Impact of coronary involvement on long-term outcomes in patients with Takayasu's arteritis

H. Wang, Z. Liu, Z. Shen, L. Fang, S. Zhang

Department of Cardiology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China.

Abstract

Objective

To identify the predictors of coronary involvement, and to determine the impact of coronary involvement on long-term outcomes in patients with Takayasu's arteritis (TAK).

Methods

This retrospective cohort study of TAK patients with coronary evaluation by angiography or computed tomography angiography was conducted in a tertiary center between 1990 and 2018. Risk factors for coronary involvement and predictors of overall survival, cardiovascular event-free survival, and relapse-free survival were investigated.

Results

The median follow-up was 4.3 years (IQR 2.8–7.1). Out of 130 consecutive TAK patients, 71 (54.6%) had coronary involvement. Multivariate analysis revealed that age (OR: 1.537 per 10-year increase, 95% CI: 1.176–2.009, p=0.002) and type V angiographic classification (OR: 3.449, 95% CI: 1.600–7.437, p=0.002) were independent predictors of coronary involvement. Coronary involvement (HR: 8.358, 95% CI: 1.887–37.033, p=0.015), left ventricular systolic dysfunction (HR: 3.889, 95% CI: 1.467–10.311, p=0.006), and aortic regurgitation (HR: 3.373, 95% CI: 1.209–9.408, p=0.020) were independent predictors of overall survival. Furthermore, coronary involvement and baseline active disease were independently associated with increased major cardiovascular events (HR: 10.333, 95% CI: 2.326–45.906, p=0.017; HR: 7.084, 95% CI: 1.677–29.914, p=0.008, respectively) and relapse (HR: 5.186, 95% CI: 2.381–11.295, p<0.001; HR: 5.694, 95% CI: 2.022–16.031, p=0.001, respectively). No immunosuppressive therapy was independently associated with increased cardiovascular events (HR: 2.560, 95% CI: 1.181–5.550, p=0.002).

Conclusion

Coronary involvement is an important predictor of poor long-term outcomes in patients with TAK. Increasing age and type V angiographic classification can help to identify TAK patients with coronary involvement.

Key words

Takayasu's arteritis, coronary artery, survival

Hui Wang, MD
Zhenyu Liu, MD
Zhujun Shen, MD
Ligang Fang, MD
Shuyang Zhang, MD

Please address correspondence to:
Zhenyu Liu,
Department of Cardiology,
Peking Union Medical College Hospital,
Beijing, 100730, China.
E-mail: pumch_lzy@163.com

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Introduction

Takayasu's arteritis (TAK) is a chronic, systemic inflammatory disease involving aorta and its main branches, resulting in stenosis, occlusion and dilation in large vessels (1, 2). The extent and distribution of the vasculitis influence the associated outcome, with coronary artery disease being the leading cause of morbidity and mortality in these cases (3). As TAK tend to occur in young women without traditional cardiovascular risk factors, early diagnosis of coronary involvement is challenging in these patients. Missing or delaying the diagnosis of coronary involvment may have a profound impact on patient outcome, as coronary disease could result in severe and often life-threatening complications. Coronary involvement is a special but not rare type of TAK. Coronary involvement is detected by coronary computed tomography angiography (CTA) in up to 53.2% of patients with TAK (4), but becomes symptomatic in only 5% to 20% of the cases (5-8). However, end-organ ischaemia associated with coronary insufficiency had already progressed, when patients started to present with ischaemic symptoms. This coronary insufficiency can lead to significant morbidity, such as acute myocardial infarction (MI), unstable angina (UA), heart failure, or ischaemic heart disease (8). Along with aortic valve disease, and heart failure, MI is a leading cause of death in TAK (5, 9).

Prior studies suggested that once TAK patients had progressed to develop vascular complications, the outcome would be poor (10, 11). Therefore, there is a significant unmet need to identify coronary involvement prior to ischaemic complications. However, it is not known which subsets of patient are at high risk for coronary involvement and cardiovascular events. The unknown aetiology and the rarity of this disease, as well as the wide variation in its clinical course (12), make the risk factors for coronary involvement difficult to assess.

Currently, clinical analyses from a large series of TAK patients with complete coronary evaluation are lacking, and the predictors of coronary involvement have not been clarified. The impact of coronary involvement on the clinical course and long-term outcomes of TAK patients has not been evaluated in a systemic manner.

The aim of this study was to identify the predictors of coronary involvement, as well as the impact of coronary involvement on long-term outcomes in patients with TAK.

