54 (68.8%) patients had hypertension, coronary artery stenosis and ascending aorta involvement, respectively. Based on the Numano classification, the most common imaging type was type V (43 cases, 55.8%), followed by type I (13 cases, 16.9%) and type IIb (10 cases, 13%). At baseline, 67 (87.0%) patients had active disease. Inflammation indicators, including ESR, hsCRP, serum TNF-α and IL-6, were 46.0 (14.5–67.0) mm/h, 16.9 (2.9–37.5) mg/ml, 7.6 (6.2–11.3) pg/ml and 7.3 (3.3–12.2) pg/ml, respectively.

By echocardiography, 56 (72.7%) cases suffered from 85 valvular abnormalities, including 50 (89.3%) aortic valve, 22 (39.3%) mitral valve and 13 (23.2%) tricuspid valve abnormalities. AR was

Table 1. Baseline clinical characteristics of patients with Takayasu's arteritis.

Characteristics	All ($n=77$)	Aortic regurgitation progression group ($n=29$)	Aortic regurgitation non-progression group ($n=48$)	*p* value
Demographics				
Female, *n* (%)	57 (74.0)	21 (72.4)	36 (75.0)	0.802
Onset age, years	36.9 (26.0–44.4)	40.7 (29.7–47.7)	32.9 (25.1–44.8)	0.274
Duration, months	12.2 (2.2–49.3)	12.2 (2.8–37.3)	14.7 (1.4–66.6)	0.760
Clinical manifestations, *n* (%)				
Chest distress	34 (44.2)	16 (55.2)	18 (37.5)	0.130
Pectoralgia	13 (16.9)	7 (24.1)	6 (12.5)	0.187
Palpitation	23 (29.9)	9 (31.0)	14 (29.2)	0.862
Dyspnea	34 (44.2)	17 (58.6)	17 (35.4)	0.047
Comorbidity, *n* (%)				
Hypertension	34 (55.8)	16 (55.2)	18 (37.5)	0.130
Coronary involvement	5 (6.5)	3 (10.3)	2 (4.2)	0.286
Diabetes mellitus	1 (1.3)	0	1 (2.1)	0.434
Smoking history	5 (6.5)	1 (3.4)	4 (8.3)	0.399
Alcohol intake history	3 (3.9)	0	3 (6.3)	0.170
BMI $>24\,kg/m^2$	27 (35.1)	10 (34.5)	17 (35.4)	0.950
Aortic root dilation	9 (11.7)	5 (17.2)	4 (8.3)	0.238
Numano classification, *n* (%)				0.753
I	13 (16.9)	4 (13.8)	9 (18.8)	
IIA	0	0	0	
IIB	10 (13.0)	3 (10.3)	7 (14.6)	
III	4 (5.2)	2 (6.9)	2 (4.2)	
IV	7 (9.1)	4 (13.8)	3 (6.3)	
V	43 (55.8)	16 (55.2)	27 (56.3)	
Kerr score, *n* (%)				
Kerr score $\geqslant 2$	67 (87.0)	27 (93.1)	40 (83.3)	0.217
Laboratory tests				
ESR, mm/h	46.0 (14.5–67.0)	59.0 (35.0–81.0)	25.0 (14.0–55.8)	0.013
hsCRP, mg/ml	16.9 (2.9–37.5)	23.1 (4.1–63.5)	11.8 (2.9–26.0)	0.133
TNF-α, pg/ml	7.6 (6.2–11.3)	8.3 (7.0–13.5)	7.4 (5.7–10.6)	0.078

(Continued)

Table 1. (Continued)

