The value of ultrasonography for predicting carotid progression of Takayasu arteritis: a prospective cohort study

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Abstract

Aim To identify valuable ultrasonography and clinical markers for predicting carotid imaging progression of Takayasu arteritis (TA) during a 1-year follow-up. Methods Seventy-seven TA patients were enrolled through a Chinese TA cohort from May 2016 to June 2019. The patients' clinical characteristics, serological tests, and carotid ultrasonography results were recorded at baseline and each visit. Carotid progression was evaluated by ultrasonography during the 1-year follow-up. Baseline clinical characteristics and ultrasonography results for predicting imaging progression were identified. Results Sixteen (20.8%) patients presented with carotid imaging progression during 1-year follow-up. The patients in the progressive group were younger (23.4±3.7 vs. 32.3±9.8 years, $p < 0.01$) at baseline. Furthermore, the proportion of patients showing treatment resistance (TR) or disease relapse (DR) (87.5% vs. 16.4%, $p < 0.01$) was higher in the progressive group than in the non-progressive group. Thicker vessel wall was observed in the progressive group than that in the non-progressive group (2.4±0.8 vs. 1.9±0.5 mm, $p = 0.041$) at baseline. According to the matrix models, patients with thickened carotid wall (≥1.9 mm), TR or DR, and younger age (≤ 30 years) would suffered from a high risk of 75% for carotid imaging progression. Conclusion Younger patients with early vascular structural changes at baseline as well as refractory disease seemed more likely to show carotid imaging progression.

1. Introduction

Takayasu arteritis (TA) is a progressive, inflammatory vasculitis mainly involving the aorta and its branches, which predominantly affects young women (age <40 years) in eastern countries. The onset and progression of TA are often insidious. Disease progression alternates with periods of exacerbation and remission and sometimes acute flares. It has been reported that some patients even showed imaging progression in the chronic stable phase[1, 2]. Glucocorticoids (GCs) combined with immunosuppressors is the first-line therapy for TA. However, approximately 20% patients have been reported to have no or poor response to current medications [3]. Thus, it is crucial to find valuable markers to monitor or predict disease progression in order to prevent adverse vascular complications.

Until now, no effective index has been found for predicting disease progression of TA. Imaging techniques are important for detecting and monitoring vascular inflammation and structure changes, and efforts have been made to point out the value of imaging techniques for disease activity assessment and progression prediction. Color Doppler ultrasonography (CDUS) and contrast-enhanced US (CEUS) are promising imaging techniques, which could afford visualization of changes in vascular structure and neovascularization of the vessel wall timely. Our previous studies indicated that US results combined with ESR could effectively diagnose active TA. The use of CEUS in the follow-up of large vascular disease can reflect inflammation of the vessel wall in a timely and sensitive manner[4]. The thickness and neovascularization of vessel walls on US are also markers of treatment response in TA[5]. However, the value of US as well as clinical measurements in the prediction of long-time disease progression for TA is unclear and need to be further studied.

Carotid involvements are very common in TA, which approximately comprised of more than 45% of the total TA patients. US has shown great advantages on evaluating carotid vascular involvements[6]. Hence, the aim of this study was to clarify progression in carotid artery and the predictive values of baseline clinical characteristics and US for carotid imaging progression during a 1-year follow-up based on a large Chinese TA cohort.

2. Patients And Methods

2.1 Patient and population

This study was designed based on a prospective cohort of Chinese population, namely ECTA cohort, centered in Zhongshan Hospital, Fudan University. Seventy-seven patients, diagnosed as TA according to the 1990 American College of Rheumatology diagnostic criteria[7] from May 2016 to June 2019 were enrolled in this study. All the enrolled patients had carotid artery involvements and were followed-up according to a designed schedule. Patients for whom US contrast agents were contraindicated or with allergies to these agents were excluded. Informed written consent was obtained from each participant. The study was approved by the ethics committee of Zhongshan Hospital, Fudan University.

2.2 Disease assessment and follow-up

All patients were followed up every month, and follow-up data were collected and recorded in a database according to the study plan. CDUS and CEUS were performed every 3 months. Clinical characteristics and physical examination results at baseline and during the 1-year follow-up were recorded. Serological tests, such as complete blood count, ESR, CRP, serum amyloid A (SAA) level, and cytokine levels, were performed within 3 days of the CEUS examination every 3 months. The Kerr index was used as the gold standard for disease activity assessment. Indian Takayasu Activity Score (ITAS) 2010 scores were also recorded.

