A novel ultrasound-based score for assessing carotid artery activity in Takayasu's arteritis

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Abstract

Objective

The role of ultrasonography for evaluating vessel wall inflammation in Takayasu's arteritis (TAK) is well-recognised; however, an effective approach for the quantitative assessment of disease activity remains lacking. This study aimed to develop a novel ultrasound-based score for determining TAK activity.

Methods

TAK patients with carotid artery involvement were prospectively followed-up for 6 months. Our proposed ultrasonographic activity score (ULTRAS, range between 0–12) consisted of wall thickness (TS, range between 0–8) and semi-quantitative echogenicity scores (ES, range between 0–4). The diagnostic performance of ULTRAS for disease activity was evaluated in terms of area under the receiver operating characteristic curve (AUC). Internal validation was subsequently performed.

Results

The patients were divided into training and validation groups (n=136 and 30. respectively). In the training group, 83 (61.0%) had active disease. At an optimal cut-off of 7, ULTRAS showed good diagnostic accuracy for active TAK (AUC, 0.88; 95% CI, 82–94). Improved diagnostic performance was achieved when combined with ESR (AUC, 0.91; 95% CI, 86–96) or CRP (AUC, 0.90; 95%CI, 86-95). In the verification group, the AUCs were 0.88, 0.95, and 0.92 for ULTRAS, ESR plus ULTRAS, and CRP plus ULTRAS, respectively. At post-treatment follow-up, the TS, ES, and ULTRAS paralleled the patients' disease remission and symptom recovery. At 3-month follow-up, an improvement in wall thickness of ≥0.3 mm correlated with symptom recovery in 50% of the patients.

Conclusion

Our proposed ultrasound-based score carries the potential in the detection of active disease among TAK patients.

Key words

disease activity, ultrasonographic activity score, wall thickness, Takayasu's arteritis

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Introduction

Takayasu's arteritis (TAK) is an autoimmune large-vessel vasculitis characterised by chronic inflammation, intimal proliferation, and endothelial damage leading to wall thickening, along with luminal stenosis and occlusion. TAK predominantly affects the aorta and its major branches, particularly the carotid arteries (1). Evaluation of vascular inflammation is necessary both for the primary diagnosis and follow-up of such patients. While erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are commonly used acute phase reactants in the assessment of TAK activity, they are limited in specificity. Cytokines such as interleukin (IL)-6, IL-17, interferon (INF)-γ, pentraxin-3 (PTX3) and tumour necrosis factor (TNF)-α may be considered potential candidates for disease activity assessment (2-4), but are not widely accepted in primary care settings owing to inconsistent results. The assessment of disease activity in TAK thereby remains a challenge due to the lack of reliable biomarkers.

The role of non-invasive imaging is increasingly recognised for TAK activity assessment (5, 6), with ultrasonography and magnetic resonance angiography (MRA) considered the modalities of choice for TAK diagnosis, followed by computed tomography (CT) and ^{18}F-fluorodeoxyglucose positron emission tomography (PET)-CT (5). Among these, ultrasonography may be considered the most convenient and inexpensive approach, allowing for clear visualisation of superficial blood vessels (7), while being radiation-free.

Carotid artery involvement has been shown in approximately 45–84% of TAK patients (1). Ultrasonography is currently deemed the most effective approach for the evaluation of carotid arteries. Carotid artery wall thickness and echogenicity have been demonstrated as useful ultrasonographic parameters for active disease assessment. In 1991, Maeda *et al*. described homogeneous and moderately echogenic circumferential wall thickening of the carotid arteries (the "macaroni sign") as a pathognomonic feature of active TAK on B-mode ultrasonography (8). Hypoechogenicity has been shown to reflect vascular wall oedema of the pre-stenotic stage, while hyperechogenicity reflect the non-inflammatory phase (9). The significant association of wall thickness and active disease has been supported by multiple studies thereafter (10). The reduction in circumferential wall thickness in response to treatment has further been reported (11, 12). Nonetheless, there remains a lack of consensus on the added value of ultrasonography in the assessment of TAK disease activity. Reports on the cut-off points of wall thickness for disease activity have been inconsistent (10, 13). The Takayasu ultrasound index proposed by Svensson *et al*. assesses TAK activity based on qualitative description of the intima-media thickness (IMT) at the common carotid arteries, brachiocephalic trunk, and aortic arch (10); however, the preliminary study is small in sample size, with no grading system established.

This study thereby aimed to develop a novel ultrasound-based score involving the measurement of wall thickness and semi-quantification of echogenicity of the common carotid arteries, and evaluate its role as a diagnostic marker for active and symptomatic TAK. We further explored the extent of wall thickness improvement for symptom relief in such patients during follow-up.

