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Clinical presentation, treatment and outcome of Takayasu's arteritis in southern Chinese: a multi-center retrospective study

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Corresponding Author:	Pui Yan, Stella Wong, MBBS, MRCP, FHKAM, FHKCP Tseung Kwan O Hospital Hong Kong, HONG KONG
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Tseung Kwan O Hospital
Corresponding Author's Secondary Institution:	
First Author:	Pui Yan, Stella Wong, MBBS(HK), MRCP(UK), FHKAM(Medicine), FHKCP
First Author Secondary Information:	
Order of Authors:	Pui Yan, Stella Wong, MBBS(HK), MRCP(UK), FHKAM(Medicine), FHKCP
	Chi Chiu Mok, MD, FRCP
	Chak Sing Lau, MBChB MD (Hons), FRCP (Edin, Glasg, Lond), FHKAM
	Man Lung Yip, MBchB, FHKAM(Medicine), FHKCP, FRCP(Edinburgh)
	Lai Shan Tam, MD
	King Yee Ying, MBChB, MRCP(UK), FHKAM(Medicine)
	Woon Leung Ng, MBBS(HK), FHKCP, FHKAM, FRCP(Edin, Glasg)
	Kam Hung Ng, MBBS, MRCP, FHKCP, FHKAM, FRCP(Edin)
	Moon Ho Leung, MBBS(HK), FRCP(Glasg)
	Tsz Yan Lee, MBChB, FHKAM
	Chi Hung To, MBChB, MRCP, FHKCP, FHKAM, FRCP(Edin)
	Ka lai Lee, MBBS(HK), FHKAM, FHKCP, FRCP(Edin)
	Man Choi Wan, MBChB, MRCP(Irel), MRCP(UK)
	Ka Lung Yu, MBBS(HK), MRCP(UK), FHKAM(Medicine), FHKCP
	Ching Han, Priscilla Wong, MBChB, FHKAM
	Chi Keung Sung, MBBS(HK), MRCP(UK), FHKCP, FHKAM, MRCP(Glasg)
	Kwok Fai Lee, MBBS(HK), FHKAM(Medicine)
	Wai Lin, Emily Kun, MBBS(HK)
Order of Authors Secondary Information:	
Funding Information:	
Abstract:	Objectives: To study the clinical presentation, treatment and outcome of southern Chinese patients with Takayasu's arteritis (TA).

Methods: This is a retrospective chart review study of 78 patients managed in 14 public hospitals in Hong Kong between the years 2000 and 2010. Patients were identified from the hospital registry using the ICD-10 diagnostic code of the disease. The classification of TA was based on the American College of Rheumatology (ACR) or modified Ichikawa's criteria. Demographic data, clinical presentation, angiographic findings, pattern of vascular involvement (Numano's classification), treatment and outcome of these patients were presented.

Results: 78 patients were studied (82% women, age at presentation 34.2±14 years). The estimated point prevalence of TA was 11/million population. The commonest initial manifestations were hypertension (62%) and vascular ischemic symptoms (38%). Systemic symptoms occurred in 9 (12%) patients only. The proportion of patients fulfilling the angiographic subtypes of the Numano's classification was: type I (13%), IIa (4%), IIb (12%), III (12%), IV (20%) and V (39%), respectively. Thirty-two patients (41%) were treated with high-dose glucocorticoids (GCs) and 22 patients (28%) received additional non-GC immunosuppressive drugs. Vascular complications occurred in 26 (33%) patients and revascularization surgery was performed in 23(29%) patients. Three (4%) patients died of vascular complication at a median of 8 years after disease onset.

Conclusions: TA is rare in southern Chinese patients of Hong Kong. Most patients present with ischemic symptoms during the stenotic phase of the disease. Although mortality is low, a significant proportion of patients developed vascular stenosis that required surgical interventions. More awareness of TA as a differential diagnosis of non-specific systemic symptoms with elevated inflammatory markers in younger patients is needed for earlier diagnosis.

