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ORIGINAL RESEARCH

Definitions of elementary ultrasound lesions in Takayasu arteritis: a study from the OMERACT Ultrasound Working Group

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ABSTRACT

Objective To systematically assess the evidence on the use of ultrasonography (US) for the detection of vascular inflammation in Takayasu arteritis (TAK), with a focus on evaluating existing scoring systems and identifying elementary sonographic lesions for diagnosis, disease monitoring and outcome prediction.

Methods A systematic literature review (SLR) was conducted using PubMed, EMBASE, the Cochrane Library and Epistemonikos from their inception until 15 March 2024. Only original research articles evaluating the diagnostic accuracy, outcome prediction or monitoring ability of US in TAK, with a minimum sample size of 15 patients, were included. Data extraction was performed independently by two reviewers. Study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 tool for diagnostic studies and the Quality In Prognosis Studies tool for prognostic studies.

Results 21 studies met the inclusion criteria. Three of them proposed a US scoring system for TAK, while the remainder focused on reporting elementary lesions. The common findings included increased intima-media thickness (IMT), stenosis, occlusion, aneurysm and increased contrast enhancement. All studies evaluated the common carotid arteries, with less frequent assessment of other vascular territories such as the subclavian and common femoral arteries and the abdominal aorta. Although increased IMT and contrast enhancement of the arterial wall correlated with clinical measures of disease activity, heterogeneity of lesion definitions and measurement thresholds, along with small sample sizes and moderate-to-high risk of bias, limits the generalisability of the findings.

Conclusions This SLR highlights the current lack of a fully validated US scoring system for TAK and underscores the need for standardised definitions of elementary sonographic lesions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Ultrasonography (US) is a valuable imaging tool for detecting vascular inflammation in large vessel vasculitis, including Takayasu arteritis (TAK).
⇒ While standardised US definitions and scoring systems exist for giant cell arteritis, no fully validated US scoring system is currently available for TAK.
⇒ The role of US in diagnosing, monitoring and predicting outcomes in TAK remains incompletely defined.

WHAT THIS STUDY ADDS

⇒ This systematic literature review (SLR) identifies key elementary US lesions in TAK, including intima-media thickness thickening, stenosis, occlusion and aneurysm formation.
⇒ The SLR highlights the heterogeneity in lesion definitions and measurement thresholds and underscores the lack of a consensus-based US scoring system for TAK.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings emphasise the need for standardised US definitions and a validated scoring system to enhance the reliability of US in TAK assessment. This could improve disease monitoring, guide treatment decisions and facilitate the use of US in clinical trials.
⇒ Future research should focus on consensus-building through Delphi exercises and the validation of comprehensive US scoring systems in large, prospective cohorts to improve diagnostic accuracy, disease monitoring and outcome prediction in TAK.

INTRODUCTION

Takayasu arteritis (TAK) is a rare but severe inflammatory form of large-vessel vasculitis (LVV) that primarily affects the aorta and its major branches.[1] It predominantly occurs in young women and can lead to serious complications, including arterial stenosis and aneurysms.[2]

Imaging plays a pivotal role in diagnosing TAK, as highlighted by the latest European

Alliance of Associations for Rheumatology (EULAR) recommendations.[3] For the diagnosis of TAK, magnetic resonance angiography (MRA) is recommended as the first-line imaging modality, while CT angiography (CTA), 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) and ultrasonography (US) are considered viable alternatives. In contrast, disease follow-up should primarily rely on clinical evaluation and acute-phase reactant assessment, with imaging reserved for selected cases.[3] With the expansion of drug trials and the development of targeted therapies, the need for a standardised imaging modality for routine disease monitoring has become increasingly critical.[4 5] However, the use of MRA, CTA and FDG-PET in follow-up is constrained by limited resources, long waiting times, and in the case of CTA and FDG-PET, radiation exposure.[6] US presents a practical option for regular use in clinical practice, yet a validated composite scoring system is necessary to ensure consistency and comparability across individuals and studies.