Patients and methods

Patient population

A prospective study involving TAK patients from the East China Takayasu Arteritis (ECTA) cohort in Zhongshan Hospital, Fudan University was performed. All patients were diagnosed with TAK according to the 1990 American College of Rheumatology classification criteria (14). The exclusion criteria included (i) presence of acute or chronic infections, cancer, or other rheumatic autoimmune diseases; and (ii) the lack of common carotid artery involvement. The patients were divided into training (136 patients diagnosed between January 2021 and December 2022) and validation groups (30 patients diagnosed between June 2023 and August 2023).

This study was performed according to the Declaration of Helsinki, and was approved by the Ethics Committees of

Zhongshan Hospital at Fudan University (B2016-168(2)R). Written informed consent was obtained from all participants.

Clinical data

Demographic and past medical data were collected upon registration to the ECTA, while clinical presentations physical examination findings, and serological test results were electronically recorded at each hospital visit. Follow-ups were performed monthly. ESR and CRP levels were tested at each visit using an automatic biochemical analyser. Any development of systemic or ischemic symptoms were noted. Disease activity was assessed using Physician Global Assessment (PGA) (15) as the gold standard. TAK activity was determined based on clinical presentation, elevated ESR, and new lesions on MRA, CTA, and PET-CT examinations. All analyses were performed by 2 experienced rheumatologists who were blinded to all ultrasonographic parameters, with any discrepancies resolved by discussion.

CDUS examination

Common carotid artery ultrasonography as performed at baseline and every 3 months using the Philips Elite device (Philips Medical Systems, Bothell, WA, USA) equipped with a L9-3 linear array probe. The measured parameters included wall thickness, lumen diameter, inter-adventitial diameter, peak systolic velocity (PSV), resistance index (RI), and echogenicity. Echogenicity was assessed in relation to adjacent tissues, and was classified as low, medium, or high (16) . A mechanical index of 0.07 and gain of 70% were maintained for all patients.

Wall thickness was defined as the maximum IMT of the carotid artery. The inter-adventitial diameter was defined as the vertical distance between the near and far wall adventitia interfaces.

Our proposed ultrasonographic activity score (ULTRAS) consists of the grading of wall thickness score (TS) and echogenicity score (ES). For TS, the maximum wall thickness of the cohort was arbitrarily classified into the 20th, 40th, 60th, and 80th percentile (17) (Supplementary Table S1). Each side of the carotid arteries was then provided a score of 0–4 accordingly to allow for a maximum score of 8. For ES, each branch of the common carotid arteries was provided a score of 0–2 (Fig. 1) to obtain a maximum score of 4. The ULTRAS of each patient may thereby range between 0–12 (Suppl. Table S2). Both parameters were systematically analysed by 2 experienced ultrasonographers with >10 years of experience who were blinded to both clinical and laboratory data.

