Evaluation of clinical measurements and development of new diagnostic criteria for Takayasu arteritis in a Chinese population

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ABSTRACT

Objective. *Takayasu arteritis (TA) is a chronic granulomatous large-vessel vasculitis. When diagnosing TA, the criteria designed by the American College of Rheumatology (ACR) are used commonly but they were just classification criteria. There is an urgent need for a new set of diagnostic criteria.*

Methods. *One hundred and thirty-one TA patients and 132 control patients with other types of vascular disease were enrolled and both groups were distributed into a "training set" and a "validation set". All general information as well as clinical, laboratory and imaging data were collected. After comparing all the medical records of two groups in the training set, logistic regression and clinical judgment were used to form the new criteria for TA. The new criteria were tested by the validation set.*

Results. *New TA diagnostic criteria within total score 26 include age (<40 years), female, chest pain/chest distress, amaurosis, vascular bruits, a decreased/absent pulse, involvement of the aortic arch or its major branches, and involvement of the abdominal aorta or its branches. Patients with a score ≥8 were diagnosed as TA. The sensitivity and specificity of our new criteria were 91.92% and 93.94%, respectively, higher than those of the ACR criteria (75.76%, 85.86%) and the Ishikawa criteria (56.57%, 94.95%). The areas under the ROC curves of the new criteria and ACR criteria were 0.981 and 0.868, respectively (p<0.001). Sensitivity and specificity tested in the validation set were 90.63% and 96.97%, respectively.*

Conclusions. *The new diagnostic criteria exhibited high sensitivity and specificity and have demonstrated to be feasible in the diagnosis of TA.*

Introduction

According to the definition set by the Chapel Hill Consensus Conference in 2012 (1), Takayasu arteritis (TA) is a type of chronic granulomatous vascular disease that mainly affects the aorta or its main branches, and occurs primarily in young (age <50 years) females. It presents with non-specific symptoms (due to the different arteries involved) and is most commonly in Japan, Southeast Asia and Mexico (2).

According to epidemiologic investigations, the sex ratio of TA varies in different countries, along with the distribution of vascular branches involved. For example, the prevalence of TA between men and women was stated to be one to nine in Japan (3), but was much higher in the United Kingdom (4). Similarly, the aortic artery was reported to be predominantly involved in Japanese patients, whereas abdominal lesions were more prevalent in patients from Israel and Asian countries. What is more, TA is a cause of renovascular hypertension in Asian countries, indicating that renal arteries were more involved in Asian populations than the other races (5). Thus, sex, race and regional differences may be significant in the pathogenesis of TA (6).

Throughout the history of reporting of TA, the diagnosis has been challenging due to its non-specific and diverse manifestations. In 1988, Ishikawa proposed the diagnostic criteria based on the clinical and angiographic data from 108 Japanese patients (96 patients with TA, 12 with other diseases of the aorta). The criteria comprised one obligatory criterion (age ≤40 years), two major criteria (lesions in the left and right mid-subclavian arteries) and nine minor criteria (7). A patient would have a high probability of TA if he/she satisfied the obligatory criterion and the following combinations: two major criteria or one major criterion and two or more minor criteria or not less than four minor criteria. In 1996, Sharma *et al*. made some modifications

to the criteria set by Ishikawa to form more integrated diagnostic criteria for TA (8). In 1990, the American College of Rheumatology (ACR) proposed the classification which involved six criteria: onset at age ≤40 years; claudication of an extremity; decreased pulse in the brachial artery; difference in systolic blood pressure between arms >10 mmHg; a bruit over the subclavian arteries or aorta; arteriographic evidence of narrowing/occlusion of aorta, its primary branches, or large arteries in the proximal upper or lower extremities. Patients presenting with three or more of the criteria could be classified as TA (9-10). Apart from the three criteria described above, the criteria set by the European League against Rheumatism/ Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society were proposed for paediatric TA (11).