2.3 Treatment response

Treatment response was classified as clinical remission (CR), treatment resistance (TR), and disease relapse (DR)[8]. Patients were considered as showing CR if the following criteria were satisfied: i) prednisone was reduced to 0.1-0.2 mg/kg/day (≤15 mg/day); ii) no new symptoms developed and there was no symptom aggravation; iii) ESR was normal after 6 months of induction treatment; iv) inactive disease status was confirmed by clinical evaluation and Kerr score was <2 during the remaining follow-up period. Patients were considered as showing TR if they did not achieve remission after treatment with GCs combined with more than two immunosuppressors or if the GC dose could not be reduced to 15 mg/day during the follow-up period. If patients went into disease remission at the end of the induction treatment but showed active disease again during the remaining follow-up, they were considered as showing DR.

2.4 CDUS and CEUS examinations

All 77 patients underwent carotid CDUS connected with CEUS. The examinations were performed using a Philips Elite US instrument (Philips Medical Systems, Bothell USA) with an L9-3 linear array probe. The extracranial carotid arteries, including the common carotid artery, internal carotid artery and external carotid artery, were all checked by an experienced physician. The wall thickness of lesions was measured. The mechanical index was 0.07 and the gain was 70%. The instrument parameters were kept consistent for all patients. CEUS was performed at the thickest part of the common carotid artery wall after the CDUS examination. An US contrast agent (SonoVue, Bracco, Italy) was used in this study. The semiquantitative visual score was used to determine the disease activity[9].

Twelve patients had unilateral carotid lesions, and we performed carotid ultrasound on their diseased side. Another 65 patients had bilateral carotid artery lesions, and we performed ultrasound on their heavier side. All patients underwent CDUS and CEUS at baseline, every 3 months, and at the 1-year follow-up. The parameters examined during the carotid US were artery wall thickness, artery diameter, proportion of vascular stenosis or occlusion, peak flow rate, and the resistance index. Carotid wall vascularization was semi-quantitatively graded according to the neovascularization at the thickening wall[4].

Patients were considered as showing imaging disease progression if there was a more than 15% increase in one of the US parameters (wall thickness, lesion range, and lumen stenosis), or aggravations on CEUS semi-quantitative analysis during the 1-year follow-up compared with the corresponding baseline finding.

2.5 Statistical analysis

Statistical analysis was performed used SPSS (version 22, IBM, USA). Continuous variables were described as mean ± SD values for normally distributed data or median (IQR) values for non-normally distributed data and compared using Student's *t*-test or Wilcoxon rank sum test. Categorical variables were described in numbers (%) and were compared using the Chi-square test. Kaplan-Meier survival curve, drawn by GraphPad Prism 7 (GraphPad), was used to depict the occurrence of imaging progression during the 1-year follow-up. Hazard ratios (HR) and 95% confidence intervals (CI) were examined by Cox regression analysis. Multivariate analyses involved adjustments for age, Kerr score, luminal stenosis, and CEUS grade 2, and included all markers of which p-value was <0.1 in the univariate analysis. Significance was defined at $p < 0.05$ (two-sided). The ability of the markers at baseline to diagnose imagine progression was assessed by receiver operating characteristic (ROC) curve analysis. Following this analysis, we constructed a matrix diagram to estimate power observations for three groups of progression risk (low, medium, and high).

3. Results

3.1 Patient characteristics at baseline

The mean age of the TA patients was 30.4±9.6 years, with female-to-male ratio of 10:1. The disease duration was 25 (5-58) months. At baseline, 49 patients (63.6%) showed active disease according to Kerr scores. The major clinical symptoms were neck pain (16.9%), hypertension (16.9%), dizziness (9.1%), fever (6.5%), and pulselessness (5.2%). The median ESR and CRP were 30 (11-66) mm/H and 8.5 (1.5-33.0) mg/dl respectively (Table 1). Prednisone (initial dosage, 0.8 mg/kg) combined with an immunosuppressor, including 5 MTX, 4 CYC, 7 MMF, 12 LEF, and 4 tocilizumab, were administrated in 32 patients as induction treatment. Prednisone (0.1-0.2 mg/kg/day) with MTX (7 patients), MMF (10 patients), and LEF (28 patients) were administrated in 45 patients as maintenance treatment.