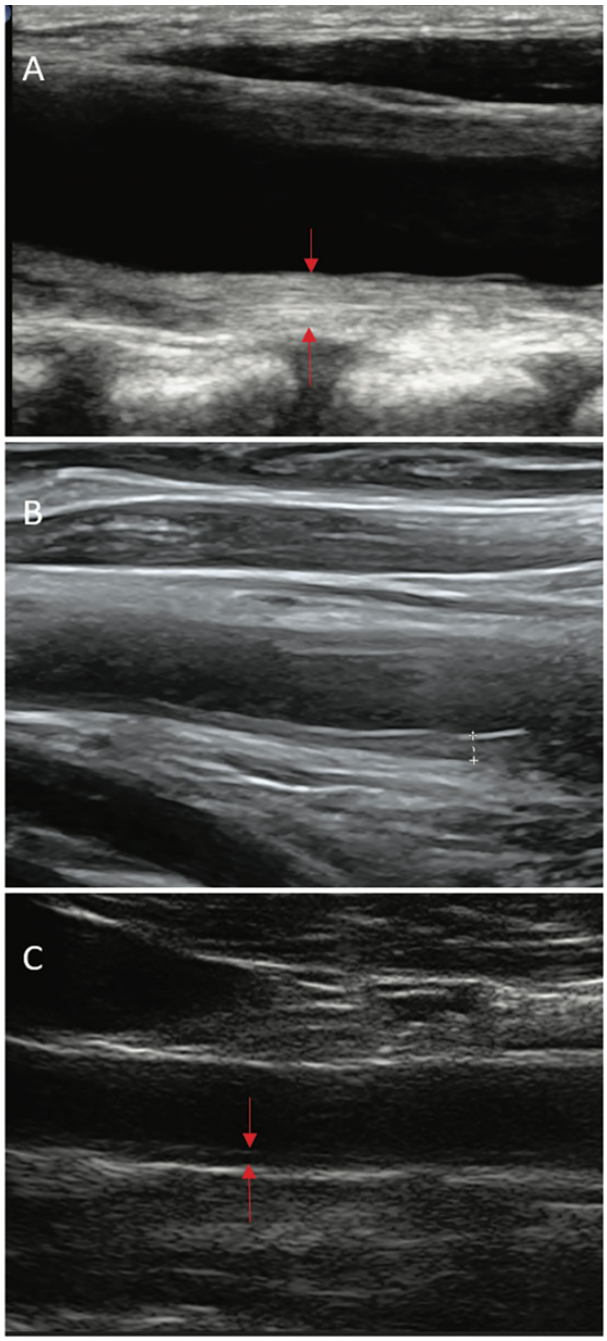

Fig. 1. Representative ultrasonographic images of the echogenicity grading scale.
A: Grade 0, high echogenicity.
B: Grade 1, medium echogenicity.
C: Grade 2, low echogenicity.

Statistical analysis

All statistical analyses were performed using the SPSS software (v. 22, IBM, Chicago, Illinois, USA). Continuous variables were expressed as mean ± standard deviation (SD) for normally distributed data, and as median (quantile 1, quantile 3) for non-normally distributed data. Comparisons were made using the Student's t-test or Wilcoxon rank-sum test. Categorical variables were expressed as number and percentage, and were compared using the Chi-square test. Reliability of the TS and ES scores

was tested in 100 common carotid arteries images from 50 patients. Interclass correlation coefficient (ICC) was used to evaluate inter-observer consistency. Association of ultrasonographic parameters with disease activity and clinical symptoms were assessed using the logistic regression model in terms of odds ratios (ORs) and 95% confidence intervals (CIs). Diagnostic performance of the ultrasonographic parameters for disease activity was assessed in terms of area under the receiver operating characteristic curve (AUC). The extent of improvement of ultrasonographic parameters for symptom recovery was assessed at the 3-month follow-up. Statistical significance was defined as two-sided p-value <0.05.

Results

Patient characteristics

A total of 136 TAK patients and 272 common carotid arteries were included in this study. The mean age was 32.72±11.28 years, and the female-to-male ratio was 10.3:1. The mean disease duration was 24 (6–60) months. The common clinical presentations were neck pain (19.6%) and dizziness/headache (16.9%). The median ESR and CRP levels were 31(10–63) mm/h and 7.5 (1.4–32.2) mg/L respectively. According to the 1996 Numano classification (18), type I, IIa, IIb, and V diseases were observed in 54 (39.7%), 11 (8.1%), 15 (11.0), and 56 (41.2%) patients, respectively.

Based on PGA, active and inactive disease were identified in 83 (61.0%) and 53 (39.0%) patients, respectively. No significant difference in sex (p=0.57) or clinical symptoms of amaurosis or syncope (p=0.08), and cerebral infarction (p=0.38) were observed between the groups. Patients with active disease were significantly younger (30.83±10.37 *vs*. 35.04±11.38 years, p=0.03), and presented with significantly higher rates of fatigue (13.3% *vs*. 1.9%, p=0.02), fever (12.0% *vs*. 0, p=0.01), dizziness or headache (25.3% *vs*. 3.8%, p<0.01), neck pain (31.3% *vs*. 1.9%, p<0.01), and visual impairment (12% *vs*. 0, p=0.01). All demographic and clinical data of the included patients were presented in Table I.

Table I. Demographic and clinical characteristics of TAK patients.