Outcome Measures in Rheumatology (OMERACT) is a global, non-profit organisation dedicated to developing and improving outcomes for patients with rheumatic and musculoskeletal diseases in clinical trials. A subgroup of the OMERACT Ultrasound Working Group, which focuses on ultrasound (US) outcome measures for LVV and polymyalgia rheumatica, has already established US definitions and a scoring system for giant cell arteritis (GCA)[7] and has embarked on a similar process for TAK. Although TAK and GCA share certain features, such as large-vessel involvement, they differ significantly in patient demographics, disease onset, vascular involvement patterns and possible disease complications.[8 9] Indeed, TAK tends to have a more insidious onset, a lower risk of acute ophthalmological complications, but a higher likelihood of long-term vascular damage.[1 2] Consequently, diagnostic and monitoring models developed for GCA may not be directly applicable to TAK.[3] Despite its limitations in assessing certain vascular territories, US offers advantages such as lower resource demands, absence of radiation and relatively low cost, making it a promising tool for clinical trials.[10]

The OMERACT Filter Instrument Selection Algorithm[11] foresees a systematic literature review (SLR) to identify existing definitions for elementary lesions and/or scoring systems. Our objectives were to evaluate whether there are available US scoring systems for diagnosis, monitoring and outcome assessment, to identify elementary US lesions tested in TAK-related studies, and to determine which arteries have been examined using US in TAK patients.

METHODS

Search strategy

Details on key questions, search strategy, data synthesis and quality assessment are reported in the online supplemental materials. In brief, a data specialist (LF) developed and performed the search in PubMed, EMBASE, Cochrane Library and Epistemonikos databases using Medical Subject Headings terms, full-text search and truncated words from the inception dates (1946, 1974, 1993 and 2009, respectively) up to 15 March 2024 (see online supplemental file for the complete search strategy). Sensitivity of the search strategy was confirmed by testing for 10 key publications proposed by the steering committee. Two authors (AT, VC) independently evaluated the titles, abstracts and full reports of identified records for compliance with the inclusion and exclusion criteria, using the online research collaboration platform Rayyan.[12] The following inclusion criteria were applied: (1) original research articles reporting on prospective, retrospective or cross-sectional studies on the diagnostic accuracy, outcome prediction and utility of US for detecting activity/relapse in TAK using an appropriate reference standard (ie, clinical diagnosis, published criteria); (2) written in English, German or Italian; (3) studies in which the population consisted of patients with TAK or suspected TAK regardless of age at onset. Studies were excluded if they featured less than 15 patients with TAK/suspected TAK. Letters, editorials and review articles without original data were excluded. Additionally, in order to identify any relevant studies that may not have been captured by the initial search, the reference lists of previously published SLRs focusing on the use of imaging in TAK and conference abstracts from major rheumatology conferences (ie, EULAR Congress and American College of Rheumatology Convergence) published within the last 3 years were reviewed.

Data extraction

A standardised template was developed and used to extract data from selected articles. The data were extracted independently by two authors (AT, VC). The data pertained to the study population, number of included patients, vessels assessed, scoring system and main findings regarding the study question.

At all stages of the SLR, any disagreements were resolved through discussion. If consensus was not reached, one of the coauthors (CD) served as a tiebreaker.

Assessment of quality

To assess the studies on diagnostic accuracy, the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool was employed.[13] This comprises four domains: patient selection, index test, reference standard, as well as flow and timing. In order to assess the quality of prognostic studies, the Quality In Prognosis Studies (QUIPS) tool was used.[14] This tool evaluates the following aspects: study participation and attrition, prognostic factor measurement, outcome measurement, study confounding, as well as statistical analysis/reporting (see online supplemental materials). In addition, we systematically evaluated whether the scores reported in the included studies were assessed for their psychometric properties in accordance with the OFISA guidelines.[11] The quality