Carotid ultrasonography was performed in all the enrolled patients. Carotid stenosis was observed in 50 (64.9%) patients, while 34 (44.2%) cases had grade 2 wall vascularization. 22 (28.6%) patients showed carotid stenosis associated with grade ≥2 wall vascularization. The mean arterial wall thickness and median diameter were 2.2±0.8 mm and 3.8(2.5-5.5) mm respectively (Table 1).

3.2 Carotid imaging progression and treatment response

Sixteen (20.8%) patients presented with carotid progression on imaging examinations, while 43 (55.8%) cases showed imaging improvement and the other 18 (23.4%) showed stable imaging status during the 1 year follow-up. Among the patients with imaging progression, 3 (7.8%) cases occurred at 3 months, 6 (9.1%) at 6 months, and 9 (18.2%) cases at 9 months (Fig 1). Among them, 5 cases suffered from increased wall thickness (increased 0.3-1.2mm), 7 enlarged lesions (increased lesion length >10mm), 3 narrower lumen (lumen stenosis from <50% to >70%), and 7 suffered from aggravations on CEUS semi-quantitative analysis (enhanced artery wall vascularization) (Fig 2). In the patients with progressive carotid imaging, higher proportion of wall vascularization grade 2 (37.5% vs. 9.8%, p = 0.014) and thicker vascular wall (2.1±0.7 vs. 1.7±0.7 mm, p = 0.048) were observed at the end of 1-year follow-up compared to those without progression (Table 1).

During the follow-up period, TR or DR were observed in 24 (31.2%) patients including 3 DR and 21 TR.

3.3 Comparisons of features between patients with and without imaging progression

Then, baseline features were compared between patients with and without carotid progression. Patients in the progressive group were younger at baseline (23.4±3.7 vs. 32.3±9.8 years, p < 0.01) and had higher baseline CRP levels, platelet count and Kerr scores as shown in Table 1. The proportion of patients showing TR or DR in the progression group (87.5% vs 16.4%, p < 0.01) was significantly higher than that in the non-progressive group (Table 1). Carotid US revealed that patients in the progressive group had thicker vessel wall (2.4±0.8 vs. 1.9±0.5 mm, p = 0.041) at baseline. Although the progressive group showed a higher proportion of patients with vascular stenosis (75.0% vs. 62.3%, p = 0.261), the difference was not significant (Table 1).

In the progressive group, 8 patients were initially diagnosed with active disease and the other 8 received maintenance treatment. The disease duration in the initially diagnosed patients was shorter (6 [2-39] vs. 48 [36-60] months, p = 0.041), and all six patients showed high disease activity with Kerr score of 3. There were no significant differences in clinical and laboratory parameters, mean prednisone dose, the use of immunosuppressive agents, and US index between these two subgroups (data not shown).

3.4 Valuable factors for predicting carotid progression

Logistic regression was further performed to identify valuable factors for predicting carotid imaging progression. The results demonstrated that age (HR 0.82, 95% CI 0.72-0.94), wall thickness (HR 5.24, 95% CI 1.49-18.48) and treatment response of TR or DR (HR 60.85, 95% CI 8.92-415.06) were positively associated with carotid imaging progression, with adjustments of ESR, Kerr scores, lumen stenosis, Carotid RI and CEUS grade 2. Then, ROC curve analysis was performed, and indicated that carotid wall thickness ≥1.9 mm, age ≤ 30 years, and TR or DR could predict imaging progression with AUCs of 0.68, 0.802 and 0.86, respectively.

Based on these results, a prognostic matrix was built to stratify patients into different progressive risk groups (low- [<30%], medium- [30%-70%], and high-risk [>70%]) according to the baseline carotid wall thickness, age, and the presence of TR or DR (Fig. 3). Patients with younger age and early vascular structural changes had a higher risk of imaging progression. When wall thickness ≥1.9 mm was combined with age ≤ 30 years and the presence of TR or DR, the incidence of imaging progression is up to 75%. The matrix model demonstrated a sensitivity of 75.0% and specificity of 93.4%.