The criteria stated above have been utilised to guide clinical practice for a long time. However, some potential limitations need further discussion. The Ishikawa criteria were created mainly based on data from Japan, where TA patients have distinct features from other regions. Additionally, a control group of 12 patients with aortic disease was too small. Over-emphasis on specific details also restricted the use of the criteria. With regard to the ACR criteria, they have been applied in most clinical trials of TA, but they are classification criteria, not diagnostic criteria (12). Furthermore, quite a few patients are aged >40 years at disease onset. Also, the sensitivity decreases if the ACR criteria are applied in other ethnic groups (*e.g.* a sensitivity of 77.4% was reported in Indian patients by Sharma *et al.*) (13). Moreover, patients whose vascular lesions located only in abdominal or pulmonary arteries are difficult for the diagnosis of TA when using the ACR criteria. In addition, current imaging methods such as magnetic resonance angiography (MRA), computed tomographic angiography (CTA) are more accurate and safer than traditional digital subtraction angiography (DSA) used in previous criteria, because of their high-resolution imaging of anatomic features such as mural thickening, luminal changes and aneurysm formation (14). Current studies also showed that colour Doppler and 18-FDG-PET are helpful for diagnosis in large-vessel vasculitis. Schmidt W.A. suggested that colour Doppler ultrasound displays a pathognomonic circumferential wall thickening in large-vessel vasculitis and is helpful in early diagnosis (15). A meta analysis showed that 18-FDG-PET had moderate diagnosis value in assessing TA activity and may add additional value to the current diagnosis methods of TA (16).

As mentioned above, it was essential to set new diagnostic criteria for TA for Chinese people in order to improve the practicality and accuracy of the diagnosis of TA, and to lay the foundations for further study of the pathogenesis of TA.

Materials and methods

Ethical approval of the study protocol

The study protocol was approved by the Ethics Committees of both participating hospitals. Written informed consent of all enrolled patients were provided in the study.

Patients

One hundred and thirty-one TA patients and 132 control patients with other vascular disease or with at least one similar symptom of TA were enrolled. TA patients were collected from two areas. One hundred and ten patients were enrolled from Zhongshan Hospital (Shanghai, China) from 1 January 2009 to 1 June 2014. Twenty-one patients were enrolled from the People's Hospital of Urumqi (Urumqi City, China) from 17 March 2011 to 16 January 2014. All control patients were enrolled from Zhongshan Hospital from 1 January 2009 to 1 June 2014. Both groups of patients were distributed into a "training set" (99 TA patients and 99 controls) and "validation set" (32 TA patients and 33 controls).

A total of 198 patients were distributed in the training set, including "TA group 1" (99 TA patients selected randomly from 110 patients collected from Zhongshan Hospital) and "control group 1" (99 patients selected randomly from the 132 controls) (Table I).

Table I. Composition of the control group in the training set.

Control group 1*	Number
ANCA-associated vasculitis	21
Microscopic polyangiitis	12
Granulomatosis with polyangiitis	9
IgG4-related disease	13
Behçet's disease	7
Retroperitoneal fibrosis	5
Antiphospholipid antibody syndrome	4
Giant cell arteritis	1
Atherosclerotic stenosis	32
Carotid atherosclerotic stenosis	15
Renal artery atherosclerotic stenosis	2
Limb arteriosclerosis	15
Aneurysm	11
Aortic dissection	5
Total	99

*Control group 1 included rheumatic vascular diseases (51 patients) and other non-rheumatic vascular diseases (48 patients).

The validation set included "TA group 2" (32 TA patients, *i.e.* the remaining 11 TA patients from Zhongshan Hospital and 21 from the People's Hospital of Urumqi) and "control group 2". The latter contained 33 control patients with other vascular disease (27 cases of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and six cases of atherosclerosis (2 carotid arteries involvement, 2 lower-extremity arteries involvement, 1 renal arteries involvement and 1 abdominal aneurysm).

In both sets, TA patients were diagnosed by at least 2 experienced rheumatology experts according to symptoms, laboratory results, and imaging findings. In the control group, patients with other rheumatic vascular diseases were diagnosed according to the ACR classification criteria and by at least 2 rheumatologists. Other patients of the control group were recruited from Vascular Surgery Departments, and all of them had been confirmed by pathologic examinations.

Clinical manifestation

General information (age and sex), medical history (symptoms and signs), laboratory results and imaging findings of all patients were collected at the time of diagnosis. Medical history referred to complaints, and physical examination focused mainly on fever, hyperten-

Table II. Patients' characteristics.