Patients and methods

Patients

In this retrospective cohort study, all patients admitted to Peking Union Medical College Hospital (PUMCH), a tertiary referral centre, between Janurary 1990 and June 2018, with an International Classification of Diseases 10th Revision code for TAK (M31.4), were identified. All medical records were reviewed to confirm the diagnosis of TAK according to the 1990 American College of Rheumatology (ACR) criteria for TAK (13). Patient without complete angiographic evaluation or dataset were excluded. The indications for coronary angiography or CTA included MI, angina pectoris, chest pain, dyspnea, abnormal ECG or echocardiograph, elevated cardiac biomarkers, or aortic angiography/CTA abnormal findings. A total of 130 TAK patients with complete coronary evaluation were included into this study. The study protocol was approved by the Institutional Review Board of PUMCH (approval no. S-K911), and informed consent was obtained from all patients or their relatives.

Data collection

Baseline clinical characteristics including age and age at onset of TAK, sex, disease activity, disease durations, cardiovascular risk factors (*i.e.* hypertension, smoking, dyslipidaemia, diabetes mellitus, family history of premature coronary artery disease [CAD]), associated diseases (*i.e.* previous MI, stroke, chronic kidney disease [CKD]), clinical features of TAK (*i.e.* systemic and/or vascular symptoms), cardiovascular presentation, physical examination (*i.e.* height, weight, blood pressure), laboratory test (*i.e.* white blood cell, serum creatinine, low-density lipoprotein cholesterol [LDL-C]), erythrocyte sedimentation rate [ESR], high-sensitivity C-reactive protein [hs-CRP]), and imaging

findings were collected and evaluated. The details of treatment (*i.e.* medication and revascularisation) and follow-up outcomes were also collected.

Definitions

Disease duration was defined as the time from TAK symptom onset to the initial coronary angiography or CTA. Disease activity was defined according to the National Institutes of Health criteria (6): (1) presence of systemic signs or symptoms (*i.e.* weight loss, fever, or myalgia); (2) biological activity of disease: increased ESR or hs-CRP; (3) onset of signs or symptoms of vascular insufficiency; and (4) new arterial lesion or worsening of preexisting lesions on imaging. Disease was considered active if the National Institutes of Health score was ≥2 (6). An ESR greater than 15 mm/h in men and 20 mm/h in women by the Westergren method and a hs-CRP greater than 3 mg/L were considered elevated. The angiographic findings were grouped according to the angiographic classification for TAK defined at International Conference in Tokyo in 1994 (14) as follows: Type I involves branches of aortic arch, Type IIa involves ascending aorta, aortic arch and its branches, Type IIb a combination of Type IIa and the involvement of thoracic descending aorta, Type III involves the thoracic descending aorta, the abdominal aorta and/or renal arteries, Type IV involves only the abdominal aorta and/or renal arteries, Type V a combination of Type IIa and Type IV. Coronary involvement included mural thickening, narrowing, or occlusion of the lumen of coronary arteries, aneurysmal coronary ectasia, and coronary aneurysm (15).

Hypertension was defined by the use of antihypertensive medication or self-reported a history of hypertension, or current blood pressure higher than 140 mmHg (systolic) or 90 mmHg (diastolic). Smoking was defined as any active regular use or a history of regular use. Diabetes was defined as fasting blood glucose greater than or equal to 7.0 mmol/L or self-reported diabetes medication use. A positive family history of premature CAD was defined as CAD before the age of 55 years in men or 65 years in women in a first-degree relative. Dyslipidaemia was defined by LDL ≥3.4 mmol/L, HDL <1.0 mmol/L, total cholesterol ≥ 5.2 mmol/L, or triglycerides ≥1.7 mmol/L(16). CKD was defined as the estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2. Aortic regurgitation was defined as the presence of aortic regurgitation with valvular regurgitation of more than a mild degree being considered significant. Left ventricular (LV) systolic dysfunction was defined as left ventricular ejection fraction (LVEF) <50%.

Study endpoints

The date of first coronary evaluation was referred to as baseline. The primary endpoint was time from baseline to all-cause death. The secondary endpoints were time to major cardiovascular events and relapse events. The major cardiovascular events were defined as the occurrence of ≥1 of the following events: cardiac death, MI, or revascularisation (17, 18). And MI was defined according to the fourth universal definition of myocardial infarction (19). A relapse was defined as the presence of active disease after a remission period requiring change of the treatment regimen (11). The achievement of remission was defined as resolution of clinical and laboratory features of active disease without new vascular lesions on sequential imaging studies (20).

Follow-up

We obtained follow-up for all patients until the primary outcome or date of censoring (March 1, 2019). Mortality and the causes of death were assessed. Coronary CTA or angiography was performed in patients with cardiac symptoms, abnormal cardiovascular tests, or reexamination after revascularisation during follow-up. The changes in disease activity based on clinical examination and laboratory tests were also assessed.