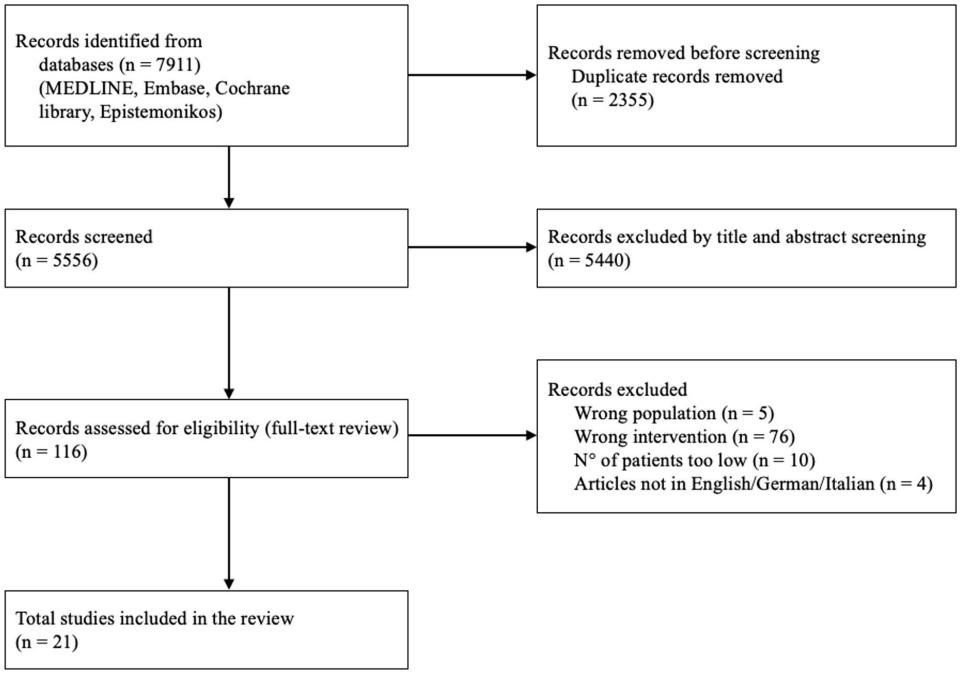

Figure 1 Flowchart of the systematic literature review with results of the selection process.

of the studies was assessed independently by two authors (AT, VC).

RESULTS

The primary search identified 5556 articles. After applying inclusion and exclusion criteria and excluding duplicates, 21 studies were finally included in the review (see figure 1 for flow chart).[15–35] Among the 21 studies, three (14%) focused on developing a US score for TAK[19 21 30]; the remaining studies (86%) only reported elementary lesions.

Assessed sites

All studies evaluated bilateral common carotid arteries (21/21, 100%). Other evaluated vascular territories included the bilateral subclavian arteries (9/21, 43%),[15 16 19 23 26 30–33] abdominal aorta (3/21, 14%),[15 16 30] bilateral vertebral arteries (3/21, 14%),[26 31 33] bilateral common femoral arteries (3/21, 14%),[16 23 30] bilateral axillary arteries (2/21, 10%).[19 32] The brachiocephalic trunk,[19] bilateral renal,[30] bilateral brachial,[30] bilateral radial,[30] bilateral popliteal,[30] bilateral posterior tibial[30] and bilateral dorsalis pedis[30] arteries were evaluated in only 1/21 study each (5%).

Key objectives of studies

The overwhelming majority of studies had a single key objective and only a single study[17] had two. Eight out of 21 studies (38%) focused on the diagnostic accuracy of US in TAK (main study characteristics, detailed results including risk of bias and definitions of US key elementary lesions are summarised in table 1 and online supplemental table S2),[15 16 23–27 33] 2/21 (10%) investigated the value of US for the prediction of outcomes in TAK (table 2 and online supplemental table S4)[17 21] and 12/21 (57%) reported the role of US for monitoring disease activity (table 3 and online supplemental table S6).[17–20 22 28–32 34 35]

Elementary ultrasound lesions

Most studies (18/21, 86%) reported an increase in the IMT as an elementary lesion of vasculitis.[16–21 23–34] Only two studies referred to this lesion as 'macaroni sign'[24 31] (online supplemental tables S2, S4, S6). Four studies provided a threshold for defining increased IMT as pathological: two and one of them defined the cut-off for the upper limit of normal as 1.1 mm[23 24] and 0.9 mm,[27] respectively, while another study set the mean IMT+2 SD of the control group as the upper limit of normal for each artery.[16] The remaining studies failed to provide a threshold. In addition to IMT, two studies (10%) described qualitative aspects of arterial wall echostructure. Specifically, they reported hypoechogenic wall thickening in active disease and medium-to-high echogenicity in chronic phases.[19 33]