4. Discussion

Carotid involvements were commonly seen in TA and was more easily to monitored by US. Thus, we designed this study to identify possible predictors including the baseline clinical characteristics as well as the US features of carotid progression over a 1-year follow-up period. Our study found that patients with the following features were more likely to show imaging progression: i) younger age with disease activity; ii) thickened carotid artery wall at baseline; iii) with treatment response of TR or DR during the follow-up.

Predicting disease progression is always an important challenge in the clinical practice of TA. With the continuous development of imaging techniques, ultrasound has become an important imaging method for evaluating vascular involvements, especially temporal artery and carotid artery. For TA patients with carotid artery involvement, ultrasound is far superior to other imaging methods[3]. Previous studies have confirmed that carotid wall thickness detected by US is associated with disease activity[4]. Furthermore, CEUS can assess wall neovascularization clearly[10]. Several studies[9, 11, 12] have confirmed that CEUS can reflect carotid wall inflammation and is associated with TA disease activity. Our previous study also yielded similar results[4]. However, these former studies yielded no evidence indicating that CEUS can predict the progression of TA.

In the present study, we analyzed the value of the features of carotid combined with CEUS for predicting disease progression of TA. We found that patients with carotid imaging progression had thicker artery wall and higher proportion of wall vascularization grade 2 at baseline. Notably, patients with a thickened carotid wall at baseline had an independent 5.24-fold higher risk of disease progression after 1 year. We also noted that patients with active-phase disease, those with early vascular structural changes, and those showing vascular remodeling seemed more likely to have imaging progression. Thus, US showed great value in assessing disease activity and predicting disease progression.

Comarmond[13] et al. reported a relapse rate of 42.7% in a 15-year long-term TA cohort, with 20% of the relapses occurring in the first year. In another Indian TA cohort of 503 patients, 7.2% of the patients were reported to show refractory disease over a median follow-up period of 42 months[14]. Similar results were found in our study. 31.2% of the patients in our cohort showed poor treatment response, including TR or DR, during the first-year follow-up. The rate increased up to 87.5% in the progressive group. In addition, we found that the CRP level was significantly higher in the progression group than that in the non-imaging progression group. However, CRP could not be identified as an independent risk factor for disease progression in further analysis. Other disease activity scores, including Kerr index and ITAS scores were not associated with disease progression. These results suggest that neither inflammatory nor active indicators were suitable for predicting imaging progression alone.

Most importantly, in order to better identify patients with high risk of imaging progressions, we build matrix models to classify patients into different risk groups for imaging progression. In cases showing carotid wall thickness $\geq$ 1.9 mm at baseline, age $\leq$ 30 years, and TR or DR, the risk of imaging progression was up to 75%, while the presence of wall thickness $\geq$1.9 mm at baseline and age $\leq$ 30 years at baseline increased the risk of disease progression from 31% to 52%. This predictive model can be used to distinguish patients with high risk of imaging progression, and a closer follow-up of these high-risk patients is required to improve prognosis.

Our study had several limitations, although the present results were convincing despite the focus on the progression of carotid lesions. First, we restricted enrolment to patients with carotid artery involvement, which limited the sample size. Subsequent studies with larger sample sizes need to be performed. Second, the follow-up period was relatively short in the present study, and longer follow-up in future studies were needed to further confirmed the conclusions.

In conclusion, during the 1-year follow-up, 20.8% of the TA patients showed imaging progression. Younger patients with early vascular structural changes, and vascular remodeling at baseline seemed more likely to suffered from imaging progression.

Declarations

Ethics approval and Consent to participate

The study was approved by the ethics committee of Zhongshan Hospital at Fudan University.

Consent for publication

Informed written consent was obtained from each patient.

Availability of data and material

Please contact the authors for data requests.

Competing interests

None.

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Authors's contributions

LYM carried out the clinical data and draft the manuscript. CLL participated in ultrasound examination. YS and RYC participated in the design of the study. XMD and ZFJ performed the statistical analysis. HH and HYC participated in its design and coordination. BJH and LDJ conceived of the study.

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Not applicable.