Key words: autoimmune, aortitis, vasculitis, large vessel, prognosis

Short running title: Takayasu's arteritis in Hong Kong

Clinical presentation, treatment and outcome of Takayasu's arteritis in southern Chinese: a multicenter retrospective study

Stella Pui Yan Wong, Chi Chiu Mok, Chak Sing Lau, Man Lung Yip, Lai Shan Tam, King Yee Ying, Woon Leung Ng, Kam Hung Ng, Moon Ho Leung, Tsz Yan Lee, Chi Hung To, Ka Lai Lee, Man Choi Wan, Ka Lung Yu, Priscilla Ching Han Wong, Chi Keung Sung, Kwok Fai Lee, Emily Wai Lin Kun; for the Hong Kong Takayasu's arteritis study group

Correspondence to: Dr. Stella Wong Pui Yan (FHKCP, FHKAM)
Department of Medicine
Tseng Kwan O Hospital
2, Po Ning Lane,
Hang Hau, Kowloon
Hong Kong SAR, China

Tel: (852) 6385 9942
Fax: (852) 2177 0161
email: wonstella@gmail.com

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Abstract

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Author Contributions:

Study design: Dr. Mok Chi Chiu, Dr. Kun Wai Lin

Data collection and interpretation: Dr. Wong Pui Yan Stella, Dr. Mok Chi Chiu, Dr. Lau Chak Sing, Dr. Yip Man Lung, Dr. Lai Shan Tam, Dr. Ying King Yee, Dr. Ng Woon Leung, Dr. Ng Kam Hung, Dr. Leung Moon Ho, Dr. Lee Tsz Yan, Dr. To Chi Hung, Dr. Lee Ka Lai, Dr. Wan Man Choi, Dr. Yu Ka Lung, Dr. Wong Ching Han, Priscilla, Dr. Sung Chi Keung, Dr. Lee Kwok Fai, Dr. Kun Wai Lin

Statistical analyses of data: Dr. Wong Pui Yan Stella, Dr. Mok Chi Chiu

Introduction

Takayasu's arteritis (TA) is a rare chronic inflammatory arteriopathy of unknown etiology that predominantly affects the aorta, its main branches, as well as the pulmonary arteries. Histologically, TA is characterized by granulomatous vasculitis of the medium and large arteries, which leads to transmural fibrous thickening of the arterial walls, multiple vascular obstructions and ischemic changes [1]. The inflammation starts at the vasa vasorum and medio-adventitial junction, which is characterized by a perivascular infiltration of mononuclear cells, mainly composed of CD4+/CD8+ lymphocytes, plasma cells and macrophages, and subsequent evolution into a pan-arteritis. Occasionally, a granulomatous reaction with giant cells circumscribing laminar necrosis of smooth muscle elements may also be visualized in the tunica media. Degeneration of elastic fibers is a striking feature and formation of aneurysms may occur when rapid and severe inflammation leads to the loss of medial smooth muscle cells. Reactive fibrosis, intimal thickening (mainly due to proliferation of the endothelial cells), thrombus formation, and neo-vascularization at the intima-medial junction are often seen in the chronic phase, resulting in tissue ischemia [2].

Although TA is more common in Asia and the Middle East than Europe and North America, there is a paucity of information of its prevalence and presentation in the Chinese population [3-6]. The insidious disease onset and rather non-specific early symptoms can lead to a significant diagnostic delay. In a recent study conducted in mainland China [5], the

median time between the onset of symptoms and diagnosis of TA was 19 months (0.5–160 months), indicating a significant time lag for the recognition of the disease. In view of the paucity of data of TA in Hong Kong Chinese, we conducted this study to evaluate the clinical characteristics, treatment and outcome of our TA patients managed in 14 public hospitals of Hong Kong between the years 2000 and 2010.

Patients and methods

Study population

This is a retrospective study of the presentation and outcome of patients with TA in Hong Kong. Patients with TA being followed in 14 public hospitals in Hong Kong were identified by the central hospital registry database using the ICD-10 diagnostic code of the disease (M31.4) from the year 2000 to 2010. The medical records of the identified patients were reviewed. TA was classified according to either the 1990 American College of Rheumatology (ACR) [7] or the 1988 Ichikawa criteria [8]. The pattern of vascular involvement was evaluated by the Numano's classification [9]. This study was approved by the New Territories West Cluster Clinical and Research Ethics Committee under the Hospital Authority of Hong Kong.