Other elementary lesions reported (mostly in combination with an increase in IMT) were stenosis (15/21, 71%),[15 17–21 23 25–31 33] occlusion (14/21, 67%)[15 17–20 23–26 28–31 33] and aneurysm/dilatation (6/21, 29%).[16 23 24 29–31] In addition, 2/21 studies (10%) investigated the presence of vessel wall calcifications but did not include this finding among the elementary lesions of TAK.[16 27] Two studies also reported more broadly on atherosclerosis in TAK. One study differentiated between diffuse wall thickening characteristic of TAK and localised atherosclerotic plaques observed in control subjects,[24] while the second found an increased prevalence of carotid plaques in patients with TAK as compared with healthy controls.[27]

Table 1 Summary of main characteristics and overall risk of bias of diagnostic studies on ultrasound in Takayasu arteritis (TAK)

Study	Patients (n) Female (n) (%)	Study design	Inclusion criteria	Reference standard	Investigated structures	US elementary lesions	Overall risk of bias
Lefebvre *et al*[23]	43 41 (95)	Cross-sectional	Clinical diagnosis of TAK*	1990 ACR criteria	Carotid, subclavian, femoral	Stenosis, occlusion, aneurysm, ↑ IMT	Moderate
Raninen *et al*[16]	16 14 (88)	Cross-sectional	Clinical diagnosis of TAK†	Angiography	Carotid, subclavian, femoral, abdominal aorta	Aneurysm, dilatation, ↑ IMT, wall calcification	High
Sun et al[33]	*16* *16 (100)*	*Retrospective cohort*	*Clinical diagnosis of TAK‡*	*Ishikawa's criteria*	*Carotid, subclavian, vertebral*	*Stenosis, occlusion, ↑ IMT*	High
Maeda *et al*[24]	23 23 (100)	Cross-sectional	Clinical diagnosis of TAK†	Angiography	Carotid	Dilatation, ↑ IMT/macaroni sign, occlusion/ stuffed macaroni sign	High
Taniguchi et al[25]	*22* *20 (91)*	*Retrospective cohort*	*Clinical diagnosis of TAK§*	*Angiography*	*Carotid*	*Stenosis, occlusion, ↑ IMT*	High
Zieliński *et al*[26]	18 15 (83)	Cross-sectional	Clinical diagnosis of TAK†	Clinical evaluation	Carotid, subclavian, vertebral	Stenosis, occlusion, ↑ IMT	High
Ucar *et al*[27]	50 44 (88)	Cross-sectional	Clinical diagnosis of TAK*	1990 ACR criteria	Carotid	Stenosis, dilatation, ↑ IMT, wall calcification	High
Raninen *et al*[15]	15 13 (87)	Cross-sectional	Clinical diagnosis of TAK†	Angiography	Carotid, subclavian, abdominal aorta	Stenosis, occlusion	High

Retrospective and case–control studies are italicised.
*1990 ACR criteria.
†No criteria.
‡Ishikawa's criteria.
§Aortitis Syndrome Research Committee of Japan.
ACR, American College of Rheumatology; IMT, intima-media thickness.

In 11 studies (52%), a definition of stenosis was provided.[15 17–21 23 25 26 29 30] In three of them, only morphological changes (eg, lumen narrowing) were considered,[15 23 25] while in the remaining eight, the definition relied on a combination of morphological findings and haemodynamic alterations.[17–21 26 29 30] Four studies (out of the eight referring to haemodynamic changes)[17 18 20 29] adopted the definition provided by the Society of Radiologists in Ultrasound (SRU)[36] (online supplemental tables S2, S4, S6).

Eight studies (38%) included a definition for occlusion.[15 17 18 20 24 25 29 30] Two of them relied on the absence of any visible colour flow in the lumen,[15 25] one on the presence of a monophasic waveform pattern[30] and one

Table 2 Summary of main characteristics and overall risk of bias of studies for outcome prediction of ultrasound in Takayasu arteritis