Characteristics	All ($n = 77$)	Aortic regurgitation progression group ($n = 29$)	Aortic regurgitation non-progression group ($n = 48$)	*p* value
IL-6, pg/ml	7.3 (3.3–12.2)	7.7 (5.7–21.6)	6.1 (2.9–10.0)	0.029
NT-proBNP, pg/ml	204.4 (84.1–1392)	1113.0 (140.9–2874.0)	151.6 (68.6–960.4)	0.010
Treatment				
Prednisone	72 (93.5)	28 (96.6)	44 (91.7)	0.399
Initial dose of prednisone, mg	40 (20–40)	40 (15–45)	32.5 (22.5–40)	0.719
Cyclophosphamide	31 (40.3)	13 (44.8)	18 (37.5)	0.525
Leflunomide	29 (37.7)	15 (51.7)	14 (29.2)	0.048
Mycophenolate mofetil	8 (10.4)	6 (20.7)	2 (4.2)	0.021
Methotrexate	11 (14.3)	6 (20.7)	5 (10.4)	0.212
Early treatment remission	67 (87.0)	22 (75.9)	45 (93.8)	0.024

BMI, body mass index; ESR, erythrocyte sedimentation rate; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; NT-proBNP, N-terminal pro b-type natriuretic peptide; TNF-α, tumour necrosis factor-α.

found in all of the above-mentioned 50 patients with aortic valve lesions, and one patient (1.3%) had AR with aortic stenosis. AR cases were grouped into mild AR (19 cases, 38.0%), moderate AR (17 cases, 34.0%) and severe AR (14 cases, 28.0%) groups. Nine cases (11.7%) also showed aortic root dilatation.

Treatment and response

Among the enrolled patients, 59 (76.6%) were first diagnosed in this study and 18 (23.4%) had been diagnosed before this study, with a median disease course of 74.1 (8.8–125.4) months. Among the previously diagnosed cases, the median initial prednisone dose was 30 (10–40) mg per day, while CTX was given in 7 (38.9%) cases and MTX in 3 (16.7%) cases.

At the baseline of the present study, the median initial prednisone dose in 72 (93.5%) patients was 40 mg per day, which was gradually tapered to 15 mg per day after 3 months. Besides, 31 (40.3%) patients received intravenous CTX, and others chose oral immunosuppressants, including LEF [29 (37.7%) patients], MMF [8 (10.4%) patients] and MTX [11 (14.3%) patients], as induction drugs. For the disease remission phase, 20 patients received LEF as an alternative to CTX, while 5 and 6 patients received MMF and MTX after CTX. In addition, 4 (5.2%) and 2 (2.6%) patients were treated with tocilizumab and adalimumab, respectively.

The early treatment remission rate reached 87.0%. Detailed information of the 10 patients who did not achieve early treatment remission is shown in Supplementary Table 1. Moreover, patients with severe AR were unlikely to experience early treatment remission ($p < 0.001$).

Dynamic detection of AR progression and cardiac function

The echocardiography images obtained during the 3-year follow-up period indicated that 29 (37.7%) patients suffered from AR progression at a median duration of 5.6 months (Figure 1(a)), whereas 15 (19.5%) patients achieved aortic valve improvement. The remaining 33 (42.9%) patients were stable. Compared with patients with mild and moderate AR, patients with severe AR were more likely to have AR progression (Figure 1(b)). In addition, the cardiac function of patients with TAK was monitored during follow-up. Twenty-two (28.6%), 23 (29.9%) and 32 (41.6%) patients had progressed, improved and stable cardiac functions, respectively. A positive correlation was