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Table

Table1. Characteristics of TA patients at baseline and the end of 1-year follow-up

	Total (77)		Progression group (16)		Alleviation or stabilization group (61)		*P* value	
	Baseline	**1-year**	**Baseline**	**1-year**	**Baseline**	**1-year**	***P1***	***P2***
Sex, female (%)	70(90.9)	/	15(93.8)	/	55(90.2)	/	0.657	/
Age, years	30.4±9.6	/	23.4±3.7	/	32.3±9.8	/	<0.001	/
Disease duration, months, median(IQR)	25(5-58)	/	36(2-52)	/	24(6-69)	/	0.486	/
Initial treatment (%)	32(41.6)	/	8(50.0)	/	24(39.3)	/	0.575	/
Hypertension (%)	13(16.9)	/	1(6.3)	/	12(19.7)	/	0.276	/
Pulselessness (%)	4(5.2)	/	2(12.5)	/	2(3.3)	/	0.193	/
Dizziness (%)	7(9.1)	/	3(18.8)	/	4(6.6)	/	0.157	/
Neck pain (%)	13(16.9)	/	3(18.8)	/	10(16.4)	/	0.845	/
Fever (%)	5(6.5)	/	2(12.5)	/	3(4.9)	/	0.282	/
TR or DR(%)	/	24(31.2)	/	14(87.5)	/	10(16.4)	/	<0.001
ESR, mm/H, median(IQR)	30(11-66)	14(5-31)	46(13-81)	15(9-31)	26(10-54)	14(3-30)	0.127	0.606
CRP, mg/L, median(IQR)	8.5(1.5-33.0)	2.9(0.9-11.5)	23.1(1.9-95.9)	2.6(1.9-18.6)	7.4(1.5-27.7)	3.1(0.7-10.3)	0.019	0.430
SAA, mg/L, median(IQR)	20.7(8.2-86.3)	13.8(5.9-6.8)	40.1(8.5-184.5)	18.5(7.9-120.7)	18.3(7.2-65.0)	10.9(5.8-42.9)	0.635	0.393
Platelet count, $\times 10^9$/L, median(IQR)	299(218-370)	250(207-300)	358(255-463)	275(198-301)	287(213-355)	246(208-300)	0.023	0.482
Hb, g/L	119.4±17.2	118.3±19.0	121.4±22.2	124.3±17.2	118.8±15.7	116.7±19.3	0.589	0.168
IL-6, pg/ml, median(IQR)	5.7(3.2-11.7)	3.3(2.2-6.9)	9.9(2.0-16.6)	4.2(2.6-9.8)	5.6(3.4-1.3)	3.2(2.1-6.4)	0.639	0.333
Kerr score ≥ 2	49(63.6)	13(16.9)	13(81.3)	5(31.3)	36(59.0)	8(13.1)	0.085	0.083
Kerr scores, median(IQR)	2(1-3)	0(0-1)	3(2-3)	0(0-2)	2(1-3)	0(0-1)	0.049	0.165
ITAS 2010 scores, median(IQR)	1(0-5)	0(0-0)	4(1-5)	0(0-2)	1(0-4)	0(0-1)	0.477	0.632
Carotid artery wall thickness, mm	2.2±0.8	1.8±0.7	2.4±0.8	2.1±0.7	1.9±0.5	1.7±0.7	0.041	0.048
Carotid artery diameter, mm, median(IQR)	3.8(2.5-5.5)	3.9±1.9	4.2(1.1-6.1)	3.5±1.9	3.8(2.6-5.3)	4.0±1.9	0.921	0.404
Proportion of vascular stenosis (%)	50(64.9)	45(58.4)	12(75.0)	10(62.5)	38(62.3)	35(57.4)	0.261	0.782
Proportion of vascular occlusion (%)	10(13.0)	11(14.3)	1(6.3)	1(6.3)	9(14.8)	10(16.4)	0.335	0.270
Carotid artery peak flow rate,		1.2±0.9	1.1(0.5-2.0)	1.2±0.6	1.3(0.7-1.9)	1.3±0.9	0.777	0.623

m/s, median(IQR)	1.3(0.7-1.9)							
Carotid RI	0.7±0.1	0.7±0.1	0.6±0.1	0.7±0.1	0.7±0.1	0.7±0.1	0.009	0.662
CEUS carotid wall vascularization grade 2 (%)	34(44.2)	12(15.6)	7(43.8)	6(37.5)	27(44.3)	6(9.8)	0.971	0.014

TA: Takayasu arteritis; TR: treatment resistance, DR: disease relapse, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, SAA: serum amyloid A, Hb: hemoglobin, IL-6: interleukin 6, RI: resistance index

P1 was defined for groups at baseline, *P2* was defined for groups at 1-year follow-up.