	Total patients n=136	Active n=83	Inactive n=53	p-value
n Age (year), mean ± SD	32.72 ± 11.28	30.83 ± 10.37	35.04 ± 11.38	0.03
Female n(%)	124 (91.2)	77 (92.8)	47 (88.7)	0.57
Disease duration (months), median (q1-q3)	24 (6–60)	12 (4–48)	48 (20–117)	<0.01
Newly diagnosed n (%)	60 (44.1)	50 (60.2)	10 (18.9)	<0.01
Hypertension, n (%)	30 (22.1)	11 (13.3)	19 (35.8)	<0.01
Diabetes, n (%)	1 (0.7)	0	1 (1.9)	0.40
Clinical symptoms n (%)				
Fatigue	12 (8.8)	11 (13.3)	1 (1.9)	0.02
Fever	10 (7.4)	10 (12.0)	0	0.01
Dizziness/headache	23 (16.9)	21 (25.3)	2 (3.8)	<0.01
Neck pain	27 (19.9)	26 (31.3)	1 (1.9)	<0.01
Visual impairment	10 (7.4)	10 (12.0)	0	0.01
Amaurosis/syncope	9 (6.6)	8 (9.6)	1 (1.9)	0.08
Cerebral infarction	2 (1.5)	2 (2.4)	0	0.38
ESR (mm/h), median(q1–q3)	31 (10-63)	50(21-84)	11 (6-31)	<0.01
CRP (mg/L), median(q1–q3)	7.5 (1.4-32.2)	18.4 (4.1-68.1)	2.2 (0.6-7.5)	<0.01
Ultrasonographic features	Total CCAs n=258	Active n=162	Inactive n=96	
Wall thickness (mm), mean ± SD	1.95 ± 0.70	2.16 ± 0.74	1.62 ± 0.44	<0.01
Lumen diameter (mm), mean ± SD	4.01 ± 2.41	4.25 ± 2.36	3.56 ± 2.44	0.03
Inter-adventitial diameter (mm), mean ± SD	8.33 ± 2.52	8.90 ± 2.47	7.37 ± 2.35	<0.01
Peak flow rate (m/s), mean ± SD	1.13 ± 0.75	1.17 ± 0.69	1.08 ± 0.83	0.37
RI, mean ± SD	1.08 ± 0.72	1.15 ± 0.76	0.96 ± 0.63	0.04
Vascular stenosis, n (%)	145 (56.2)	84 (51.9)	61 (63.5)	0.11
Vascular occlusion, n (%)	32 (12.4)	13 (8.0)	19 (19.8)	0.01
Low echogenicity, n (%)	106 (41.1)	89 (54.9)	17 (17.7)	<0.01
Ultrasound-based score, median (q1–q3)				
ES	2 (2–4)	4 (2–4)	2 (0–2)	<0.01
TS	4 (2–5)	5 (3–6)	2 (1–3)	<0.01
ULTRAS	6 (3–8)	8 (6–10)	3 (2–5)	<0.01

TAK: Takayasu's arteritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CCA: common carotid artery; RI: resistance index; ES: echo score; TS: thickness score; ULTRAS: ultrasonographic activity score.

The baseline prednisone doses were 0.8–1 mg/kg/day and 0.1–0.2 mg/kg/day in patients with active and inactive TAK, respectively. Immunosuppressors administered included leflunomide (LEF, 20 mg/day, p.o.; n=79), cyclophosphamide (CYC, 0.5–0.75 g/m^2 i.v. every 4 weeks up to a cumulative dose of 6–7 g during induction treatment; n=9), methotrexate (MTX, 10–15 mg/week, p.o.; n=16), mycophenolate mofetil (MMF, 30 mg/kg/day, p.o.; n=5), azathioprine (AZA, 1–1.5 mg/kg/day, p.o.; n=8), and tocilizumab (8 mg/kg/m^2, i.v. every 4 weeks; n=10). A total of 9 inactive disease patients did not receive pharmacological treatment.

Among the 136 patients enrolled, 60 (44.1%) were newly diagnosed at baseline. Of the remaining 76 patients, 73 (96.1%) received glucocorticoid therapy. In terms of immunosuppressor therapy, 45, 5, 11, 4, 5, and 3 patients received LEF, CYC, MTX, MMF, AZA, and tocilizumab respectively. Three inactive patients did not receive treatment.

Carotid ultrasonographic features

Unilateral and bilateral CCA lesions were observed in 14 (10.3%) and 122 (89.7%) patients, respectively. Among the 258 arteries involved, 145 (56.2%) and 32 (12.4%) showed stenosis and occlusion, respectively. The average wall

Table II. Association between carotid ultrasonographic parameters and disease activity on logistic regression.

	Unadjusted model	*p* value	Model 1	*p* value
Wall thickness	4.9 (2.7, 8.9)	<0.01	3.65 (1.85, 7.20)	<0.01
Lumen diameter	1.10 (0.99, 1.23)	0.09	1.07 (0.93, 1.23)	0.36
Inter-adventitial diameter	1.29 (1.13, 1.47)	<0.01	1.25 (1.06, 1.49)	<0.01
RI	1.49 (0.98, 2.26)	0.07	1.37 (0.77, 2.46)	0.28
Vascular occlusion	0.38 (0.18, 0.81)	0.01	0.54 (0.19, 1.57)	0.26
Low echogenicity	6.97 (3.83, 12.71)	<0.01	2.49 (1.15, 5.38)	0.02

RI: resistance index.
Model 1: adjusted for age, disease duration, neck pain, visual impairment, dizziness/headache, ESR, and CRP.