Study	Inclusion criteria	Patients (n) With follow-up (n) (%)	Time period follow-up	Investigated structures	US key elementary lesions	Summary of main findings	Overall risk of bias
Ma *et al*[17]	Clinical diagnosis of TAK*	77 77 (100)	12 months	Carotid	Stenosis, occlusion, ↑ IMT, contrast enhancement	Higher IMT at baseline in patients with a progressive disease at 12 months (=more than 20% increase in IMT thickness and lesion range, or aggravations on lumen stenosis or CEUS semi-quantitative analysis)	Moderate
Wang *et al*[21]	Clinical diagnosis of TAK	295 Not specified	Not specified	Carotid	↑ IMT, stenosis, IMT/diameter ratio (IDR)	A higher carotid IDR and a lower carotid PSV were associated with a higher risk of neurological severe ischaemic events	High

*1990 ACR criteria.
ACR, American College of Rheumatology; CEUS, contrast-enhanced ultrasound; IMT, intima-media thickness; PSV, peak systolic velocity; SMI, superb microvascular imaging; SUV, standardised uptake value; TAK, Takayasu arteritis.

Table 3 Summary of main characteristics and overall risk of bias of studies for monitoring disease activity by ultrasound in Takayasu arteritis

Study	Inclusion criteria	Patients (n) With follow-up (n) (%)	Time period follow-up	Investigated structures	US key elementary lesions	Summary of main findings	Overall risk of bias
Ma *et al*[17]	Clinical diagnosis of TAK*	77 77 (100)	12 months	Carotid	Stenosis, occlusion, ↑ IMT, contrast enhancement	Higher IMT in patients with a Kerr/NIH score ≥2. Higher frequency of grade 1 and 2 enhancements in patients with a Kerr/NIH score ≥2; higher frequency of grade 0 enhancement in patients with a Kerr/NIH score <2. Higher frequency of stenosis <50% in patients with a Kerr/NIH score <2	Moderate
Dong *et al*[18]	Clinical diagnosis of TAK*	115 107 (93)	3–6 months	Carotid	Stenosis/occlusion, ↑ IMT, contrast enhancement	Higher IMT and higher external vessel diameter in patients with a Kerr/NIH score ≥2.	Moderate
						Contrast enhancement grade showed a significant correlation with disease activity.	
						Patients with grade 3 enhancement had higher ITAS2010 scores	
Svensson et al[19]	*Clinical diagnosis of TAK (new-onset and chronic)**	*25* *All the 9 patients with new-onset disease*	*1–13 years*	*Carotid, subclavian, axillary, brachiocephalic, aortic arch*	*Stenosis, occlusion, ↑ IMT 'Ultrasound index'*	*IMT of carotids decreased in patients prescribed with medical treatment, while increased in those prescribed with no treatment.*	High
						In seven of the patients (two excluded since they only had axillary stenosis), the ultrasound index significantly decreased between the first and the last evaluation.	
						Five patients had a flare (symptoms and/or elevated inflammatory laboratory levels): they all showed a sudden increase of IMT and/or increase of vessel diameter and/or increase of velocities in stenotic areas	
Wang *et al*[20]	Clinical diagnosis of TAK†	28 No follow-up (cross-sectional)	No follow-up (cross-sectional)	Carotid	Stenosis, occlusion, ↑ IMT, contrast enhancement	Higher frequency of grade 2 and 3 wall enhancements in patients with a Kerr/NIH score ≥2.	Moderate
						Contrast enhancement grades positively correlated with disease activity, wall thickness and ESR	
Li et al[22]	*Clinical diagnosis of TAK**	*71* *No follow-up (cross-sectional)*	*No follow-up (cross-sectional)*	*Carotid*	*Contrast enhancement*	*Higher frequency of grade ≥2 wall enhancements in patients with active disease according to the ITAS2010 criteria.*	High
						The sum score of two-sided carotid arteries was higher in patients with clinically active disease.	
						Total vascularisation score significantly associated with scores on Kerr/NIH criteria and ITAS2010.	
						Total vascularisation score significantly associated with levels of CRP and ESR.	
						When visual grade ≥2 on FDG-PET/CT was used as the standard for active vasculitis, US had 100% sensitivity and 80% specificity, positive predictive value of 79.2%, and negative predictive value of 100%	
Ma *et al*[28]	Clinical diagnosis of TAK*	84 38 (45)	3 months	Carotid	Stenosis, occlusion, ↑ IMT, contrast enhancement	IMT higher in the active group (according to Kerr/NIH criteria and ITAS2010).	High
						In the inactive group, the proportion of stenosis and occlusion was higher.	
						Grade 2 vascularisation higher in patients with active disease.	
						Moderate correlation between ESR, CRP, and SAA levels and IMT	