Figures

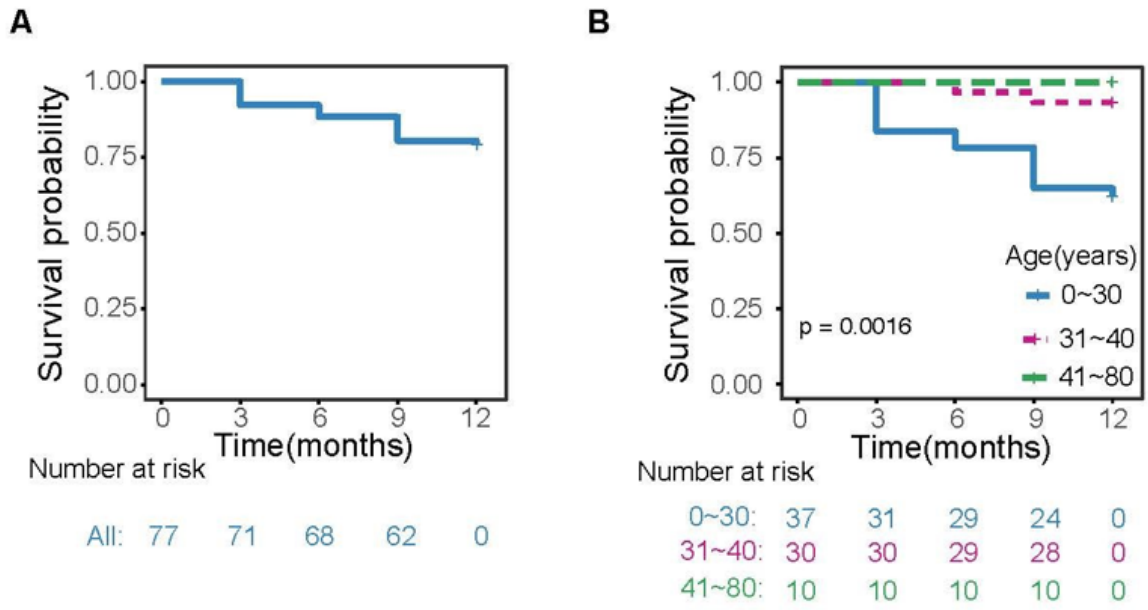

Figure 1

Kaplan-Meier curve of imaging progression. A, Kaplan-Meier curve of imaging progression in 1-year follow-up. B, Kaplan-Meier curve of imaging progression in age subgroups.