Statistical analysis

Categorical data were presented as frequency and percentage. Continuous variables were reported as mean ± standard deviation or median and interquartile range (IQR). An independent t-test or Mann-Whitney U-test, chi-squared test or Fisher's exact test were performed as appropriate for intergroup comparison. Univariate and multivariate logistic regression analyses were used to identify independent factors associated with coronary involvement. The variables with a probability value <0.1 in the univariate analysis and the cardiovascular risk factors were candidates for the multivariable regression model building. Odds ratios (ORs) and their 95% confidence intervals (CIs) were presented as a measure of association. Survival functions were estimated through Kaplan-Meier survival curves. Overall survival was defined as the time from first coronary evaluation to all-cause death, or last follow-up. Cardiovascular event-free survival was defined as the time from first coronary evaluation to the date of first major cardiovascular event, or last follow-up. Relapse-free survival was defined as the time from first coronary evaluation to the date of first relapse, or last follow-up. Predictors of overall survival, cardiovascular event-free survival, and relapse-free survival were identified using Cox regression analysis, described with hazard ratios (HR) and 95% CIs. Significant candidates for multivariate analysis consisted of complete variables with a *p*-value <0.1 in the univariate Cox model, and potential confounding factors including age, sex, disease duration ≥5 years, elevated ESR and hs-CRP, disease activity and immunosuppressive drugs. A stepwise selection algorithm was performed in the multivariate model. Follow-up estimation (median and IQR) was calculated with an inverse Kaplan-Meier method. All statistical analyses were performed at a two-sided significance level of 0.05 using SPSS software version 22.0 (IBM corporation).

Results

Baseline characteristics

A total of 130 consecutive patients with TAK (78.5% female) were enrolled with an age of 32 (IQR 23-46) years. Of these patients, 71 patients with evidence of coronary involvement were included in the coronary artery involved group, and the other 59 patients were treated as the control group. Patients with coronary involvement were older,

Table I. Baseline data.

Characteristics	Total (n=130)	Coronary artery involved group (n=71)	Control group (n=59)	*p* value
Age, median (p25-p75) years	32 (23-46)	39 (24-50)	28 (20-41)	0.002
Age at onset of TAK, median (p25-p75) years	26 (19-36)	28 (19-41)	25 (18-32)	0.063
Female, n (%)	102 (78.5)	58 (81.7)	44 (74.6)	0.393
Disease duration ≥ 5years, n (%)	41 (31.5)	28 (39.4)	13 (22.0)	0.038
Baseline active disease, n (%)	87 (66.9)	49 (69.0)	38 (64.4)	0.708
Constitutional findings, n (%)				
Fever	31 (23.8)	16 (22.5)	15 (25.4)	0.837
Weight loss	30 (23.1)	15 (21.1)	15 (25.4)	0.677
BMI, mean (SD) kg/m^2	21.7 (4.3)	21.9 (4.3)	21.3 (4.5)	0.622
Laboratory findings, median (p25-p75)				
ESR level, mm/h	24 (11-38)	23 (11-36)	24 (11-38)	0.874
hs-CRP level, mg/l	4.7 (1.1-15.2)	4.5 (1,4-14.1)	4.8 (1.0-15.8)	0.749
eGFR, mL/min/1.73m^2	103.8 (83.6-133.6)	105.0 (81.5-134.4)	103.1 (84.0-125.8)	0.522
LDL-C (mmol/L)	2.86 (2.09-3.88)	2.63 1.74-3.88)	2.93 2.34-3.98)	0.144
Cardiovascular risk factors and comorbidity, n (%)				
Hypertension	66 (50.8)	33 (46.5)	33 (55.9)	0.297
Diabetes mellitus	7 (5.4)	7 (9.9)	0 (0.0)	0.016
Dyslipidaemia	30 (23.1)	17 (23.9)	13 (22.0)	0.837
Smoke	7 (5.4)	4 (5.6)	3 (5.1)	1.000
Premature CAD family history	2 (1.5)	2 (2.8)	0 (0.0)	0.500
CKD	9 (6.9)	6 (8.5)	3 (5.1)	0.510
Previous MI	8 (6.2)	8 (11.3)	0 (0)	0.008
Previous stroke	11 (8.5)	8 (11.3)	3 (5.1)	0.343
Numano angiographic classification, n (%)				
Type I	20 (15.4)	11 (15.5)	9 (15.3)	1.000
Type IIa	8 (6.2)	4 (5.6)	4 (6.8)	1.000
Type IIb	7 (5.4)	2 (2.8)	5 (8.5)	0.244
Type III	7 (5.4)	2 (2.8)	5 (8.5)	0.410
Type IV	11 (8.5)	1 (1.4)	10 (16.9)	0.003
Type V	77 (59.2)	51 (71.8)	26 (44.1)	0.002
Medical treatment, n (%)				
Glucocorticoid	106 (81.5)	50 (70.4)	56 (94.9)	<0.001
Immunosuppressants	92 (70.8)	42 (59.2)	50 (84.7)	0.002
Antiplatelet drugs	87 (67.7)	63 (88.7)	24 (40.7)	<0.001
Statins	56 (43.1)	47 (66.2)	9 (15.3)	<0.001