Methods

The medical records of TA patients identified were reviewed by a rheumatologist in the corresponding hospitals. A standard data entry form was designed and used to collect data from these patients, which included demographic characteristics, initial clinical presentation, angiography findings, classification of vascular involvement, treatment (medical / surgical) and outcome of our patients. The choice of imaging modalities for the diagnosis of TA was determined by the attending physicians. Echocardiogram was performed in patients with cardiac symptoms.

Classification of Takayasu's arteritis

The 1988 Ichikawa criteria for TA were based on the clinical and angiographic data from 108 Japanese patients [8]. The criteria comprise one obligatory criterion (age ≤40 years), two major criteria (lesions in the left and right mid-subclavian arteries) and nine minor criteria. A patient is classified as having high probability of TA when the obligatory criterion and the following combinations of criteria are fulfilled: two major criteria; one major criterion plus ≥2 minor criteria; or ≥4 minor criteria. The ACR proposed a newer classification in 1990 which involved six criteria: (1) onset at age ≤40 years; (2) claudication of an extremity; (3) decreased pulse in the brachial artery; (4) difference in systolic blood pressure between arms >10 mmHg; (5) a bruit over the subclavian arteries or aorta; and (6) angiographic evidence of narrowing/occlusion of aorta, its primary branches, or large arteries in the proximal upper or lower extremities. TA is classified when patients fulfill ≥3 of the above criteria [7].

The Numano's criteria were developed to classify the pattern of vascular involvement in TA [9]. Distribution of the site of vascular involvement is grouped as follows: type I - aortic arch and branches; type II a - ascending aorta, aortic arch and its branches; type IIb - combination of II a and thoracic descending aorta; type III - thoracic descending aorta, abdominal aorta, and/or renal arteries; type IV - abdominal aorta and /or renal arteries; and type V - combined features of types IIb and IV.

Statistical analyses

Data in this study were expressed as either mean ± standard deviation (SD) or median ± interquartile range (IQR). All statistical analyses were performed with SPSS statistical software (version 17.0 for Windows 10, Chicago, USA).

Results

A total of 95 patients were identified from the hospital registry but 17 patients were excluded because of inaccurate coding or incomplete medical records. Finally, 78 patients were studied. All were ethnic Chinese with their family origin in the southern part of China. Based on the Government by-census data, the population size of Hong Kong in year 2006 was nearly 7 million. Therefore, the estimated point prevalence of TA in Hong Kong was 1.1/100,000 population. Of the patients studied, there were 64 women (82%) and 14 men (18%). The mean age at diagnosis was 34.2±14 years (range 7-73). Sixty nine percent of the patients were diagnosed before age 40 years and four patients (5%) were diagnosed before the age of 16 years (childhood onset). Fifty-two (67%) patients fulfilled the ACR and 46 (59%) patients fulfilled the modified Ichikawa's criteria for TA. At the time of analysis, the mean duration of follow-up of the patients since diagnosis was 14.4 ±8.9 years, corresponding to 1123 patient-years.

Clinical manifestations

The commonest initial manifestations of TA in our patients were hypertension (62%) (attributed to renal artery stenosis in 13 patients) and vascular ischemic symptoms (38%) that included angina pectoris / acute coronary syndrome (ACS), cerebrovascular accidents (CVA) and intermittent claudication / rest pain of the limbs (Table 1). Vascular bruits could be detected clinically in 41(52%) patients, most often over the renal arteries (35%) but less common in the carotid (19%) and femoral (11%) arteries. Constitutional symptoms were present in 9 (12%) patients only. Of these systemic symptoms, fever, weight loss, pyrexia of unknown origin, malaise and night sweating were most frequently reported. Anemia of chronic inflammation was present in 10 (13%) patients. Among those 30 patients who presented with ischemic symptoms, only 2 (7%) had systemic symptoms and 13 (43%) had elevation of either the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level.

Other presenting symptoms of our TA patients included arthritis, skin lesions (of which 80% were erythema nodosum), serositis and valvular heart lesions (most common aortic valvular regurgitation related to aortic root dilation) that occurred in 8 (10%), 5 (6%), 3 (4%) and 7 (9%) patients, respectively. Neurological symptoms such as CVA, headache and visual disturbances (namely left retinal vein thrombosis) occurred in 10(13%), 5(6%) and 1(1%) respectively.