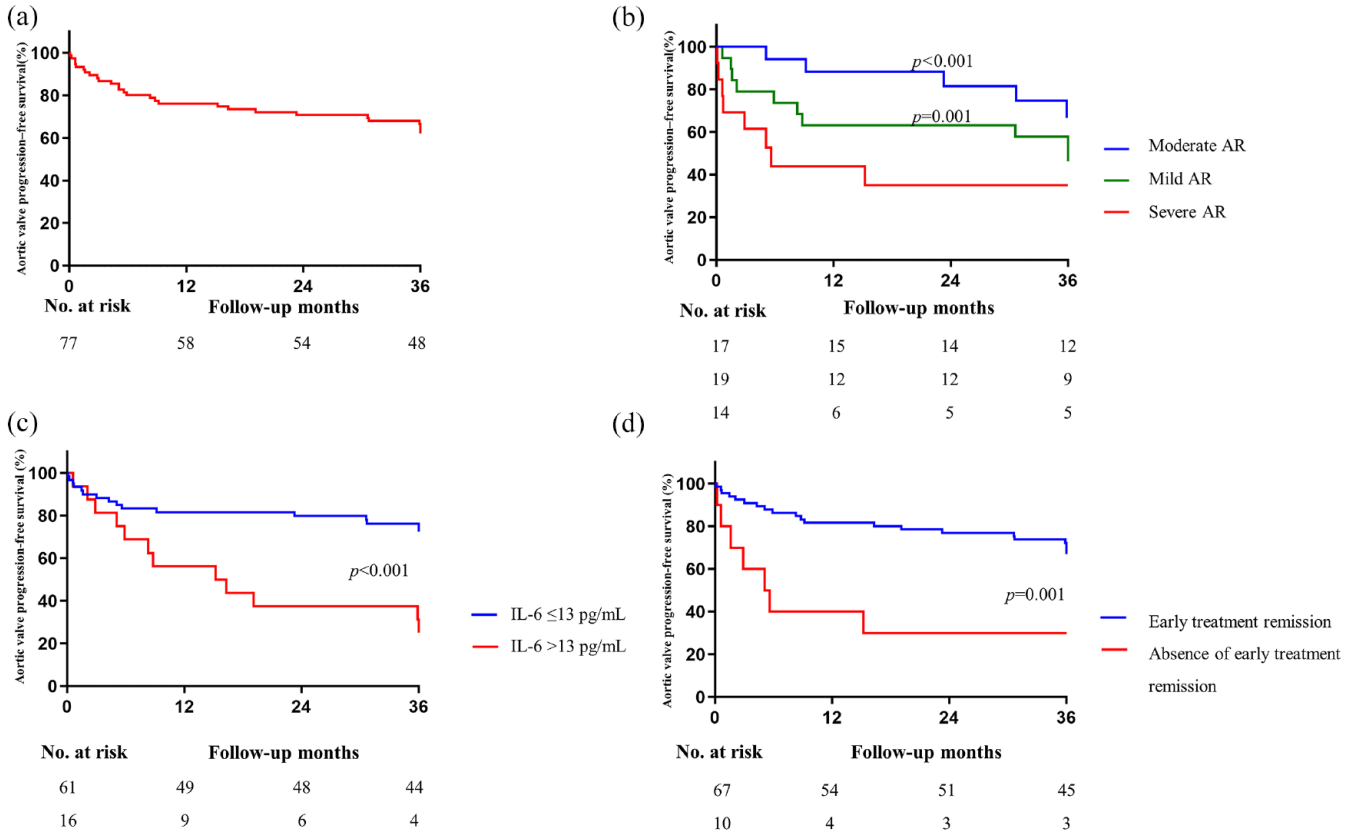

Figure 1. Aortic regurgitation progression-free survival curves in Takayasu's arteritis overall (a), with varying degrees of aortic regurgitation (b) and with different risk factors (c, d).

observed between valve structure and cardiac function changes ($p < 0.001$). Notably, all the severe AR patients with AR structural progression experienced cardiac function progression (Supplementary Figure 1). Among the 48 patients without AR progression, 6 (12.5%) experienced cardiac function deterioration due to coronary artery involvement (3 cases), severe pulmonary hypertension (1 case), acute pulmonary infection (1 case) and severe anaemia (1 case).

Comparison of clinical characteristics between the patients with and without AR progression

In the AR progression group, most patients complained of dyspnea ($p = 0.047$) at baseline; these patients had higher baseline ESR ($p = 0.013$) and serum IL-6 ($p = 0.029$) levels. No significant differences were observed between the two groups in terms of onset age, disease duration, hypertension, coronary artery involvement, Kerr score and Numano classification.

Patients with AR progression were more likely to be treated with LEF ($p = 0.048$), MMF ($p = 0.021$) and tocilizumab ($p = 0.008$). No difference was observed between the different AR progression groups in the treatment with CTX and MTX. Patients with TAK and AR progression were unlikely to experience early treatment remission ($p = 0.024$) (Table 1).