TAK: Takayasu's arteritis; IQR: interquartile range; BMI: body mass index; ESR: erythrocyte sedimentation rate, hs-CRP: high-sensitivity C-reactive protein; eGFR: estimated glomerular filtration rate; LDL-C: low-density lipoprotein cholesterol; CAD: coronary artery disease; CKD: choronic kidney disease; MI: myocardial infarction.

with a higher rate of disease duration more than 5 years in comparison with those without coronary involvement (Table I). The prevalence of cardiovascular risk factors including gender, hypertension, smoking, obesity, family history of premature CAD, and dyslipidaemia was comparable between the 2 groups; only the frequency of diabetes mellitus was higher in coronary artery involved group.

Laboratory and angiographic features

Elevated ESR and hs-CRP were found in 66.2% and 63.1% of patients, with an ESR and hs-CRP levels of 24 mm/h (IQR 11-38) and 4.7 mg/L (IQR 1.1-15.2), respectively. The frequencies of elevated acute phase reactants and active disease did not differ between the two groups.

With regard to angiographic type, type V (59.2%) was the most common type, followed by type I (15.4%), type IV (8.5%), type IIa (6.2%), type IIb (5.4%), and type III (5.4%) diseases. Type V was significantly more frequent in the coronary artery involved group, while type IV was more frequent in the control group.

Ischaemic presentations and coronary imaging features

Ischaemic symptoms occurred in 64.8% of patients with coronary involvement. The most common manifestation was UA (42.3%), followed by non-ST-segment elevation MI (15.5%), ST-segment elevation MI (7.0%), and stable angina (2.8%).

In total, 169 coronary artery lesions were found in 71 patients. Of these lesions, 47.9% were ostial stenosis, 45.1% at the proximal segment, 45.1% at the midsegment, and 22.5% at the distal segment. Single-vessel disease (47.9%) was the most common disease type, followed by double-vessel disease (29.6%) and triple-vessel disease (19.7%).

Echocardiographic findings

Aortic regurgitation was found in 28 (21.5%) patients, with no statistical difference between the patients with and without coronary involvement (19.7% *vs*. 23.7%, p=0.670). The LVEF (64% IQR [45-67%] *vs*. 60% IQR [43-65%], respectively, p=0.060) and the frequency of LV systolic dysfunction (28.2% vs. 32.2%, p=0.702) were comparable between the coronary artery involved group and the control group. Segmen-