Variables	Training set					Validation set	
	TA group 1 (n=99)			Control group (n=99)	*p* (0.01)§	TA group (n=32)	Control group (n=33)
	Total patients (n=99)	Active patients (n=58)	Inactive patient (n= 41)				
Mean age at onset age (year)	32.23 ± 12.52	33.12 ± 13.56	31.26 ± 12.67	58.06 ± 15.92	<0.01+	-	-
Mean age at the diagnosis (year)	36.8 ± 13.65	37.67 ± 14.43	35.28 ± 12.19	58.06 ± 15.92	0.39+	36.50 ± 13.50	57.03 ± 15.93
Sex (M:F)	18:8 (1:4.5)	8:55 (1:6.88)	10:26 (1:2.6)	68:31 (2.19:1)	<0.01++	7:25 (1:3.57)	18:15 (1.2:1)
Age <40 years	62 (62.63%)	38 (38.38%)	24 (24.24%)	13 (13.13%)	<0.01++	-	-
Mean disease duration (year)	2.54	2.53	2.55	-	-	-	-
Haemoglobin (g/L)	119.79 ± 17.76	117.08 ± 18.17	124.53 ± 16.19	121.73 ± 20.97	0.34#	124.19 ± 16.67	104.18 ± 28.92
White blood cells ($\times10^{-9}$)	8.53 ± 3.55	8.96 ± 4.02	7.79 ± 2.41	8.28 ± 3.36	0.61+	8.31 ± 3.28	9.33 ± 3.68
Platelets ($\times10^{-9}$)	260.61 ± 85.02	276.98 ± 89.73	231.97 ± 68.22	258.41 ± 95.60	0.87+	282.97 ± 90.13	241.06 ± 82.58
Erythrocyte sedimentation rate (mm/h)	41.86 ± 29.83	49.83 ± 30.22	27.39 ± 23.35	45.34 ± 35.43	0.77#	43.84 ± 45.43	47.29 ± 39.52
C-reactive protein (mg/L)	20.14 ± 24.47	25.15 ± 27.72	11.38 ± 13.81	31.76 ± 48.15	0.92+	17.73 ± 26.62	22.93 ± 54.96
Mouth ulcer	4 (4.04%)	4 (4.04%)	0 (0.00%)	7 (7.07%)	0.54++	-	-
Hearing loss	4 (4.04%)	3 (3.03%)	1 (1.01%)	1 (1.01%)	0.37++	-	-
Arthralgia	5 (5.05%)	3 (3.03%)	2 (2.02%)	9 (9.09%)	0.41++	-	-
Intermittent claudication	8 (8.08%)	8 (8.08%)	0 (0.00%)	7 (7.07%)	1.00++	-	-
Weight loss	8 (8.08%)	7 (7.07%)	1 (1.01%)	5 (5.05%)	0.57+	-	-
Blurry eyes	9 (9.09%)	7 (7.07%)	2 (2.02%)	2 (2.02%)	0.056++	-	-
Amaurosis	12 (12.12%)	8 (8.08%)	4 (4.04%)	1 (1.01%)	<0.01++	7 (21.88%)	4 (12.12%)
Acroanesthesia	14 (14.14%)	13 (13.13%)	1 (1.01%)	11 (11.11%)	0.67++	-	-
Fever	16 (16.16%)	11 (11.11%)	5 (5.05%)	15 (15.15%)	1.00++	-	-
Hypertension	27 (27.27%)	17 (17.17%)	10 (10.10)	19 (19.19%)	0.12++	5 (15.63%)	0 (0%)
Chest pain or chest distress	33 (33.33%)	26 (26.26%)	7 (7.07%)	12 (12.12%)	<0.01++	7 (21.88%)	4 (12.12%)
Headache	28 (28.19%)	20 (20.20%)	8 (8.08%)	11 (11.11%)	<0.04++	-	-
Dizziness	13 (13.13%)	8 (8.08%)	5 (5.05%)	8 (8.08%)	0.35++	-	-
Decreased pulse or absent pulse*	45 (45.45%)	36 (36.36%)	9 (9.09%)	1 (1.01%)	<0.01++	23 (71.88%)	1 (3.03%)
Weakness	48 (48.48%)	42 (42.42%)	6 (6.06%)	11 (11.11%)	<0.01++	15 (46.88%)	4 (12.12%)
Neck tenderness	6 (6.06%)	4 (4.04%)	2 (2.02%)	0 (0.00%)	0.03++	2 (6.25%)	0 (0%)
Vascular bruits**	63 (63.64%)	47 (47.47%)	16 (16.16%)	12 (12.12%)	<0.01++	13 (40.63%)	1 (3.03%)
Aortic arch or its branches	83 (83.84%)	56 (56.57%)	27 (27.27%)	17 (17.17%)	<0.01++	23 (71.88%)	3 (9.09%)
Abdominal aorta or its branches	40 (40.40%)	24 (24.24%)	16 (16.16%)	10 (10.10%)	<0.01++	11 (34.38%)	5 (15.15%)