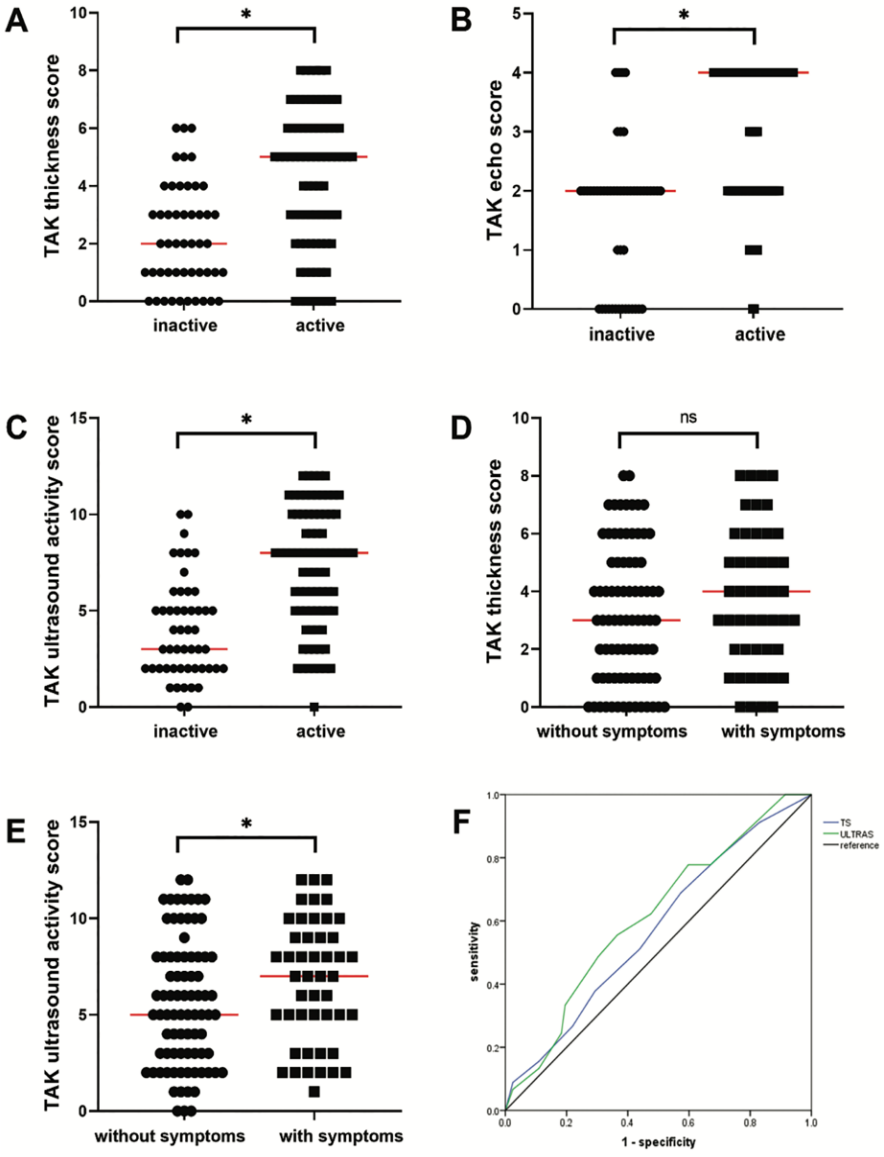

Fig. 2. Diagnostic accuracy of our proposed ultrasonography-based activity score for active and symptomatic disease.
A: Baseline thickness score (TS) of active *versus* inactive disease. **B**: Baseline echo score (ES) of active *versus* inactive disease. **C.** Baseline ultrasonographic activity score (ULTRAS) of active *versus* inactive disease. **D**: Baseline TS of symptomatic (n=46) *versus* asymptomatic disease (n=90). **E**: Baseline ULTRAS of symptomatic (n=46) *versus* asymptomatic disease (n=90). **F**: ROC curve showing the diagnostic accuracy of TS and ULTRAS for asymptomatic TAK.

thickness was 1.95±0.70 mm (Table I). Active disease patients demonstrated significantly higher wall thickness (2.16±0.74 *vs*. 1.62±0.44 mm, $p<0.01$), lumen diameter (4.25±2.36 *vs*. 3.56±2.44 mm, $p=0.03$), inter-adventitial diameter (8.90±2.47 *vs*. 7.37±2.35 mm, $p<0.01$), and proportion of low echogenicity (54.9% *vs*. 17.7%, $p<0.01$). In contrast, inactive disease patients showed significantly higher proportion of luminal occlusion (19.8% *vs*. 8.0%, $p=0.01$).