Angiographic findings

Seventy (90%) patients had undergone angiogram for diagnostic evaluation: conventional angiogram 46%, computerized tomographic angiography (CTA) 29%, and magnetic resonance angiography (MRA) 49%. Positron emission tomography (PET) or gallium scan was used in 7% of patients for the initial diagnosis of the disease during the systemic phase (Table 2). Three patients had missing angiography data.

Regarding the site and extent of vascular involvement (Table 3), the proportion of patients fulfilling the subtypes according to Numano's classification was as follows: type I (13%), IIa (4%), IIb (12%), III (12%), IV (20%) and V (39%). Overall, the subtype V was the most common angiographic type in both sexes. Twenty-two women (34% of all female patients) and 7 men (50% of all male patients) had type V vascular involvement.

Treatment and outcome

Thirty-two patients (41%) were treated with high-dose GC, defined as prednisolone or equivalent ≥0.8mg/kg/day. Additional non-GC immunosuppressive agents were used in 22 patients (28%), mainly for GC refractory or dependent disease (GC sparing) (Table 4). Azathioprine and methotrexate were the most commonly used non-GC immunosuppressive agents. Anti-platelet agents (aspirin and clopidogrel) were used in 44 (56%) patients.

During follow-up, twenty-three (29%) patients had undergone percutaneous or open vascular revascularization procedures. Sixteen patients received angioplasty procedures with or without stenting. These procedures (in descending order of frequency) included renal artery angioplasty (7), carotid angioplasty (4), aortic angioplasty (1), subclavian angioplasty (1), femoral artery angioplasty (1), common iliac artery angioplasty (1) and coronary angioplasty (1). Renal and ascending aorta grafting were performed in 2 and 3 patients respectively. Arterial bypass surgery was required in 5 patients (1 femoral-popliteal; 2 aorto-iliac; 1 ilio-femoral and 1 renal artery bypass).

Morbidity and mortality

Vascular complications occurred in 26 (33%) patients (CVA in 14; ACS in 13; rest limb pain in 5, digital ulcer in 1 and digital gangrene in 1 patients, respectively). The single patient with digital (toe) gangrene had multiple stenosis of the carotid, subclavian, coronary and femoral arteries, which could not be explained by his age and other atherosclerotic risk factors. Three (4%) of our patients died of vascular complication at a median of 8 years after onset of the disease during the study period and 4 (5%) patients developed end stage renal failure. The causes of death of the three patients were end stage cardiomyopathy, acute myocardial infarction and sudden cardiac arrest (thought to be related to cardiovascular cause; no autopsy done).

Discussion

Although TA has a worldwide distribution, it is more commonly observed in the Asian populations. The highest ever prevalence of TA was reported in Japan (40 per million of population) and the lowest prevalence was reported in US (0.9 per million population) [10]. The reported prevalence of TA in the European countries varies between 4.7 and 33 per million population [10-11]. The estimated point prevalence of TA (11 per million population) in our locality was lower than that reported in Japan. However, this estimated prevalence figure may have been under-estimated as not all TA cases were coded to the hospital registry by attending doctors and there were patients who were managed by private doctors (covering about 15% of populations in Hong Kong).

The clinical characteristics of our TA patients and major Asian series are summarized in Table 1. In our cohort of patients, the mean age at presentation of TA was 34.2 years, which is older than that from previous reports of mainland China [5] and other Asian countries that included India, Korea and Malaysia [12-14]. Although we did not have data regarding the time lag between disease onset and diagnosis of TA, most of our patients presented with ischemic symptoms at the stenotic phase of the disease. This may reflect that either the initial systemic symptoms were too mild for the patients to seek consultation or a lack of awareness of the primary care physicians of the differential diagnosis of TA when younger patients present with non-specific systemic symptoms such as fever, influenza like

symptoms, malaise and weight loss, with and without elevation of the inflammatory markers.

Female predominance in TA patients has been consistently reported in previous studies [5,12-17]. In our TA patients, the female/male ratio was 4.3:1, which is similar to the Korean studies (female/male ratio 4.3-5.4:1) [13,16]. However, the female preponderance of our TA patients appears to be lower than that reported by mainland China (female/male ratio of 6.35:1) [5]. Apart from the gender difference in the incidence of the disease, some authors have postulated that it is the gender rather than ethnicity that accounts for the difference in the distribution of vascular involvement by the disease [17,18]. For instance, several studies have revealed that involvement of the thoracic aorta and its branches was more common in women but abdominal aorta and its branches were more often observed in men [17,18]. In our patients, such a gender difference in the vascular involvement was not observed and the Numano's subtype V aortic involvement was the most common type in both sexes.