* Decreased or absent pulse is considered to be positive if the pulse is decreased or absent in 1 of the arms, or if the blood-pressure difference is >10 mmHg between arms.
** Vascular bruits denote vascular murmurs heard during physical examination including parts of carotid arteries, subclavian arteries, abdominal aorta and renal arteries.
# Variables were compared by a non-parametric test. + Variables were compared by the Student's *t*-test. ++ Variables were compared by the chi-squared test.
§ *p* (0.01) means *p*-value of comparison between TA group and control group in the training set.

sion, headache, dizziness, hearing loss, blurred eyes, oral ulcers, amaurosis, arthralgia, chest pain, diminished or absent pulse, and vascular bruit. Blood tests, urine tests and blood biochemistry tests were taken regularly, including ESR and serum levels of C-reactive protein (CRP). Data from MRA or CTA were collected to determine the distribution of the arteries involved.

Statistical analyses

Complete data were required for each patient. Data were entered into SPSS v18.0 (SPSS, Chicago, IL, USA) to create a primary database. The training set was used to establish new criteria. The validation set was applied for further testing. In the training set, the Student's *t*-test and chi-square test were used to compare all information between the two groups. With regard to the combined opinions of rheumatology experts, some of those variables that had $p<0.01$ were chosen for binary logistic regression and tested with forward selection. Variables with $p<0.05$ were used for the final diagnostic model. Based on the results, each recruited variable was reassessed in terms of its rationality by rheumatology experts and statisticians, and a final scoring scheme was established. Each selected variable was defined with a point equal to the round off value of its regression coefficient (B) and the total scores of each patient calculated. By comparing different sensitivities and specificities at different cumulative scores, an optimal cut-off point was selected. An agreed set of criteria was compared with previous ACR classification criteria and Ishikawa criteria by estimating their sensitivities, specificities and areas under the receiver operator characteristic (ROC) curve in the training set, and tested further in the validation set to assess its efficacy. SPSS v18.0 was used to compare all information, whereas MedCalc v13.3.1.2.0 was used to analyse ROC curves.

Table III. Comparison of different arteries involved in the two groups.

	TA group 1 n=99	Control group 1 n=99	*p* (χ^2 test)
External carotid artery	3 (3.03%)	1 (1.01%)	0.62++
Pulmonary arteries	4 (4.04%)	1 (1.01%)	0.37++
Brachial artery	4 (4.04%)	0 (0%)	0.12++
Axillary artery	5 (5.05%)	1 (1.01%)	0.21++
Internal carotid artery	5 (5.05%)	15 (15.15%)	0.03++
Superficial femoral artery	7 (7.07%)	15 (15.15%)	0.11++
Iliac arteries	8 (8.08%)	13 (13.13%)	0.36++
Aortic arch	8 (8.08%)	2 (2.02%)	0.10++
Coeliac trunk	9 (9.09%)	0 (0%)	<0.01++
Superior mesenteric artery	10 (10.1%)	3 (3.03%)	0.08++
Ascending aorta	13 (13.13%)	2 (2.02%)	<0.01++
Descending aorta	13 (13.13%)	4 (4.04%)	0.04++
Brachiocephalic artery	16 (16.16%)	0 (0%)	<0.01++
Vertebral artery	16 (16.16%)	3 (3.03%)	<0.01++
Thoracic aorta	19 (18.18%)	6 (6.06%)	<001++
Abdominal aorta	27 (27.27%)	18 (18.18%)	0.174++
Renal arteries	33 (33.33%)	6 (6.06%)	<0.01++
Common carotid artery	54 (54.55%)	11 (11.11%)	<0.01++
Subclavian artery	59 (59.6%)	4 (4.04%)	<0.01++
Total	313 (315.15%)	105 (106.06%)	
Combination			
Aortic arch or its branches*	83 (83.84%)	17 (17.17%)	<0.01++
Abdominal aorta or its branches*	40 (40.40%)	10 (10.10%)	<0.01++
Other large vessels	8 (8.08%)	74 (74.75%)	<0.01++

Aortic arch or its branches* means abnormal imaging findings (mainly by MRA, CTA and/or ultrasound) including stenosis, occlusion, thickness or aneurysm of aortic arch or its branches (brachiocephalic artery, left common carotid artery and left subclavian artery).
Abdominal aorta or its branches* means abnormal imaging findings of the abdominal aorta or its branches (renal arteries, superior mesenteric artery, coeliac trunk).