Continued

Table 3 Continued

Study	Inclusion criteria	Patients (n) With follow-up (n) (%)	Time period follow-up	Investigated structures	US key elementary lesions	Summary of main findings	Overall risk of bias
Huang et al[29]	*Clinical diagnosis of TAK**	*86 Not specified*	*Not specified*	*Carotid*	*Stenosis, occlusion, aneurysm, ↑ IMT, contrast enhancement*	*Higher IMT in patients with a Kerr/NIH score ≥2.*	High
						Higher frequency of stenosis in patients with a Kerr/NIH score ≥2.	
						Mean enhanced intensity of artery wall higher in patients with a Kerr/NIH score ≥2	
Sinha *et al*[30]	Clinical diagnosis of TAK*	19 No follow-up (cross-sectional)	No follow-up (cross-sectional)	Carotid, subclavian, renal, femoral, brachial, radial, popliteal, posterior tibial dorsalis pedis, abdominal aorta	Stenosis, occlusion, aneurysm, ↑ IMT, 'CDUS-K'	Significant correlation between the CDUS-K score and ITAS2010	High
Seth *et al*[34]	Clinical diagnosis of TAK†	37 No follow-up (cross-sectional)	No follow-up (cross-sectional)	Carotid	↑ IMT	Higher IMT in patients with a Kerr/NIH score ≥2.	High
						US-based measurement of the outer diameter appeared to be not a reliable measure (differentiation between the adventitia and surrounding tissues not clear in almost 70% of patients and intra-observer variability was 30%)	
Goudot *et al*[35]	Clinical diagnosis of TAK*‡	16 No follow-up (cross-sectional)	No follow-up (cross-sectional)	Carotid	Circulating microbubbles (MB)	Higher number of MB per second in patients with a Kerr/NIH score ≥2.	High
						Increased vascular flow rate in patients with a Kerr/NIH score ≥2.	
						The number of MB significantly correlated with the carotid SUV max and the carotid-to-liver SUV ratio in FDG-PET/CT	
Liu *et al*[31]	Clinical diagnosis of TAK*§¶	96 No follow-up (cross-sectional)	No follow-up (cross-sectional)	Subclavian, carotid, vertebral	Stenosis, occlusion, aneurysm, ↑ IMT/macaroni sign, contrast enhancement	Median SMI grades were higher in patients with a Kerr/NIH score ≥2	High
Lottspeich *et al*[32]	Clinical diagnosis of TAK†	17 No follow-up (cross-sectional)	No follow-up (cross-sectional)	Subclavian, carotid, axillary	↑ IMT, contrast enhancement	Patients with active disease had a significantly higher maximum IMT compared with inactive patients and maximum IMT showed a significant correlation to disease activity scores (NIH, ITAS)	Moderate

Retrospective and case–control studies are italicised.
*1990 ACR criteria.
†No criteria.
‡Ishikawa's criteria modified by Sharma *et al*.
§2012 international Chapel Hill Consensus Conference Criteria.
¶ANCA 2012 Workshop on Takayasu Arteritis criteria.
CDUS, colour doppler ultrasound; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FDG-PET/CT, 18F-fluorodeoxyglucose positron emission tomography/CT; IMT, intima-media thickness; ITAS, Indian Takayasu clinical activity score; NIH, National institute of health; SAA, serum amyloid A; TAK, Takayasu arteritis.

used a definition based on the presence of heterogeneous echogenic substance filling the lumen.[24] This latter study adopted the definition of the 'stuffed macaroni sign' to describe an occlusion in the context of a diffuse thickening of the intima-media complex. Finally, four studies[17 18 20 29] applied the definition by the SRU for vascular occlusion[36] (online supplemental tables S2, S4, S6).

Two studies (10%) reported a definition of aneurysm/dilatation.[23 24] According to the first study, which evaluated the carotid, subclavian and common femoral arteries, an aneurysm was defined as an expansion of the calibre of the respective artery by 50% as compared with the contralateral unaffected artery.[23] The second study assessed carotid arteries only and defined an aneurysm as a luminal diameter greater than 9 mm[24] (online supplemental tables S2, S4, S6).