Similar to what was reported from studies in mainland China and India (Table 1) [5,12], hypertension was the most common initial presentation in our patients. Hypertension was most often secondary to renal artery stenosis and coarctation of aorta. Valvular lesions were present in a small proportion of our patients (9%). In particular, aortic regurgitation was only detected in 4% of the subjects. The prevalence of valvular abnormalities in our patients was much lower than that reported by the mainland Chinese investigators (66%) [6].

This can be explained by the universal screening of valvular heart disease by echocardiogram in the mainland study [6] whereas in our study, echocardiogram was only performed in those who had cardiac symptoms or clinically audible murmur. As cardiac involvement in TA is not uncommon, particularly in those patients with Numano type V aortic involvement, echocardiogram was suggested to be routinely performed in all patients with TA [6].

Systemic symptoms were relatively uncommon in our cohort and were present in only 12% of the patients. This is in contrast to the report from mainland China in which 38.4% of their patients presented with systemic symptoms [5]. The clinical course of TA was thought to progress through three distinct stages. The first stage is an early phase in which constitutional and systemic symptoms such as fatigue, weight loss, fever and arthralgia predominate. This is followed by a second phase occurring months or years later, with clinical manifestations mainly caused by vascular ischemia due to stenotic or occlusive lesions. The final phase (also known as "burnt-out" phase) refers to the state when patients do not have obvious clinical disease activity but with fixed vascular abnormalities [19]. However, in real life, this "burnt-out" phase is difficult to define as studies have shown that new vascular lesions may develop in up to 60% of TA patients who are apparently in clinical remission [19]. Moreover, histological examination of the vascular specimens in patients who have undergone surgery revealed evidence of inflammation in 50% of patients with clinical quiescent disease [19,20]. The small proportion of our patients who experienced

systemic symptoms suggests that they were not recognized by patients themselves or the attending doctors.

Angiography remains the main stay of diagnosis of TA (Table 2) in our patients. In recent years, conventional angiography seems to be replaced by the newer imaging modalities, such as MRA, PET or ultrasound, which are less invasive [21,22]. PET, often combined with computer tomography (CT), is gaining acceptance as a tool for the diagnosis of TA and assessment of disease activity [23]. Further research into the validity of CTA, MRA, and PET-CT in the quantitative assessment of TA activity and damage, including the development of a radiologic damage score [24] and MRI scoring system [25], are required.

At the time of our study period (2000-2010), validated outcome measures of TA have not yet developed and data on the serial assessment of disease activity and damage in our patients were unavailable. New disease activity scoring systems (e.g. the Indian Takayasu Arteritis Clinical Activity Score [26] and the disease-extent index by the Turkish Takayasu Study Group [27]) are being developed in recent years. The OMERACT Vasculitis Working Group has also finished a Delphi exercise with an expert panel to develop a core set of validated outcome measures for large vessel vasculitis [28].

The pattern of vascular involvement of TA varies among different studies. This may indicate that ethnic factors may play an important role in the pathogenesis of TA. Table 3 compares the angiographic characteristics of our TA patients with other Asian series

[5,12,13,17,29]. Type V angiographic involvement was the most common in our patients, which is similar to the Indian [12,15,30,31] and Thai [29] series. However, our observation is different from that reported in the mainland Chinese [5], Korean [13] and Japanese [17] series, in which type I and V were more commonly reported.

Glucocorticoid remains the first-line of treatment for active TA (Table 4). In our cohort, only 41% of our patients were treated with high-dose GC (prednisolone or equivalent ≥0.8mg/kg/day) at presentation. This is probably due to the fact that most of the patients presented with ischemic symptoms, a chronic stage when stenotic or occlusive lesions have already occurred, such that GC therapy was not given by the attending physicians. Although remission was achieved in most patients who required GC therapy, GC refractoriness and disease relapse during GC tapering was not infrequent, leading to the use of additional non-GC immunosuppressive agents in 28% of our patients. This might explain the relatively high proportion of patients (29%) who subsequently required surgical interventions.