Correlation of carotid ultrasonographic parameters with disease activity at baseline

Univariate analysis showed that active disease significantly associated with increased wall thickness (OR=4.9, 95%CI 2.7–8.9, $p<0.01$), inter-adventitial diameter (OR=1.29, 95%CI 1.13–1.47, $p<0.01$), and low echogenicity (OR=6.97, 95%CI 3.83–12.71, $p<0.01$). Such associations remained significant after adjusting for age, disease duration, neck pain, visual impairment, dizziness or headache, ESR, and CRP (Table II). In the scatter plot, ESR, wall thickness, and low echogenicity were observed to be significantly higher in active disease patients (Suppl. Fig. S1).

Ultrasonographic activity score and diagnostic accuracy

A median ES and TS of 2 (2-4) and 4 (2-5) were calculated, respectively, obtaining a median ULTRAS of 6 (3-8). The interobserver agreement for ES (κ=0.80) and TS (κ=0.89) were both strong. Active TAK showed significantly higher scores in both parameters (Table I, Fig. 2A-C). In the correlation analysis, ESR significantly associated with wall thickness (r=0.23, $p<0.01$), ES (r=0.38, $p<0.01$), TS (r=0.29, $p<0.01$), and ULTRAS (r=0.34, $p<0.01$) (Suppl. Table S3).
ULTRAS showed better diagnostic accuracy for active TAK compared to TS, with AUCs of 0.88 (95% CI, 82–94) and 0.80 (95% CI, 72–87) observed, respectively (Table III, Suppl. Fig. S2 A). At an optimal cut-off point of 7, the sensitivity and specificity of ULTRAS were 73% (95% CI, 62-82) and 94% (95% CI, 83-98), respectively.

Table III. Predictive performance of parameters.

	SE	SP	PPV	NPV	+LR	-LR	Accuracy (%)
ESR (>30)	71 (59–80)	76 (62–86)	86 (70–90)	63 (50–74)	2.94 (1.79–4.81)	0.39 (0.2–0.55)	73
CRP (>6.3)	72 (61–81)	70 (56–82)	79 (67–87)	62 (49–74)	2.43 (1.58–3.74)	0.40 (0.28–0.57)	71
Systemic symptoms	23 (15–34)	96 (86–99)	90 (68–98)	45 (36–55)	6.26 (1.52–25.78)	0.80 (0.70–0.90)	52
Ischaemic symptom	57 (46–68)	94 (84–99)	94 (82–98)	59 (48–70)	10.32 (3.38–31.48)	0.45 (0.35–0.58)	72
Wall thickness (>1.75)	65 (56–72)	74 (64–83)	81 (73–87)	56 (46–64)	2.49 (1.72–3.62)	0.48 (0.38–0.60)	68
Inter-adventitial diameter (>7.85)	64 (55–71)	60 (48–70)	73 (64–80)	49 (39–59)	1.58 (1.18–2.11)	0.61 (0.48–0.77)	62
Low echogenicity	61 (50–71)	83 (70–92)	85 (73–92)	58 (47–69)	5.55 (3.01–10.24)	0.71 (0.54–0.94)	70
TS (4)	71 (5–80)	78 (64–88)	83 (72–90)	64 (51–75)	3.18 (1.90–5.34)	0.38 (0.27–0.53)	74
ULTRAS (7)	73 (62–82)	94 (83–98)	95 (86–99)	69 (57–79)	12.68 (4.20–38.34)	0.28 (0.20–0.41)	82
ESR plus TS	88 (80–95)	57 (43–70)	76 (66–84)	78 (61–89)	2.09 (1.52–2.88)	0.19 (0.10–0.37)	76
ESR plus ULTRAS	89 (80–95)	74 (60–85)	84 (74–91)	82 (67–91)	3.43 (2.17–5.42)	0.15 (0.08–0.28)	83
CRP plus TS	88 (80-70)	54 (40-69)	76 (66-84)	76 (58-88)	1.97 (1.44-2.70)	0.20 (0.10-0.38)	75
CRP plus ULTRAS	89 (81-95)	66 (52-79)	81 (71-88)	81 (65-91)	2.70 (1.82-4.02)	0.14 (0.07-0.29)	81

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TS: thickness score; ULTRAS: ultrasonographic activity score; SE: sensitivity; SP: specificity; PPV: positive predictive value; and NPV: negative predictive value; LR: likelihood ratio.
SE, SP, PPV, NPV and LR were presented as percentage and 95% confidence intervals, while accuracy is presented as percentage only.

Table IV. Follow-up ultrasonographic parameters.