Results

Training set

• *Demographic data*

In the training set, there were 81 women and 18 men in the TA group with: a mean age at the diagnosis of 36.8±13.65 years; a mean age of onset of 32.23±12.52 years; mean disease duration of 2.54 years. Seventy-six of the 81 (62.63%) women were aged <40 years at diagnosis.

In the control group, there were 31 women and 68 men, and the female: male ratio was significantly different from that of the TA group (p<0.01). The mean age at onset was 58.06±15.92 years, significantly older than that of the TA group (p<0.01) (Table II). Each characteristic was calculated for its p-value and odds ratio.

• *Symptoms*

According to the criteria set by Kerr *et al*., "active disease" is present if at least two of the following are observed: (i) systemic features with no other cause; (ii) elevated ESR; (iii) features of vascular ischaemia or inflammation (claudication, diminished or absent pulse, bruit, vascular pain, asymmetric blood pressure; (iv) typical angiographic features (including any imaging method in addition to conventional angiography) (17). Fifty-eight of 99 (58.59%) TA patients were defined as active disease (Table II).

Almost half of TA patients (48 cases) had weakness as the first symptom, followed by chest pain or chest distress and headache. With respect to clinical signs, vascular bruits and abnormal pulses were specific for TA, involved in 63 and 45 cases, respectively. There were also significant differences in amaurosis between the two groups (p<0.01, Table II).

• *Imaging*

At enrolment, 93 TA patients in the training set underwent imaging (56 patients carried out MRA, 37 CTA, 1 ultrosound and 3 DSA. Among them, 4 patients completed both MRA and CTA tests). Forty patients with vasculitis involving small vessels in the control group did not undergo imaging of any artery because of the lack of clinical evidence of large vessels affected. Arteries that could have been involved were compared between the TA group and control group. The most commonly affected artery was the common carotid (59.60%), followed by the subclavian (54.55%) and renal artery (33.33%) (Table III).

According to classifications created by Nasu and Ueno (18), type 3 was the most common (46.46%), followed by type 1 (38.38%), type 2 (14.14%), type 5 (8.08%) and type 4 (4.04%).

Foundation of new clinical diagnostic criteria for TA

• *Selection of candidate variables in the new diagnostic model*

According to the analyses detailed above, variables with p<0.01 were candidate factors for new criteria. These variables were: sex; age (<40 years); decreased or absent pulse; amaurosis; weakness, distress or pain in the chest; headache; vascular bruits; the aortic arch or its branches; the abdominal aorta or its branches. Detailed information (sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio) regarding these variables was shown in Table IV.

• *Formation of new scoring criteria for TA*

In this part, with discussion by rheumatologists, some variables with a significant difference (p<0.01) were selected into the diagnostic model. Stepwise binary logistic regression with forward selection was used to screen the chosen variables and create a scoring system for TA (Table V).

Each variable was scored by its rounded-off coefficient B value to form a scoring system. Then, variables selected were defined as points seen in the Table V. The points of each patient in TA and control groups were then summated (Table VI).

After analysing the scores distributed in Table VI, the score eight was proposed as the "dividing line" to distinguish patients with a high probability of TA from the other patients. Hence, patients with a score ≥8 can be diag-

Table IV. Sensitivity, specificity, PPV, NPV, PLR and NLR of variables with $p<0.01$.