Despite a high proportion of our TA patients developed vascular complications, the overall mortality was low. Recently, a chart review of 810 TA patients followed in a referral center in mainland China from between 1983 and 2014 reported mortality in only 12 (1.5%) patients [32]. The relatively low mortality rate (4%) in our patients is consistent with the Korean and mainland Chinese studies [13, 32]. In the largest prospective study of

GC in TA [33], patients were initially treated with high-dose prednisone 1mg/kg/day for 1-3 months and gradually tapered to discontinuation in 48 months when disease activity was controlled. Introduction of GC-sparing agents can be considered in relapsing or resistant cases. However, there are no randomized controlled trials to show the efficacy of GC-sparing in reducing morbidity and disease flares in TA. With the development of new tools for disease assessment [26-28] and more clinical trials on biological therapy of TA [34-36], it is anticipated that better outcome of TA can be achieved in the future.

There are several limitations of our study. First, it is retrospective and data on cardiovascular risk factors, disease flares, serial assessment of disease activity and damage were not available in our patients. However, we have tried our best effort to gather the largest sample of TA in our locality and the data presented are useful for future research and service planning. Second, the prevalence of TA is likely to be under-estimated as coding of the diagnosis in our territory-wide hospital registry was not compulsory. Some other patients might be managed by private specialists, who contribute up to 10-15% of all medical services in Hong Kong. Thirdly, some of our patients were diagnosed after the age of 40. Although the ACR and Ichikawa's criteria are not validated for older patients, all these patients fulfilled at least one of these criteria after disregarding the age. In fact, many patients had TA symptoms long before the age of 40 years but they could not recall the exact time of symptom onset. The diagnosis of TA in these patients was based on the clinical

features and typical angiographic findings which were not explained by the atherosclerotic risk factors present. Finally, the treatment regimens used were not protocol-based and varied substantially among different rheumatologists. As a result, the effect of different regimens on the disease outcome could not be compared.

In conclusion, this is the first multi-center study of TA patients in Hong Kong Chinese. We have shown that systemic symptoms were uncommon and most patients presented during the stenotic phase of the disease. Involvement of both the aortic arch branches and the descending aorta was the most common angiographic finding in both female and male patients. While GC and non-GC immunosuppressive agents were the mainstay of treatment, a relatively high proportion of our patients subsequently required surgical revascularization. Despite this, the overall mortality of our patients was low. More awareness of TA as a differential diagnosis of non-specific systemic symptoms with elevated inflammatory markers in younger patients is needed for earlier diagnosis. To acquire a better understanding of the clinical epidemiology and outcome of TA patients in our locality, further prospective studies on different aspects of the disease such as disease activity and damage scores other outcomes like quality of life are required.

Declaration

1. Ethical approval: New Territories West Cluster Research and Ethics Committee, Hospital Authority, Hong Kong (date of approval: 29-8-2011; NTWC/CREC/967/11).
2. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
3. Funding of this project and writing assistance: NIL
4. All authors did not have any conflict of interests to be declared

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Table

Table 1: Clinical features of Takayasu's arteritis in our patients in comparison with other Asian series