	Total patients n=136	Active n=83	Inactive n=53	*p*-value	Symptomatic n=56	Asymptomatic n=80	*p*-value
Improvement rate, n(%)							
At 3 months		69 (83.1%)	–	–	53 (94.6%)	–	–
At 6 months		79 (95.2%)	–	–	53 (94.6%)	–	–
		n=79	n=53		n=53	n=80	
Wall thickness (mm), mean (SD)							
Baseline	1.95 (0.70)	2.08 (0.83)	1.62 (0.44)	<0.01	1.88 (0.86)	1.78 (0.72)	0.34
At 3 months	1.69 (0.54)*	1.70 (0.59)**	1.62 (0.42)	0.46	1.66 (0.58)	1.69 (0.51)	0.74
At 6 months	1.74 (0.71)	1.72 (0.72)*	1.63 (0.34)	0.49	1.61 (0.58)	1.76 (0.66)	0.33
TS, median (q1–q3)							
Baseline	4 (2–5)	5 (3–6)	2 (1–3)	<0.01	4 (2–6)	3 (1–5)	0.04
At 3 months	2 (1–4)**	3 (1–5) **	2 (1–3)	<0.01	2 (1–4) **	2 (1–4)	0.40
At 6 months	2 (1–4)**	3 (1–4) **	2 (1–3)	0.01	2 (1–4) **	2 (1–4)	0.56
ES, median (q1–q3)							
Baseline	2 (2–4)	4 (2–4)	2 (0–2)	<0.01	4 (2–4)	2 (2–4)	<0.01
At 3 months	2 (1–2)	2 (2–2) **	2 (1–2)	0.04	2 (2–2) **	2 (1–2)	0.18
At 6 months	2 (1–2)	2 (1–2) **	2 (1–2)	0.06	2 (1–2) **	2 (1–2)	0.33
ULTRAS, median (q1–q3)							
Baseline	6 (3–8)	8 (6–10)	3 (2–5)	<0.01	8 (5–9)	5 (2–8)	<0.01
At 3 months	4 (2–6)**	5 (3–7) **	3 (2–4)	<0.01	4 (3–7) **	4 (2–6)	0.28
At 6 months	4 (2–6)**	4 (2–7) **	4 (2–4)	<0.01	4 (2–6) **	4 (2–6)	0.47

TS: thickness score; ES: echo score; ULTRAS: ultrasonographic activity score.
*p<0.05 compared with baseline; **p<0.01 compared with baseline.

Improved diagnostic accuracy was achieved with combined ULTRAS and ESR, and combined ULTRAS and CRP, with AUCs of 0.91 (95% CI, 86-96) and 0.90 (95% CI, 86-95), respectively, and a sensitivity of 89% for both. However, the diagnostic performance of ULTRAS in symptomatic patients was poor, with AUC of 0.67 (Fig. 2 D-F).

In the verification group, the female to male ratio was 5:1, with active disease observed in 14 (46.7%) patients. The clinical characteristics and ultrasound-based scores were shown in Supplementary Table S4. With an ULTRAS of 7, the sensitivity and specificity for diagnosing active disease were 79% (95% CI, 49–94) and 94% (95% CI, 68–99), respectively, and the AUC was 0.88. Combined ESR and ULTRAS achieved an increased diagnostic sensitivity and specificity of 93% (95% CI, 64–99) and 81% (95% CI, 54–95), respectively. Combined CRP and ULTRAS demonstrated a sensitivity, specificity, and AUC of 91% (95% CI, 63-98), 87% (95% CI,60-98), and 0.92, respectively (Suppl. Fig. S2 B).

Wall thickness for the prediction of TAK remission and symptom recovery

The results of wall thickness and ultrasound-based scores during follow-up were shown in Table IV. Among the 83 patients with active disease at baseline, 69 (83.1%) demonstrated improvement in clinical symptoms and serology at 3-month follow-up, while 79 (95.2%) showed disease inactivity at 6-month follow-up. Of the 4 patients with active disease at 6 months, 3 associated with persistently elevated acute phase reac-

tants with amaurosis, and 1 with raised ESR and new vascular lesion on MRA. Among the 56 (41.2%) patients with clinical symptoms at baseline (systemic, n=21; and ischaemic, n=40), 53 (94.6%) demonstrated remission of clinical symptoms at 3-month follow-up. Three patients had symptoms of amaurosis, which remained at 6 months. Compared to baseline, patients with disease remission or symptom recovery showed significant improvement in TS, ES, and ULTRAS during follow-up (Table IV). To evaluate the relationship between wall thickness and clinical symptoms, we calculated the extent of wall thickness reduction among patients with disease remission and symptom recovery during follow-up. At 3 months, a reduction of 0.40 (0.06) mm and 0.41 (0.09) mm from baseline were observed in patients with disease remission and symptom recovery, respectively (Suppl. Table S5). Among cases of ≥1.0 mm reduction in wall thickness, 10.7% achieved symptom recovery at 3 months; while >0.7 mm and >0.3 mm reduction associated with 25% and 50% rate of symptom recovery, respectively.