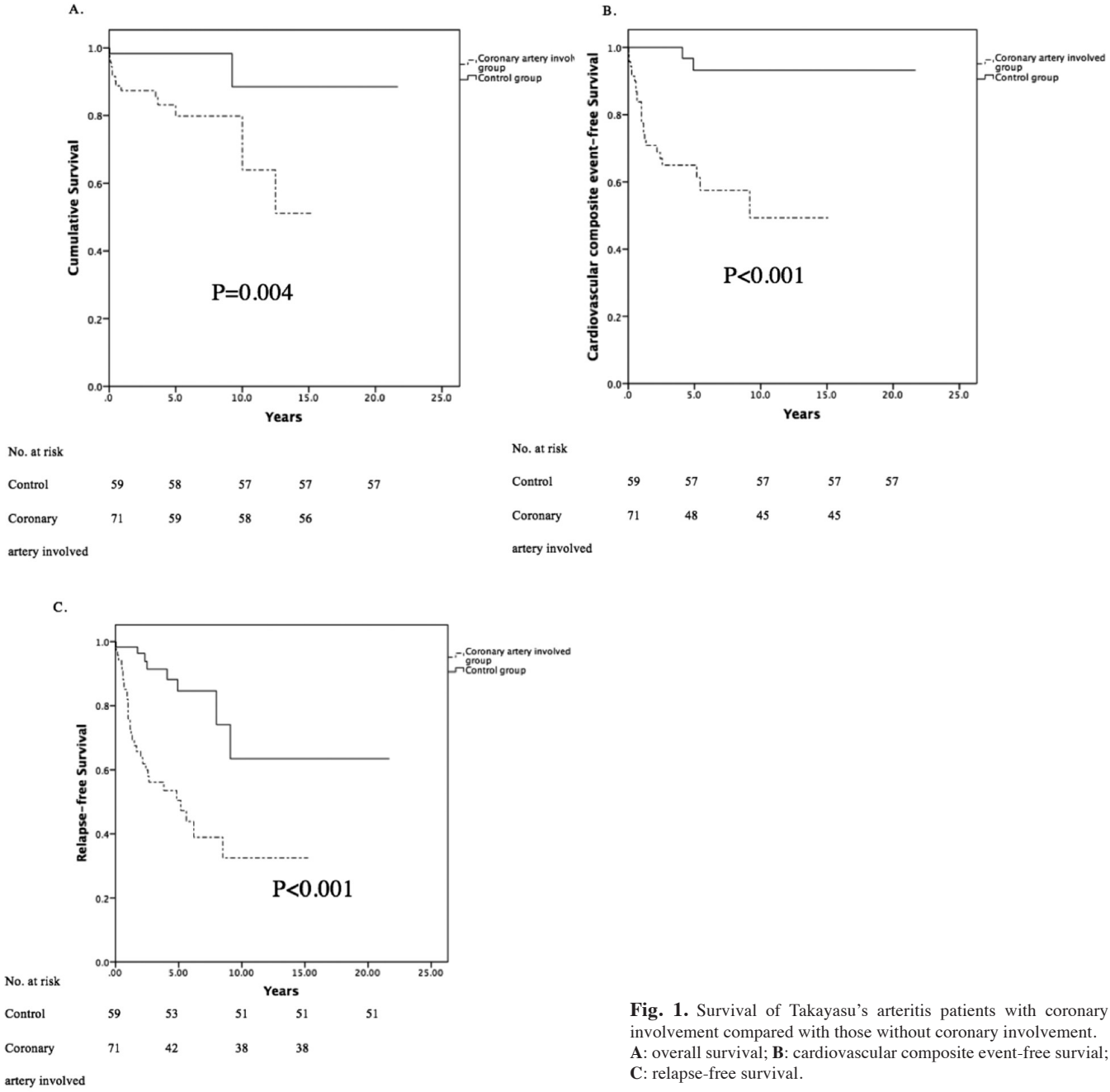

Fig. 1. Survival of Takayasu's arteritis patients with coronary involvement compared with those without coronary involvement. **A**: overall survival; **B**: cardiovascular composite event-free survial; **C**: relapse-free survival.

tal LV wall motion abnormality was more common in the coronary artery involved group (26.8% *vs*. 5.1%, *p*= 0.019).

Treatment

With respect to immunosuppressive therapy, 106 (81.5%) received glucocorticoids, either alone (13.1%) or in combination with immunosuppressants (68.5%). Glucocorticoids were started at a dose of 0.5–1 mg/kg/day for 1 month and tapered to a maintenance dose of 5–10 mg/ day by approximately 6 to 12 months. Immunosuppressants were used in 92 (70.8%) patients, either as an add-on drug to corticosteroids (68.5%) or as a steroid-sparing agent (2.3%). These included cyclophosphamide in 52.3%, methotrexate in 10.8%, mycophenolate mofetil in 5.4%, azathioprine in 3.1%, leflunomide in 3.1%, and biotherapy in 3.1% of cases.

Antiplatelet therapy was administered to 87 (66.9%) patients, with aspirin monotherapy in 42 (32.3%), clopidogrel monotherapy in 5 (3.8%), and duel antiplatelet therapy in 40 (30.8%) patients. Statins were given to 56 (43.1%) patients.

Patients with coronary involvement were less likely to have been treated with immunosuppressive therapy, but were more likely to have received antiplatelet and lipid-lowering medications than those without coronary involvement (Table I). Revascularisation was performed in 28 (39.4%) of 71 patients with coronary involvement, including percutaneous coronary intervention in 18 (25.4%) and coronary artery bypass grafting in 10 (14.1%) patients.

Table II. Predictors of primary and secondary endpoints in univariate analysis.