Variable	Odds ratio	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	PLR (95% CI)	NLR (95% CI)
Sex (M:F)	9.87	81.82 (72.52, 88.59)	68.69 (58.48, 77.43)	72.32 (62.93, 80.15)	79.07 (68.69, 86.80)	2.61 (1.92, 3.55)	0.26 (0.17, 0.41)
Age <40 years	11.09	62.63 (52.28, 71.98)	86.87 (78.24, 92.55)	82.67 (71.82, 90.09)	69.92 (60.89, 77.68)	4.77 (2.81, 8.09)	0.43 (0.33, 0.56)
Decreased or absent pulse	40.6	45.45 (35.53, 55.74)	98.99 (93.70, 99.95)	97.83 (87.03, 99.89)	64.47 (56.26, 71.94)	45 (6.32, 320.09)	0.55 (0.46, 0.66)
Amaurosis	13.52	12.12 (6.69, 20.59)	98.99 (93.69, 99.95)	92.31 (62.09, 99.60)	52.97 (45.53, 60.29)	12 (1.59, 90.54)	0.89 (0.82, 0.96)
Weakness	7.53	48.48 (38.40, 58.69)	88.89 (80.59, 94.05)	81.36 (68.67, 89.89)	63.31 (54.67, 71.20)	4.36 (2.41, 7.90)	0.58 (0.48, 0.70)
Headache	3.24	28.28 (19.70, 38.20)	88.89 (81.00, 94.30)	71.80 (54.88, 85.15)	55.35 (47.27, 63.22)	1.24 (1.08, 1.43)	0.39 (0.21, 0.75)
Dizziness	14.68	13.13 (7.2, 21.4)	91.92 (84.7, 96.4)	61.90 (37.83,82.33)	51.41 (43.80,58.98)	0.615 (0.267,1,419)	1.085 (0.961,1.165)
Chest pain or chest distress	3.63	33.33 (24.37, 43.61)	87.87 (79.41, 93.31)	73.33 (57.79, 84.90)	56.86 (48.62, 64.76)	2.75 (1.51, 5.01)	0.76 (0.66, 0.87)
Vascular bruits*	12.69	63.64 (53.30, 72.90)	87.88 (79.41, 93.31)	84 (73.32, 91.11)	70.73 (61.74, 78.41)	5.25 (3.03, 9.11)	0.41 (0.32, 0.54)
The aortic arch or its branches	25.02	83.84 (74.78, 90.2)	82.83 (73.65, 89.40)	83 (73.89, 89.51)	83.67 (74.54, 90.10)	4.88 (3.14, 7.59)	0.20 (0.12, 0.31)
Abdominal aorta or its branches	6.03	40.40 (30.80, 50.76)	89.90 (81.80, 94.78)	80 (65.86, 89.50)	60.14 (51.75, 67.99)	4 (2.12, 7.54)	0.66 (0.56, 0.78)

PPV: positive predicted value; NPV: negative predicted value; PLR: positive likelihood ratio; NLR: negative likelihood ratio.

Table V. B points of variables in binary logistic regression analyses and the new criteria.

Sign, symptoms or imaging findings	B points	Rounded-off coefficient B value / Points
Female	2.714	3
Age (<40 years)	4.126	4
Chest pain or chest distress	2.235	2
Amaurosis	3.323	3
Vascular bruit	1.879	2
Decreased or absent pulse	4.815	5
Aortic arch or its branches	3.815	4
Abdominal aorta or its branches	2.557	3
Total		26

nosed as TA. Results of the sensitivity, specificity and the area under ROC curves of different criteria were shown in Table VII and Figure 1. As seen from Table VII, the new criteria had higher sensitivity and specificity than those of the ACR and Ishikawa. The area under the ROC curve of the new area was 0.982, more than that of the ACR classification criteria (0.803, $p<0.001$). Ishikawa's criteria are not quantitative data, so construction of the ROC curve was not possible.

Performance of the new criteria in the validation set

In the validation set, the same general and clinical information of patients was collected when they were recruited. In TA group 2, CTA, B-ultrasound and MRA examinations were carried out in 14, 9, and 9 patients respectively. Patient characteristics of the two groups are shown in Table V (numeric data are given as the mean and categorical data expressed as ratios).

Based on materials in the validation set, sensitivity and specificity of new criteria were tested. Meanwhile, sensitivities and specificities of the ACR classification criteria and Ishikawa criteria were estimated. The sensitivity of the new criteria was 90.63%, considerably higher than that of the ACR criteria and Ishikawa's criteria (75% and 25%, respectively). The specificity of the new criteria was 96.97%, similar to that of the ACR criteria (96.97%), but less than that of Ishikawa's criteria (100%).

Discussion

TA has been reported in several countries, including Japan, Turkey, France and Mexico (19-22). Criteria used for the diagnosis of TA were reviewed by Alexandre *et al*. in 2013. They stated that each previous criteria used to diagnose TA had limitations. Thus, new feasible criteria are needed urgently (23).