Discussion

Ultrasonography is a reliable non-invasive imaging modality for the characterisation of vessel wall inflammation in TAK patients. This study assessed the feasibility of our proposed scoring system, ULTRAS, which utilises carotid wall thickness and echogenicity for the discrimination of disease activity among a Chinese cohort with TAK. Our study further assessed the association between improvements in carotid artery wall thickness and the remission of clinical symptom within a 6-month follow-up period.

Hypoechogenicity as an indication of vascular wall oedema was first described by Schmidt *et al*. in the study on temporal arteritis patients (19). Meanwhile, extensive hyperechoic streaks reflect the presence of fibrosis (20, 21). However, there still remains a lack of research on vessel wall echogenicity, possibly owing to the heterogeneity in machine resolution, parameter setting, and imaging assessment. Hypoechogenicity was found to associate with significantly higher rates of active disease (54.9%) compared to inactive disease (17.7%) at baseline in our study. However, a diagnostic sensitivity of only 60% was shown, implying that it is limited as an independent indicator of disease activity. Instead, the integration of echogenicity with wall thickness was found to achieve favourable diagnostic accuracy. In this study, echogenicity was graded as a joint parameter and analysed together with carotid artery wall thickness.

Carotid artery wall thickness has been well-recognised as an indicator for disease monitoring in TAK. In the study by Barra *et al*. on the assessment of IMT of the carotid arteries, a cut-off value of 1 mm demonstrated significant diagnostic accuracy for inflammatory vascular diseases (22). Thereafter, a wall thickness range of 1.9–2.9 mm have been shown in active diseases (10, 13, 23). Our previous studies not only confirmed that carotid artery wall thickness associated with TAK activity, but also demonstrated that it can vary with disease remission and recurrence(12, 24). In this study, the maximum wall thickness was graded.

Different from the model by Svensson *et al*. (10), our approach involves the grading of wall thickness and echogenicity for each carotid artery separately. The combined score, ULTRAS, demonstrated satisfactory diagnostic performance for active TAK, with an AUC of 0.88 (95%CI, 82-94) and an optimal cut-off of 7. The diagnostic specificity was 73%, which increased to 89% when combined with ESR or CRP. The combination of ULTRAS with either CRP or ESR achieved similar diagnostic efficacy in our study. The potential reason for this may be our exclusion of patients with acute and chronic infections at enrolment. Our ultrasound-based score is thereby easy to implement, and may enable the rapid evaluation of vascular inflammation in primary care settings.

Poorer diagnostic efficacy was observed among symptomatic patients. In the current study, ULTRAS was developed to facilitate with the identification of active diseases, which was not only based on clinical symptoms. There were 56 symptomatic patients at baseline, among whom, 51 (91.1%) were classified as active based on PGA. The remaining 5 patients (8.9%) were evaluated as inactive disease according to PGA, and had been diagnosed and treated prior to enrolment, and were thereby demonstrating persistent or improved symptoms during our study. In addition, of the 80 asymptomatic patients at baseline, 31 (38.8%) were evaluated as active disease according to their elevated ESR and imaging findings. Therefore, this might diminish the diagnostic efficacy of ULTRAS in symptomatic patients.

We further analysed the relationship between improvement of carotid artery wall thickness and patient outcomes. After regular treatment, a reduction in wall thickness from 2.08 mm to 1.70 mm and 1.71 mm were observed in patients with disease remission at 3 and 6 months, respectively. Interestingly, an average improvement of 0.4 mm associated with both disease remission and clinical symptom recovery at the 3-month follow-up. The rate of improvement in vessel wall thickness was significant in the first 3 months, and tapered 3 months thereafter. We also found that a wall thickness reduction of 0.3 mm correlated with a 50% rate of symptom recovery at 3-month follow-up. Such decrease in wall thickness may reflect a subsidence in oedema of the arterial walls, rendering it conducive for the recovery of organ blood supply. Altogether, our results suggest that early treatment of TAK patients may significantly reduce vessel wall oedema and wall thickness within 3 months, allowing for recovery of ischemia symptoms, and ultimately control disease activity.

There were several limitations in our study. First, only the carotid arteries were assessed; as such, the clinical application of ultrasonographic features of other involved vessels, including the vertebral and subclavian arteries, require further validation. Second, this was a single-centre study. While internal validation of our scoring system was performed, external validation remains warranted. Cooperation with other centres for conduction of a multi-

centre study should thus be considered. Third, the follow-up period was relatively short. Further validation of our proposed ultrasound-based score with long-term studies is thereby warranted.

Conclusion

Our proposed ultrasound-based score, ULTRAS, may play a role as a non-invasive imaging modality for the evaluation of disease activity in TAK patients. The optimal cut-off point of 7 showed satisfactory diagnostic accuracy.

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