Follow-up arterial imaging

Arterial imaging was systematically performed in 64 TAK patients every 6 months during follow-up, of which 12 patients (18.8%) developed 27 new arterial lesions, including 8 (29.6%) lesions in the subclavian artery, 2 (7.4%) in vertebral artery stenosis, 4 (14.8%) in the common carotid artery, 5 (18.5%) in the renal artery, 2 (7.4%) in the abdominal aorta, 2 (7.4%) in the left common iliac artery, 1 (3.7%) in the external iliac artery and 3 (11.1%) in the popliteal artery. Among the 12 cases with new arterial lesions, 5 patients

Table 2. Risk factors for aortic regurgitation progression in Takayasu's arteritis.

Variable	Univariable Cox regression		Multivariable Cox regression	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Female	1.4 (0.6–3.3)	0.405		
Onset age, years	1.0 (1.0–1.0)	0.243		
Duration, months	1.0 (1.0–1.0)	0.614		
Hypertension	1.7 (0.8–3.5)	0.185		
Pulmonary hypertension	1.6 (0.7–3.6)	0.289		
Coronary artery involvement	1.7 (0.5–5.8)	0.381		
ESR, >45 mm/h	3.0 (1.3–6.9)	0.008		
IL-6, >13 pg/ml[a]	3.6 (1.7–7.8)	0.001	2.4 (1.0–5.8)	0.042
Absence of early treatment remission[b]	3.8 (1.6–9.2)	0.003	3.3 (1.3–8.2)	0.010

CI, confidence interval; ESR, erythrocyte sedimentation rate; HR, hazard ratio; IL-6, interleukin-6.
[a]With adjustment for onset age, hypertension, ESR (>45 mm/h) and absence of early treatment remission.
[b]With adjustment for onset age, hypertension, ESR (>45 mm/h) and IL-6 (>13 pg/ml).

(41.7%) experienced AR worsening. No significant relationship was observed between the new arterial lesions and AR worsening ($p = 0.741$).

Risk factors for AR progression in patients with TAK

In the univariate analysis (Table 2), baseline ESR and IL-6 and absence of early treatment remission were associated with AR progression in TAK (all $p < 0.1$). Further multivariate Cox regression analysis revealed that baseline serum IL-6 (>13 pg/ml, HR = 2.4, 95% CI = 1.0–5.8, $p = 0.042$) and absence of early treatment remission (HR = 3.3, 95% CI = 1.3–8.2, $p = 0.010$) were independent risk factors for AR progression with adjustment.

The Kaplan–Meier analysis revealed that patients with higher baseline serum IL-6 level (>13 pg/ml, $p < 0.001$) and absence of early treatment remission ($p = 0.001$) also showed worse progression-free survival during the 3-year follow-up period (Figure 1(c) and (d)).

Tracking TAK patients with AR progression

Among the 29 patients with AR progression, 9 (31.0%) underwent cardiac surgery because of severe AR and gradually aggravated hemodynamic instability, and the other 20 progressive patients had medical treatment only.

For patients who underwent surgery, five and four patients accepted AVR and CGR, respectively, after comprehensive assessment by a multidisciplinary team. Eight surgeries were performed in the first follow-up year. After surgery, the artificial valves remained normal in all patients (Figure 2(a)), and no surgical complications occurred. Medical therapy after cardiac surgery consisted of prednisone and immunosuppressant therapy in all nine patients. The immunosuppressive therapy included CTX (4/9, 44.4%), LEF (3/9, 33.3%), MMF (1/9, 11.1%) and tocilizumab (2/9, 22.2%). In addition, eight patients (88.9%) were administered anticoagulants. For patients who underwent medical treatment only, AR progressed (13/20, 65%) distinctly within the second prolonged follow-up year (Figure 2(b)). After AR progression, 6 cases (30%) received an increased oral dose of the original immunosuppressant (3 MMF, 1 LEF, 1 rapamycin, 1 azathioprine); 2 cases (10%) added another oral immunosuppressant (thalidomide); and 2 patients (10%) were treated with tocilizumab additionally. No new progression of AR was observed after medication changes in these 10 patients. The remaining 10 patients with non-severe AR did not progress again after continuous medical treatment. In addition, a total of 27 TAK