In 8/21 studies (38%), US was performed in combination with the use of a contrast agent (contrast-enhanced US, CEUS).[17 18 20 22 28 29 31 32] All these studies evaluated the common carotid arteries; in one of them, also the subclavian and the vertebral arteries were assessed.[31] Contrast enhancement was graded either from 1 to 3 or from 0 to 2 (ie, 0 or 1=no enhancement; 1 or 2=limited enhancement; 2 or 3=extensive enhancement) and interpreted as a semi-quantitative surrogate of vasculitis activity (ie, a higher score indicating more active vasculitis) (online supplemental tables S2, S4, S6).

None of the studies provided a specific definition to distinguish between acute and chronic vasculitic lesions.

Ultrasound scores

As mentioned earlier, three studies reported on US scores for TAK. One devised an 'Ultrasound index', calculated by summing the maximum IMTs of the right and left common carotid arteries, brachiocephalic trunk and aortic arch and dividing the result by the number of vessels with reliable IMT measurements.[19]

Another study developed the 'Colour Doppler Ultrasound-Kolkata' (CDUS-K) score, a system that evaluates stenosis and flow patterns at 19 arterial sites, including the common carotid, subclavian, brachial, radial, renal, common femoral, popliteal, posterior tibial, and dorsalis pedis arteries and the abdominal aorta.[30] Specifically, this scoring system incorporates three flow patterns: triphasic (normal), biphasic (stenosis) and monophasic (occlusion).

The third study proposed a score obtained by calculating the ratio of IMT to vessel diameter ('IMT/diameter ratio') in common carotid arteries.[21]

The first two scores were conceived to monitor disease activity,[19 30] whereas the latter was developed to predict severe ischaemic neurological events.[21] None of these three studies included an evaluation of the psychometric properties according to OFISA.[11]

Quality assessment

Most studies (n=17) were retrospective or cross-sectional.[15 16 19 20 22–27 29–35] Only four studies were prospective.[17 18 21 28] Studies on diagnostic accuracy were evaluated by QUADAS-2. Studies on the assessment of outcome prediction and of monitoring disease activity underwent appraisal by QUIPS. All studies revealed a moderate or high risk of bias, with most concerns related to outcome measurement and confounding (online supplemental tables S3, S5, S7).

DISCUSSION

This systematic SLR highlighted the scarcity of data on the value of US in TAK. Currently, no fully validated scoring system exists for monitoring disease activity. The three US scores identified exhibited notable limitations, particularly regarding the selection of arteries evaluated. Defining elementary sonographic lesions is a crucial step in developing a new US scoring system. This SLR identified IMT thickening, stenosis, occlusion and aneurysms as commonly-used US elementary lesions in TAK, while CEUS has been used in cross-sectional studies to assess disease activity.

All the reviewed studies included carotid arteries, which are the most frequently affected site in TAK and also the most accessible for US assessment. Additionally, more than one-third of the studies examined the subclavian arteries. Although TAK often involves multiple vascular territories, relatively few studies have explored elementary lesions in infra-diaphragmatic arteries, such as the abdominal aorta or common femoral arteries. This is likely due to limited sonographer expertise in these regions, limited acoustic window for abdominal vessels in case of meteorism or high body mass index, and the high prevalence of atherosclerotic lesions, which may complicate the assessment.

A homogeneous wall thickening, commonly known as the macaroni sign, was the most frequently described elementary lesion in the included studies. This sign reflects arterial wall thickening caused by inflammatory cell infiltration and can be readily assessed in most vascular sites. Despite its widespread recognition as a hallmark of TAK, the precise definition of the macaroni sign remains elusive. Additionally, a standardised IMT cut-off distinguishing normal from vasculitic arteries is still lacking, both for individual vessels as well as for all large-calibre arteries, and only a few studies described qualitative changes in wall echogenicity in patients with TAK. A similar challenge exists for aneurysms in TAK, as no universally accepted definition or threshold for a diameter increment has been established. One possible approach would be to adopt general arterial aneurysm definitions; however, these were primarily developed for the aorta and may not be applicable to other vessels, such as the carotids. In contrast, standardised definitions for stenosis and occlusion, such as those proposed by the SRU in 2004, are commonly used.[36] However, they

were specifically developed for evaluating the common carotid arteries, and their applicability to other vessels remains to be investigated. Notably, accurate visualisation of these lesions requires a combination of morphological assessment of vessel lumen changes and colour and pulsed-wave Doppler flow analysis.[10]