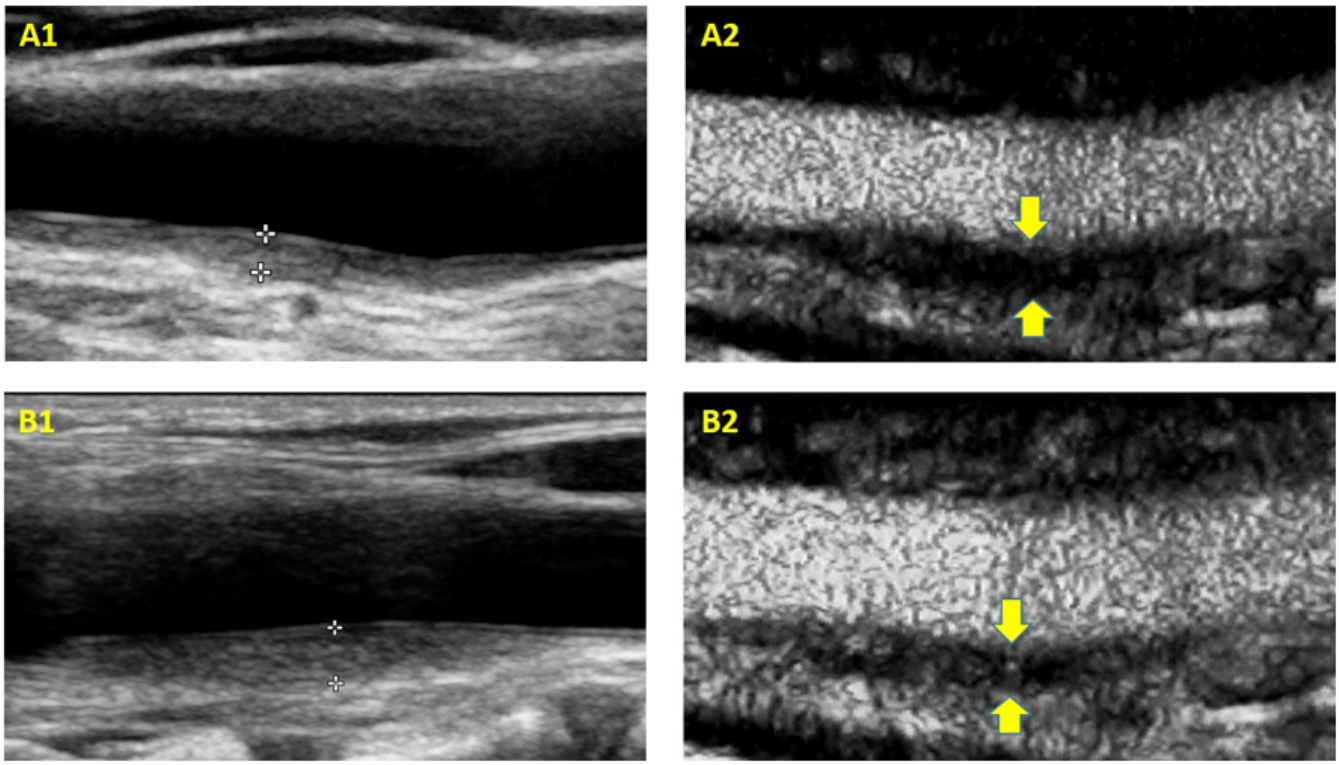

Figure 2

Progression of carotid CEUS after 6-month treatment in one TA patient One 25-years old female patient complained of fatigue and low-grade fever for 2 years before diagnosed with TA in our hospital. The carotid artery CDUS at baseline showed significant thickened vessel wall (A1). Further CEUS examination showed limited or moderate vascularization in thickened wall (A2). After treatment of glucocorticoid and cyclophosphamide for 6 months, the lesion wall thickness increased from 1.6mm to 2.8mm (B1), with severe vascularization at CEUS (B2).

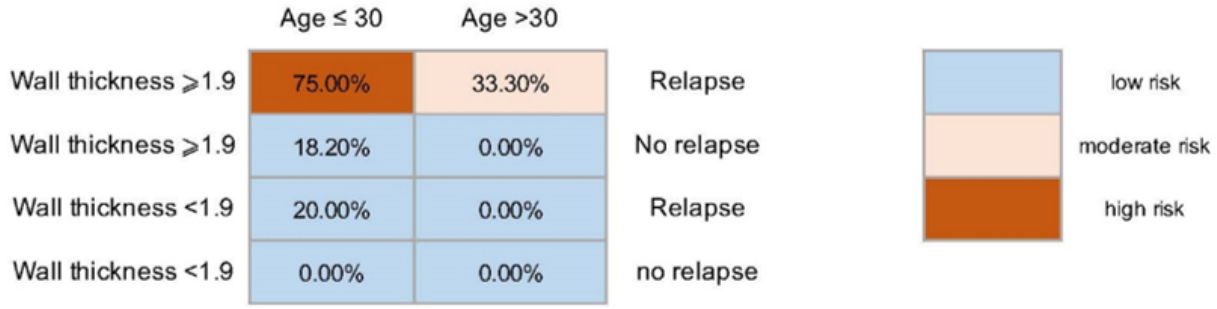

Figure 3

Matrix-models Risk of TA imaging progression according to carotid wall thickness, age and treatment resistant or disease relapse at baseline. Three groups of risk could be identified: high risk (red≥70%), medium (yellow, between 30 and 70%) and low risk (blue, ≤30%).