Some researchers have evaluated the characteristics of TA patients in China, however they just studied one or more aspect of TA patients in each study (*e.g*. sex, age, clinical manifestation, and treatment) (24, 25). Systematic analyses on the characteristics of TA in China have not been carried out. Our study demonstrated several differences in the clinical manifestations and lesion distribution compared with reports from other countries.

Table VI. Distribution of total scores in TA patients and controls.

Score	Control group 1 no. cases	TA group 1 no. cases
0.00	31	0
2.00	7	0
3.00	23	1
4.00	10	1
5.00	7	0
6.00	3	0
7.00	12	6
8.00	3	4
9.00	3	10
10.00	0	4
11.00	0	10
12.00	0	6
13.00	0	6
14.00	0	9
15.00	0	2
16.00	0	6
17.00	0	4
18.00	0	12
19.00	0	2
20.00	0	2
21.00	0	6
22.00	0	1
23.00	0	5
24.00	0	2

Table VII. Comparison between our criteria, ACR classification criteria and Ishikawa criteria.

	New criteria	ACR	Ishikawa
Sensitivity % (CI*)	91.92 (84.24, 96.19)	75.76 (65.92, 83.56)	56.57 (46.24, 66.38)
Specificity % (CI*)	93.94 (86.76, 97.51)	85.86 (77.07, 91.78)	94.95 (88.06, 98.13)
Area under the ROC#(CI*)	0.981 (0.951, 0.995)	0.868 (0.813, 0.912)	
p-value	<0.0001		

*CI: confidence interval; #ROC: receiver operating characteristic curve.

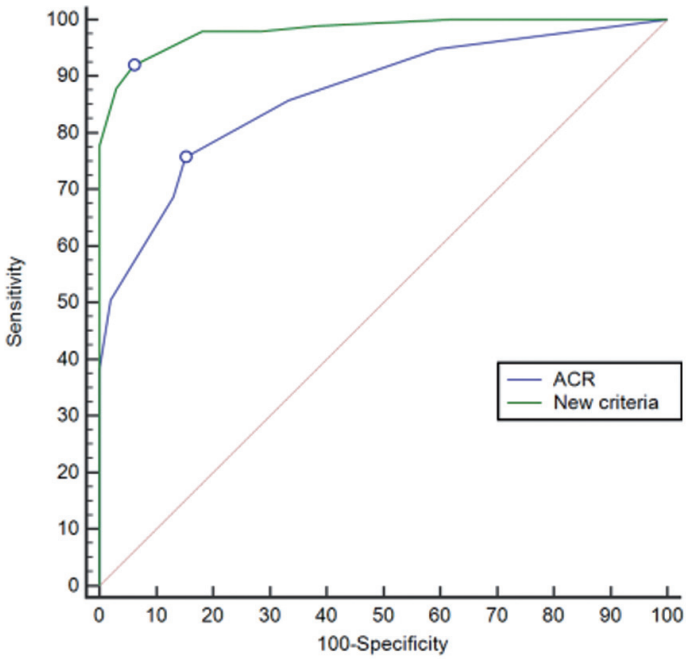

Fig. 1. ROCs of the new criteria and the ACR criteria

In our study, the mean age at onset in the TA group was 36.8 years, which was significantly younger than that of the control group. The prevalence was 4.5-fold higher in females than in males. These two general characteristics of TA are in accordance with epidemiologic investigations of TA in Japan, but the sex ratio is much lower than that of Japan, where gender ratio between female and male is about nine.