Variables	Overall survival		Cardiovascular event-free survival		Relapse-free survival	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age	1.016 (0.986-1.047)	0.292	1.023 (1.000-1.046)	0.049	1.021 (1.002-1.040)	0.032
Age at onset of TAK	1.376 (0.687-2.758)	0.368	1.025 (1.000-1.051)	0.049	1.017 (0.996-1.038)	0.106
Male	1.165 (0.379-3.577)	0.790	1.363 (0.577-3.223)	0.480	1.618 (0.805-3.256)	0.177
Disease duration ≥5years	1.338 (0.490-3.650)	0.570	1.022 (0.460-2.268)	0.958	1.533 (0.808-2.906)	0.191
Coronary involvement	6.604 (1.509-28.899)	0.012	14.275 (3.383-60.232)	<0.001	4.781 (2.204-10.370)	<0.001
Previous MI	3.099 (0.683-14.068)	0.143	4.278 (1.590-11.512)	0.004	3.166 (1.216-8.239)	0.018
Previous stroke	1.666 (0.472-5.879)	0.427	1.948 (0.738-5.137)	0.178	1.479 (0.621-3.523)	0.377
Elevated ESR	1.127 (0.396-3.209)	0.823	1.525 (0.648-3.589)	0.334	2.558 (1.133-5.774)	0.024
Elevated hs-CRP	2.679 (0.769-9.335)	0.122	1.014 (0.468-2.200)	0.971	1.831 (0.897-3.737)	0.096
Baseline active disease	0.848 (0.313-2.300)	0.746	6.759 (1.604-28.484)	0.009	5.159 (1.838-14.479)	0.002
Type V angiographic classification	3.499 (1.005-12.187)	0.049	1.899 (0.836-4.315)	0.126	1.640 (0.849-3.168)	0.141
LV systolic dysfunction	2.773 (1.069-7.194)	0.036	1.597 (0.748-3.413)	0.227	1.155 (0.598-2.233)	0.667
Aortic regurgitation	2.973 (1.072-8.247)	0.036	0.969 (0.368-2.555)	0.949	0.778 (0.326-1.856)	0.572
Steroids	0.758 (0.262-2.194)	0.609	0.241 (0.114-0.507)	<0.001	0.453 (0.234-0.876)	0.019
Immunosuppressants	0.658 (0.246-1.763)	0.406	0.495 (0.234-1.045)	0.065	0.561 (0.300-1.047)	0.070
Steroids + immunosuppressants	0.772 (0.286-2.085)	0.609	0.572 (0.271-1.208)	0.143	0.664 (0.355-1.242)	0.200
No steroids or immunosuppressants	1.632 (0.566-4.705)	0.364	5.278 (2.503-11.130)	<0.001	2.927 (1.513-5.664)	0.001

HR: hazard ratio; CI: confidence interval; TAK: Takayasu's arteritis; MI: myocardial infarction; ESR: erythrocyte sedimentation rate; hs-CRP: high-sensitivity C-reactive protein; LV: left ventricular.

Risk factors for coronary involvement

Baseline variables, including cardiovascular risk factors, body mass index (BMI), CKD, LDL-C levels, elevated ESR or hs-CRP, disease activity, and ascending aorta involvement did not correlate with coronary involvement (all $p>0.05$). In univariate analysis, age (OR 1.505 per 10-year increase, 95% CI 1.166–1.944, $p=0.002$), age at onset of TA (OR 1.361 per 10-year increase, 95% CI 1.020–1.817, $p=0.036$), over 5 years of disease duration (OR 2.304, 95% CI 1.058–5.017, $p=0.036$), type IV (OR 0.070, 95% CI 0.009–0.565, $p=0.013$), and type V angiographic classification (OR 3.237, 95% CI 1.561-6.710, $p=0.002$) were associated with coronary involvement. Multivariate analysis revealed that age (OR 1.537 per 10-year increase, 95% CI 1.176–2.009, $p=0.002$) and type V angiographic classification (OR 3.449, 95% CI 1.600–7.437, $p=0.002$) were independent predictors of coronary involvement in patients with TAK.

Overall survival

During a median follow-up of 4.3 years (IQR 2.8-7.1), 17 (13.1%) patients died. The deaths were due to heart failure (n=5, 29.4%), acute MI (n=2, 11.8%), pulmonary infection (n=2, 11.8%), haemorrhage (n=2, 11.8%), stroke (n=2, 11.8%), end stage renal disease (n=1, 5.9%), septic shock (n=1, 5.9%), postoperative complication (n=1, 5.9%), and end-stage malignancy (n=1, 5.9%). The 1-, 5-, and 10-year overall survival were 92.3%, 90.0%, and 87.7% respectively, with a mean survival of (17.0±1.2) years (95% CI 14.7–19.3).

Patients in the coronary artery involved group had significantly higher rates of all-cause death and cardiac death compared with the control group (21.1% *vs.* 3.4%, $p=0.003$; 9.9% *vs.* 0%, $p=0.016$, respectively). The survival rate was significantly lower in patients with coronary involvement ($p=0.04$, log-rank) (Fig. 1A).

In univariate analysis, coronary involvement, Type V angiographic classification, LV systolic dysfunction, and aortic regurgitation were associated with overall survival (Table II). Coronary involvement, LV systolic dysfunction, and aortic regurgitation were independent prognostic predictors of overall survival in multivariate analysis (Fig. 2).

Major cardiovascular events

A total of 28 (21.5%) patients experienced at least one major cardiovascular event, with the 1-year, 5-year, and 10-year cardiovascular event-free survival of 90.0%, 80.8%, and 78.5%, respectively. The cardiovascular event-free survival of the coronary artery involved group were significantly lower than the control group (Fig. 1B).

Univariate analysis demonstrated an increased risk of major cardiovascular events in patients with older age, late onset of TAK, baseline active disease, coronary involvement, previous MI, no use of glucocorticoids or immunosuppressive therapy (Table II). In multivariable models, baseline active disease, coronary involvement and immunosuppressive therapy were independently associated with cardiovascular event-free survival (Fig. 2).