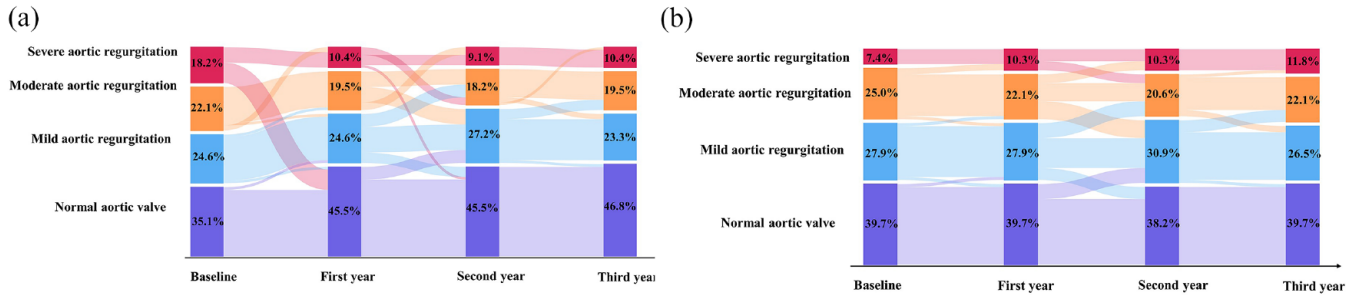

Figure 2. The changing trend of different degrees of aortic regurgitation in Takayasu's arteritis during the 3-year follow-up period ((a) total and (b) with medical therapy alone).

patients did not have AR at baseline, of which 5 patients (18.5%) showed progression during the 3-year follow-up period. All five patients developed moderate AR at the end of the follow-up.

The multivariate Cox regression analysis (Supplementary Table 2) revealed that absence of early treatment remission (HR = 14.6, 95% CI = 3.4–63.1, $p < 0.001$) was significantly associated with aortic valve surgery in patients with TAK, after adjusting for onset age, hypertension, ESR (>45 mm/h) and IL-6 (>13 pg/ml).

Discussion

This study, conducted on the ECTA prospective cohort, sought to assess the dynamic changes in AR among Chinese patients with TAK. Seventy-seven patients with TAK were followed up and assessed with echocardiography for 3 years, and 37.7% of the TAK patients showed AR progression. Patients with TAK were likely to experience obvious changes in aortic valve function during the second follow-up year. Importantly, the elevated IL-6 level (>13 pg/ml) at baseline and absence of early treatment remission were two independent risk factors for AR progression in TAK.

AR is the most common type of TAK valvular involvement. Previous studies have shown that the incidence of AR is between 20.0% and 44.8% in different patient populations with TAK,[4] whereas 64.9% of TAK patients had AR in our study. AR could lead to myocardial remodelling and left ventricular dysfunction. Moreover, it is the main cause of heart failure and death.[10,25] The mechanism of AR remains unclear, but some meaningful findings have been reported. First, aortic root dilation, which has a direct relationship with AR, affects about 25% of patients with TAK.[26] Previous studies have shown that the proportion of valvular involvement is significantly higher in those with ascending aorta dilation in TAK.[4] Second, the disease activity of TAK may affect AR significantly. A study on 204 Korean patients with TAK revealed an association between disease activity and high incidence of AR.[27] In our study, about 87.0% of cases were active at baseline. Among the 77 cases enrolled in the study, 68 showed no aortic root dilatation. Active disease was indicated in 60 (88.2%) of the 68 cases. Moreover, 10 (90.9%) of the 11 TAK patients with Type I Hata's classification were active as well. Patients who did not experience early remission faced an elevated risk of AR progression. Third, chronic inflammation may destroy the normal structure of the aortic valve. Unlike the major finding of mucus degeneration of the aortic valve in the past, current evidence indicated the presence of *in situ* inflammation.[27,28] Inflammatory cells, such as T lymphocytes and macrophages, infiltrated the aorta and valves, and released numerous cytokines and matrix metalloproteinases, which initiated the immune reaction cascade and made the aortic valve fragile.[25,26] The aforementioned evidence indicates a close link between inflammation and the incidence and development of AR in TAK.