Presenting features	**Hong Kong** N =78	**Mainland China** [5] N = 125	**India** [12] N = 251	**Korea** [13] N = 108	**Malaysia** [14] N = 40	**Japan** [17] N = 1372
	N (%), mean ± standard deviation					
Mean age, years	34.2 ±14	26.9	24 ± 11.0	29.5±12.0	25.5	35(median)
Female gender	64 (82)	108 (86.4)	205 (81.7)	91 (84.3)	37 (92.5)	1150 (83.8)
Follow-up period	2000-2010	1993- 2008	1998-2016	1991 - 2003	2006-2013	2001-2011
Hypertension	48 (62)	82 (65.6)	148 (59)	-	17 (42.5)	540 (39)
Renal function impairment	9 (12)	-	-	-	3/27 (11)	154 (11.2)
Proteinuria	3 (4)	-	-	-	-	-
Vascular ischemic symptoms						
Any	30 (38)	-	-	-	-	-
Myocardial infarction / angina	10 (13)	9 (7.2)	27 (10.8)	21 (19.4)	-	146 (10.6)
Cerebrovascular accidents	10 (13)	20 (16)	11 (4.4)	-	6 (15)	181 (13.2)
Limb claudication / rest pain	14 (18)	55 (44)	152 (60.6)	41 (38.0)	17 (42.5)	131 (9.5)
Headache	5 (6)	32 (25.6)	59 (23.5)	61 (56.5)	8 (20)	113 (8.2)
Retinal artery occlusion	1 (1)	-	-	-	-	-
Vascular bruits						
Any	41 (52)	78 (62.4)	142 (56.6)	78 (64.8)	21 (52)	-
Renal bruit	27 (35)	-	-	-	-	-
Systemic symptoms						
Any	9 (12)	48 (38.4)	-	-	-	-
Fever	9 (12)	22 (17.6)	55 (21.9)	10 (9.3)	6 (15)	476 (34.7)
Fever of unknown origin	7 (9)	-	-	-	-	-
Weight loss	5 (6)	3 (2.4)	23 (9.2)	11 (10.2)	8 (20)	-
Malaise	7 (9)	32 (25.6)	79 (31.5)	70 (64.8)	6 (15)	166 (12.1)
Night sweating	3 (4)	5 (4.0)	-	-	-	-
Anemia of chronic inflammation	10 (13)	39 (31.2)	-	-	7/27 (25.9)	-
Raised ESR	33 (42)	62 (49.6)	-	90 (83.3)	18/27 (66.7)	-
Raised CRP	21 (27)	61/101	-	55 (50.9)	8/16 (50)	-
Raised ESR or CRP	33 (42)	-	-	-	-	-
Arthritis	8 (10)	11 (8.8)	3 (1.2)	-	3 (7.5)	-
Skin lesions	5 (6)	-	4 (1.6)	-	2 (5.0)	-
Serositis (pericarditis / pleuritis)	3 (4)	-	-	-	-	-
Valvular heart lesions						
Any	7 (9)	-	-	-	-	-
Aortic regurgitation	3 (4)	-	17 (6.8)	-	-	455 (33.2)

ESR = erythrocyte sedimentation rate; CRP = C-reactive protein

Table 2: Imaging diagnosis of Takayasu' arteritis in our patients

Imaging modalities	Number (%)
Any angiogram	70 (90)
Conventional angiogram	36 (46)
CT angiogram	23 (29)
MR angiogram	38 (49)
PET scan	5 (6)
Gallium scan	1 (1)
Missing angiography data	3 (4)
Total	78 (100)

CT = computer tomography; MR = magnetic resonance; PET = positron emission tomography

Table 3: Angiographic characteristics of Takayasu's arteritis in our patients in comparison with other Asian series

Type	Hong Kong *N=75	China [5] N=125	India [12] N=251	Korea [13] N=108	Japan [17] N=1335	Thai [29] N=63
			Number (%)			
I	10 (13)	50 (40)	45 (18)	39 (36.1)	374 (28)	0 (0)
IIa	3 (4)	6 (4.8)	1 (0.4)	3 (2.8)	218 (16.3)	0 (0)
IIb	9 (12)	2 (1.6)	10 (4.0)	5 (4.6)	222 (16.6)	7 (11.1)
III	9 (12)	3 (2.4)	14 (5.6)	8 (7.4)	98 (7.3)	2 (3.2)
IV	15 (20)	26 (20.8)	45 (18)	17 (15.8)	79 (5.9)	12 (19.0)
V	29 (39)	38 (30.4)	136 (54.2)	36 (33.3)	344 (25.8)	42 (66.7)

*****3 patients had missing data on angiographic characteristics, resulting in a total of 75 patients

Table 4: Treatment of Takayasu's arteritis in our patients

Treatment modalities	Number (%)
Immunosuppressive treatment	
*High-dose steroid	32 (41)
Any non-steroid immunosuppressive agents	22 (28)
Methotrexate	9 (12)
Azathioprine	19 (24)
Hydroxychloroquine	2 (3)
Cyclosporin A	4 (5)
Mycophenolate mofetil	2 (3)
Cyclophosphamide	1 (1)
Anti-platelet agents	44 (56)
Anti-coagulation	5 (6)
Vascular surgery	
Any	23 (29)
Percutaneous procedures	15 (19)
Open procedures	11 (14)

*****prednisolone or equivalent ≥0.8mg/kg/day