Relapse

Forty-one (31.5%) patients experienced at least one relapse with the 1-year, 5-year, and 10-year relapse-free survival of 89.2%, 73.1%, and 68.5%, respectively. The relapse-free survival was significantly worse in the coronary artery involved group ($p<0.001$) (Fig. 1C). Univariate analysis demonstrated an increased risk of relapse in patients with older age, baseline active disease, coronary involvement, previous MI, elevated ESR, no use of glucocorticoids or immunosuppressive therapy (Table II). In multivariate analysis, baseline active disease and coronary involvement were independent predictors of relapse (Fig. 2).

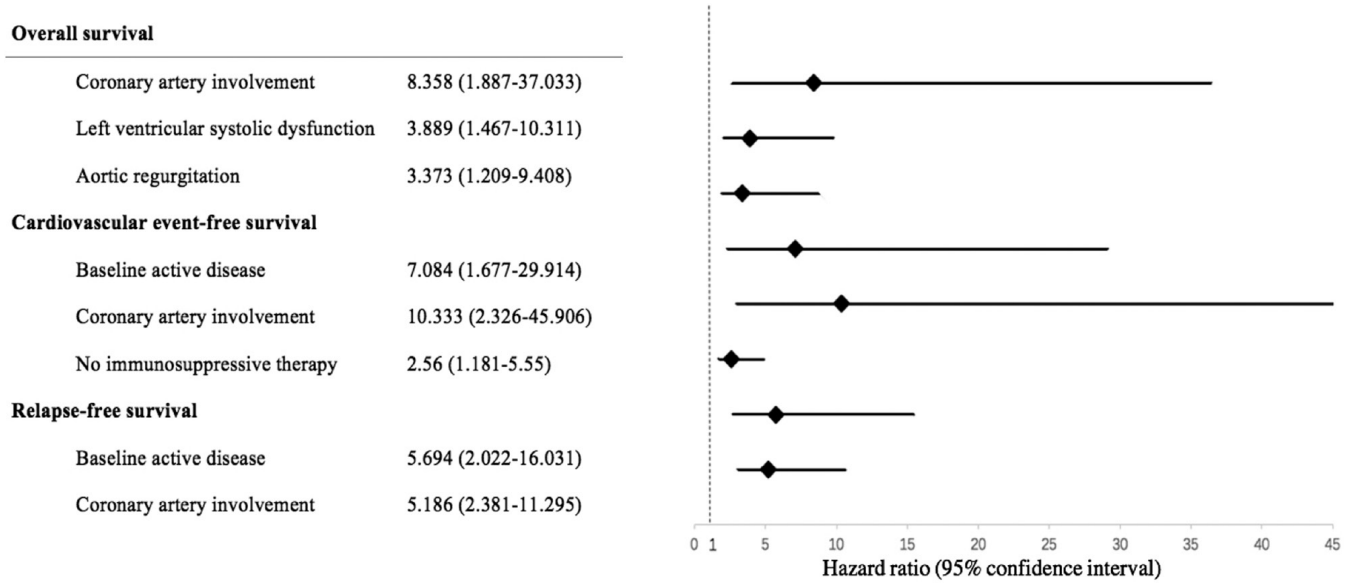

Fig. 2. Forest plots of multivariate analysis of overall survival, cardiovascular event-free survival, and relapse-free survival.

Discussion

To our knowledge, this work is the first and largest study evaluating coronary involvement in a cohort of TAK patients with complete coronary evaluation. Our work confirms the high prevalence of coronary involvement in TA, which concerns 54.6% of our patients. It is important to note that up to 35% of TAK patients with coronary involvement had no ischaemic symptoms, similar to what was found in a previous study (4). Therefore, nonspecific signs and lack of symptoms at presentation may delay the diagnosis of coronary involvement in TAK patients. Single-vessel disease was the most common disease type, with the ostia and proximal segments being the most frequently involved, which was consistent with prior studies (4, 21).

We found older age was independently associated with coronary involvement in patients with TAK. Also, patients with coronary involvement tend to have longer disease duration, in agreement with the previous study (4). It suggested that local vascular inflammation can lead to arterial fibrosis and stenosis in patients with TAK (22). Furthermore, growing evidence have showed that chronic inflammatory diseases can lead to premature atherosclerosis (23, 24). Thus, patients with older age as well as longer disease duration may have coronary artery exposed to a prolonged inflammation and progress to arterial stenosis eventually. Our findings highlighted that coronary screening tests are of particular importance for TA patients with older age and longer disease duration.