Follow-up studies on dynamic echocardiography in TAK are rare. Hashimoto *et al.*[29] conducted a 4-year echocardiographic follow-up of 11 patients and observed no significant changes in the symptoms and cardiac structure of TAK patients with severe AR. In this study, we found that 37.7% of patients with TAK experienced AR progression during a 3-year follow-up period, especially in the second follow-up year. As mentioned above, the inflammatory activity is closely related to AR progression.[30] Ren *et al.*[31] reported that patients with

TAK-AR had higher levels of ESR, CRP, Kerr score, ITAS and ITAS-A. Similarly, our study found that elevated baseline IL-6 was an independent risk factor for AR progression in TAK. IL-6, an important pro-inflammatory factor in the pathogenesis of TAK, can regulate the expression of matrix metalloproteinases and promote wall fibrosis through the IL-6/Jak1 signalling pathway.[32,33] Therefore, tocilizumab, the IL-6 receptor antagonist, successfully demonstrated its efficacy on the treatment of refractory TAK.[34] Therefore, studies on the effects of tocilizumab on the outcomes of TAK-AR are necessary in the future.

Absence of early treatment remission was another independent risk factor for AR progression, which further confirmed the importance of anti-inflammatory treatment for improving the prognosis of TAK. Currently, glucocorticoids and disease-modifying anti-rheumatic drugs (DMARDs) are still recommended as first-line drugs in TAK. A previous study found that patients with TAK who had been treated with prednisone and CTX or azathioprine could maintain a stable condition for a long term within a short period.[35] CTX is one of the most common immunosuppressants that was used for induction in our study. However, no significant differences were found between the control of AR progression with and without CTX. In addition, our study also found that TAK patients with severe AR were less likely to experience treatment remission. Regular follow-up and normative assessment during the early treatment period should be emphasized to ensure that treatment strategies can be altered on-time.

Since the benefits and prognosis of surgical interventions remain unclear, whether patients with TAK and aortic valve involvement should undergo surgery remains controversial.[36] However, if TAK patients with severe AR show cardiac hemodynamic disorders, surgery may be inevitable.[13] In this study, before nine patients received cardiac surgeries (5 AVR and 4 CGR cases), they had been medically treated for not less than 3 months. CGR may help reduce the direct pressure on the vulnerable valvular ring and remove more inflammatory tissues, making patients who underwent CGR more likely to experience long-term valvular stability.[37–39] Furthermore, Kaku *et al.*[40] reported that post-operative mortality within 30 days was 4.5%, and the 5-year survival rate was 90.9%. However, few post-operative complications were observed in our study. For instance, the artificial valves and vessels retained a normal structure and function under the maintenance of clinical remission by sustaining medical treatment.

This study had certain limitations. Since TAK is a rare disease, our study was based on current evidence derived from studies with small sample sizes. Although this study had the largest sample size among studies investigating TAK with dynamic echocardiographic follow-up, further studies with larger sample sizes and longer follow-up periods based on the ECTA cohort should be conducted on the prognosis of aortic valve involvement in patients with TAK. In addition, the absence of a single treatment protocol is an important limitation of this study.

Conclusion

This ECTA-based prospective cohort showed that 37.7% of patients with TAK experienced AR progression. Elevated IL-6 level (>13 pg/ml) at baseline and absence of early treatment remission were the independent risk factors for AR progression in TAK. After identifying the patients with TAK at high risk of AR progression, more vigorous strategies can be recommended to prevent or reduce AR deterioration and cardiac morbidities. In the future, the effectiveness and safety of IL-6 receptor antagonists in the treatment of TAK-related aortic valve disease can be further studied.

Declarations

Ethics approval and consent to participate

This study was approved by the Zhongshan Hospital Ethics Committee (B-2016-168(2)R) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Author contributions

Yujiao Wang: Conceptualization; Data curation; Methodology; Writing – original draft.

Lili Ma: Conceptualization; Data curation; Funding acquisition; Software; Writing – original draft.

Ying Sun: Formal analysis; Investigation; Writing – review & editing.

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Competing interests
The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Availability of data and materials
Please contact the corresponding author for data requests.

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