With regard to laboratory tests, some parameters that usually reflect disease activity (*e.g.* ESR, CRP) did not show prominent differences between the two groups, because patients with other vasculitis in the control group may also have high ESR and CRP. The value of hemoglobin was slightly low while the levels of leukocytes and platelets were normal in TA patients. This strange phenomenon may be explained by higher serum levels of IL-6 in the early stage of TA (26). IL-6 could stimulate hepatocytes to produce hepcidin, a polypeptide that inhibits intestinal absorption and reticuloendothelial release of iron and cause anemia indirectly. A total of 131 patients in the TA group underwent imaging at the recruitment. Structural changes in blood vessels can be shown clearly using MRA or CTA, including stenoses, occlusions, angiectasis and aneurysms. The subclavian artery was the most common involved artery, followed by the common carotid, renal and abdominal aortic arteries, which were significantly different compared with the control group except the abdominal aorta. This result was not in accordance with data reported in Japanese populations, in which the main involved artery was the aortic arch. Another distinct discrepancy was that renal arteries involvements were demonstrated in 33 patients of 99 cases (33.33%) in our investigation; such a high prevalence has not been observed in Japan and other countries, probably because current imaging modalities have higher sensitivity than previous ones. Since previous imaging methods such as DSA were always used to evaluate the targeted aorta, renal arteries might be neglected unless patients presented the manifestations of severe high blood pressure. This phenomenon could explain the higher proportion of hypertension in the TA group, which was in accordance with previous studies in Asian countries (5), although no significant difference was shown between two groups in present study. The prevalence of involvement of the abdominal aorta was consist with an autopsy study of Takayasu arteritis in India, which had proved that abdominal aorta was the most common site of involvement (27). To some extent, different races present different frequencies of involved arteries. After combining these arteries into three main parts, the aortic arch or its branches were the most common involved part in our study.

Our new criteria had two main characteristics. Firstly, the database of the training set was established on the clinical features of patients from Shanghai and environs, whereas the database of TA patients in the validation set was based primarily on the clinical features of patients from Xinjiang Province. These two locations may represent

Asian areas to some extent. Secondly, the control group included patients with at least one similar symptom to TA disease manifestations, which can provide sufficient information to establish new diagnostic criteria. GCA has a low incidence in China, so just one case of GCA was collected in the control group. Although GCA and TA are both large-vessel vasculitis and share many similar clinical characteristics, several points can help us to differentiate it from TA. GCA patients have older ages (>50 years), rapid progression, obvious systematic manifestation (such as feve, blindness and tinnitus) and different distribution of involved arteries which mainly refer to extracranial arteries such as temporal arteries and axillary arteries. Therefore, GCA and TA aren't possible same disease in terms of epidemiologic and clinical profile (28).

In addition, compared with previous criteria, the new criteria have three main advantages. Firstly, in contrast with Ishikawa's criteria, our new criteria are more convenient and applicable. Only if the score of a patient is ≥8 points, diagnosis of TA could be made. The new criteria eliminate some unreasonable aspects of the Ishikawa's criteria, such as the age restriction in the obligatory criterion, and the lesions in the mid-subclavian artery in the major criteria, which may cause the missing diagnosis of TA. In fact, patients with an age of onset >40 year are not rare, and trunk-branch corners can also be involved. Secondly, compared with the ACR classification criteria, our new criteria do not limit the age of onset to ≤40 years, and can cover more involved arteries (including the abdominal aorta or its branches). Thirdly, our new criteria contain not only general information, symptoms and signs but also the characteristics of advanced imaging and systematic assessment of TA. Conventional angiography, the "gold standard" method for the initial diagnosis, has been replaced by MRA and CTA in recent years (29). Development of delayed-enhancement MRI and MRI-based reconstruction of blood-vessel walls has also been helpful for TA assessment. Inclusion of imaging results emphasises the importance of imaging (especially MRA) in the early diagnosis of TA.

Even though the TA patients of the validation set were primarily from Xinjiang province (where there are some regional and ethnic differences from the mainland of China), the results of the validation part showed that the new criteria had high sensitivity and specificity, which confirmed the feasibility and practicability of our new criteria. However, these criteria also have some defects. From one hand, parameters in the new criteria have covered age, clinical manifestation and distribution of involved arteries, which can discriminate GCA from TA based different characters mentioned above. However, more cases need to be collected to estimate the efficacy of these new criteria because of low incidence of GCA in our country. On the other hand, present study was carried out only in China, so the sample size was limited to some extent. Clinical validations in other centres need to be done in future studies. We have listed the final scoring criteria in article in detail. It is hoped that more researchers would pay attention to it, thus a international database of TA could be established in further, so as to validate this new set of diagnostic criteria.

Conclusions

Clinical characteristics of 99 TA patients were analysed and compared with other vascular involved cases to ascertain the intrinsic differences of TA from other vascular diseases. Using comparison and binary logistic regression methods, a systematic scoring scheme was created. In contrast with the ACR classification criteria, our new criteria had higher sensitivity and specificity. Creating standardised criteria for TA will be beneficial for further studies on its pathogenesis and be more practical for its diagnosis, laying a foundation for future clinical trials. However, further validation of these criteria in more places, not only in other centres in China but also in non-Asian countries, should be carried out before its universal application.

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