Type V was the most common angiographic classification followed by types II, I, IV and III in this cohort. This pattern is similar to the those reported from Korea, Japan, North America, and Mexico (6, 9, 14, 25, 26). It has been suggested that type V, the most extensive disease type, may be associated with systemic hypertension, TAK activity, cardiovascular morbidity and late mortality (9, 25). Recently published studies demonstrated that type V was one of the strongest determinants for brachial-ankle pulse wave velocity which was independently associated cardiovascular events in patients with TAK (27, 28). This may, at least in part, explain the high prevalence of coronary involvement detected in this population. In the present study, type V was found to be independent associated with coronary involvement which was an important predictor of poor long-term outcome in patients with TAK. Our findings add to previous documentation showing that type V was associated with a higher risk of cardiovascular involvement which might be due to the more aggressive and severe inflammatory procession of this disease type. Therefore, coronary artery screening might be necessary in this subset of patients at high-risk for coronary involvement.

In the present study, we did not identify any association between TAK disease activity or acute phase reactants and the development of coronary involvement, in accordance with previous reports (4, 25, 29). The explanation could be possibly stated as follows: first, disease development of TA begins at an initial phase characterised by elevation of inflammatory markers, followed by a chronic phase with vascular damage (8, 15). Therefore, when coronary artery lesions being found by imaging test, the inflammatory markers may have become normal. Second, and even more important, is the lack of reliable parameters reflecting disease activity of TAK (30). Neither inflammation markers nor imaging of vessel wall could reliably correlate with disease activity (6, 31-33). Histopathologic evaluation may show active arteritis even in patients with apparent clinical and laboratory remission (6, 20, 31). Third, chronic inflammation could cause accelerated atherosclerosis which also leads to coronary artery stenosis (34). With the advance of imaging tools, such as PET (35), combined with the development of inflammatory biomarkers (36), it will allow more accurate assessment of disease activity and may improve identification of

pathology associated with coronary artery lesions in TAK.

Outcomes data in recent large case serie of TAK patients have been much better than that in earlier serie (10), with 97% at 10 years (20). However, the 10-year overall survival was only 87.7% in this cohort. This higher incidence of mortality could be explained by a higher proportion of cases with coronary involvement (54.6%). As the long-term outcome for patients with TAK seems predicted by vascular complications (10, 11), patients with coronary involvement had a poor outcome with the 15-year survival of 78.9% in this study. In contrast, the 15-year overall survival in patients without coronary involvement was 87.7%, in agreement with the recent report (20). As coronary involvement is an important prognostic factor, early identification of coronary artery lesions, especially before artery occlusion, could help to prevent deaths and cardiovascular events in patients with TAK.

TAK is a chronic, relapsing and progressive disease, with the majority of patients will demonstrate a relapsing/remitting or progressive course (6). In the present study, patients with coronary involvement experienced significantly higher rate of relapse. In addition, major cardiovascular events occurred more common in patients who experienced a relapse in comparison with those without relapse (56.1% *vs*. 5.6%, $p<0.001$). It likely reflects that patients with coronary involvement may have more extending inflammation, that demonstrate a relapsing and progressive clinical course. Moreover, a progressive course of TAK with frequent relapses indicating a progressive vasculitis which will promote coronary artery stenosis and lead to cardiovascular events. Taken together, close monitoring for disease activity and aggressive control of vasculitis to reduce relapse will aid preventing cardiovascular events in patients with TAK.

Strikingly, immunosuppressive therapy significantly improved the cardiovascular prognosis of our patients. Early case report and small series have demonstrated the effect of glucocorticoids on the angiographic features of TAK patients (37, 38). Furthermore, use of immunosuppressive agents has also been reported to be effective in controlling disease activity and halting angiographic progression in TAK patients (39, 40). Therefore, early inflammation control by proper immunosuppressive therapy might improve cardiovascular prognosis of patients with TAK and coronary involvement. However, the current study design does not allow us to comment on the efficacy of specific immunosuppressive regimens, further randomised control trial is needed to determine the optimal anti-inflammtory therapy in patients with TAK and coronary involvement.

Antiplatelet therapy was not associated with reduced cardiovascular events in this stuyd, similar to a recent retrospective study (29). It may be due to confounding by indication. Moreover, statin therapy failed to prevent ischaemic events in the present study, which is consistent with prior study (41).

The retrospective design of this study has a potential for selection bias and recall bias which might compromise the power of the conclusion. The lack of a standardised protocol for treatment is another important limitation. Finally, the statistical power might not be strong because of the limited sample size for this rare disease. Further prospective longitudinal study with large sample is needed.

In conclusion, an increasing age and type V angiographic classification were independent risk factors for coronary involvement; and those with coronary involvement had poor clinical outcomes, including higher rates of all-cause death, cardiovascular adverse events and relapse. Immunosuppressive therapy was associated with a reduction of cardiovascular events in TAK patients.

Therefore, TAK with coronary involvement should be classified as a high-risk subtype with more probability of further events, requiring close monitoring and relatively aggressive management. Early diagnosis and implantation of immunosuppressive therapy to control inflammation progress might also decrease cardiovascular adverse events in patients with TAK.

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