Some studies also included signs of increased vascularisation of the vessel wall, detected by CEUS, among key elementary lesions. This technique represents an advancement over simple IMT measurement but has several drawbacks, including greater invasiveness, higher costs and longer examination times compared with traditional vascular US. Furthermore, the availability of CEUS is limited in many clinical centres, and its grading system(s) still require standardisation and validation in a broader clinical context. It is also important to note that the assessment of vessel wall perfusion using CEUS is not yet approved for this specific indication.

Among the three US scoring systems identified, the 'Ultrasound index' and the 'IMT/diameter ratio' are limited by their exclusive focus on supra-diaphragmatic arteries.[19 21] This narrow approach may be inadequate for a complex and widespread disease like TAK, which affects infra-diaphragmatic arteries in up to 50% of cases.[37] Additionally, the 'Ultrasound index' includes the brachiocephalic trunk and aortic arch, regions that are challenging to assess accurately, even for experienced sonographers. In contrast, the 'CDUS-K' incorporates a broader range of arteries, covering both supra- and infra-diaphragmatic vessels, rendering it a more comprehensive reflection of TAK's complexity.[30] However, this expanded score requires the evaluation of 19 vascular territories, raising concerns about its feasibility in routine clinical practice. Furthermore, all three scoring systems were developed using small patient cohorts—one based on retrospective data—and none have undergone validation according to OFISA.[11]

Most of the studies included in this SLR support the role of US for monitoring of TAK, particularly through the assessment of IMT changes or variations in the size of the macaroni sign. This lesion appears to correlate directly with disease activity, as measured by clinical scores (eg, Inflammatory Disease Activity Score 2010 and Kerr criteria[38 39]) and other imaging modalities such as FDG-PET.[22] Notably, IMT has also demonstrated sensitivity to change, with reductions observed following the initiation or escalation of therapy.[18 19] However, the evidence remains preliminary, and studies are of small sample size and limited quality. Further prospective studies are thus needed to confirm the utility of IMT as a marker of treatment response in TAK. Similarly, increased vascular wall vascularisation detected by CEUS has shown a strong correlation with clinical scores.[17 18 20 22 28 29 31 32] In contrast, the role of other key elementary lesions—such as stenosis, occlusion and aneurysm—in disease monitoring remains elusive so far. Interestingly, neither IMT nor CEUS correlated with laboratory markers of inflammation, such as C reactive protein. This suggests that laboratory parameters and US may reflect different aspects of disease activity in TAK and could serve as complementary tools in clinical practice and trials.

The role of US in diagnosing TAK remains poorly explored, with only limited and low-quality data available. Most studies included in the SLR focused on patients with long-standing disease, where the diagnosis had already been established and therapy initiated, rather than on those with suspected disease. Additionally, TAK onset is typically subtle and insidious, unlike GCA, which often presents (sub)acutely. As a result, in most clinical settings, TAK diagnosis primarily relies on whole-body imaging techniques, such as MRI, FDG-PET or CTA. Evidence on the role of US in predicting disease course is also scarce, with only two studies addressing this issue.

Finally, it is important to emphasise that all included studies had small sample sizes and moderate-to-high risk of bias. Bias was mainly due to study design, as most of the studies were retrospective or cross-sectional, and featured an inhomogeneous patient population. This highlights the urgent need for international collaboration to conduct prospective, well-designed studies on the role of US in TAK.

In conclusion, this SLR on US in patients with TAK highlights the absence of validated scoring systems and that the macaroni sign is the elementary lesion most evaluated by sonographers. Among vascular territories, supra-diaphragmatic vessels, particularly the common carotid and subclavian arteries, are those most commonly investigated. Therefore, there is a critical need for a more rigorous evaluation of US role in the diagnosis, monitoring and risk prediction of patients with TAK. The next steps for the development of a new US composite score will be a Delphi exercise to establish consensus on the definitions of elementary US lesions in TAK.

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