Performance characteristics and predictors of temporal artery ultrasound for the diagnosis of giant cell arteritis in routine clinical practice in a prospective cohort

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ABSTRACT

Objective. *The diagnosis of giant cell arteritis (GCA) is primarily a clinical one. Temporal artery (TA) ultrasound (US) has been proposed as a new diagnostic tool. We aimed to assess the performance characteristics of TA US in routine clinical practice.*

Methods. *All patients presenting with suspected GCA to our institution are recruited to a prospective registry. Patients who had both a TA US and biopsy (TAB) performed at the time of presentation were included in the current study. The performance characteristics of TA US was compared to physician diagnosis at six months following presentation. Predictive factors for a positive TA US were explored in univariate and multivariable logistic regression analyses.*

Results. *162 patients were included, 123 (76%) with GCA. Mean (SD) duration of glucocorticoid therapy was 6.6 days (19.4) at the time of TA US. TA US had a sensitivity of 52.8% (95%CI 43.7, 61.9) and specificity of 71.8% (95%CI 54.9, 84.5) for the diagnosis of GCA. Glucocorticoid duration did not significantly impact the results. A sequential strategy of TA US followed by TAB in the case of a negative US had a sensitivity of 78.9% (95%CI 70.1, 85.5) and specificity of 71.8% (95%CI 54.9, 84.5), equivalent to a simultaneous testing strategy. The only factor independently predictive of a positive TA US was male sex (OR 5.53, 95% CI 2.72 to 11.22, p<0.001).*

Conclusion. *TA US is potentially useful in the diagnosis of GCA; however, interpretation of its results requires knowledge of the performance characteristics in the target population.*

Introduction

The diagnosis of giant cell arteritis (GCA) is primarily a clinical one. Supportive investigations exist, but there is no definitive diagnostic test. Temporal artery biopsy (TAB) has long been considered the gold standard investigation (1). A positive TAB is highly suggestive of GCA; however, it may also be seen in other forms of systemic vasculitis (2-6). A negative TAB does not exclude GCA and is seen in up to 61% of cases (7-9).The reasons for this include skip lesions, sampling of an artery unaffected by vasculitis, or a GCA phenotype that does not affect the cranial arteries (5, 10-15).

Temporal artery ultrasound (TA US) is a relatively recent development in the diagnostic armamentarium in GCA (16, 17). The characteristic ultrasound finding in GCA is the "halo sign", which is defined as a hypoechoic area around the vessel lumen (16). Several studies have assessed TA US in GCA reporting sensitivities ranging from 10-100% and specificities from 61-100% (6, 18-26). Two meta-analyses reported a sensitivity of 55-69% and specificity of 82-94% for the halo sign compared to either TAB or the ACR classification criteria (27, 28). The recent TABUL prospective multicentre cohort study reported a sensitivity of 54% and specificity of 81% compared to physician diagnosis at 6 months (9).

There are several issues with implementing the more widespread use of TA US. Specific training is required in the skills to identify vascular inflammation on TA US, as small degrees of blood vessel abnormality are common in healthy people. It has been suggested that TA US abnormalities are highly sensitive to glucocorticoid treatment and may resolve rapidly in treated patients, although changes may persist for over 6 months in some cases (29-33). To date most studies have focused on specialist centres, highly trained and

experienced operators, rapid patient review following symptom onset, and frequent performance of TA US prior to the introduction of glucocorticoids. Positive reports on the use of TA US in these settings will inevitably result in its introduction to general clinical practice, where TA US will be used to guide diagnostic and treatment decisions while being performed with significant delay since symptom onset and following the introduction of glucocorticoids. The patient population in the clinic setting will also be more heterogeneous than that which met the inclusion criteria of previous studies. The interpretation of the results of any test requires knowledge of the performance characteristics in the target population. A prospective real-world assessment of the performance characteristics of TA US in the diagnosis of GCA is lacking and is urgently needed. Therefore, we performed this prospective study evaluating the performance of TA US and TAB compared to expert clinician judgement in patients presenting with suspected GCA.

Materials and methods

Giant cell arteritis registry

We have established a prospective GCA registry recruiting from three hospitals in Dublin, Ireland. All patients presenting with suspected GCA are invited to participate. A dedicated clinical research infrastructure exists to coordinate patient recruitment, and prospectively collect clinical data and biological samples. The registry has recruited 334 participants from inception in August 2011 to June 2017. Registry participants include 3 separate groups, a) TAB positive GCA (42%), b) TAB negative GCA (42%), and c) patients initially referred with suspected GCA but in whom GCA is ultimately excluded (16%). Patients included in the current study were recruited from this existing registry.

Inclusion criteria

Patients were eligible to participate if they were referred with a new presentation of suspected GCA and had both a TA US and TAB performed. The study was conducted between 5th August 2011 and 31st December 2016, participants were required to have been followed up for at least 6 months following their presentation. Treating physicians were responsible for the timing of initiation and dosage of glucocorticoids. This decision was based on clinical judgement and as such no restrictions were imposed. All patients gave written informed consent and the study was approved by the ethics committee at the three institutions.

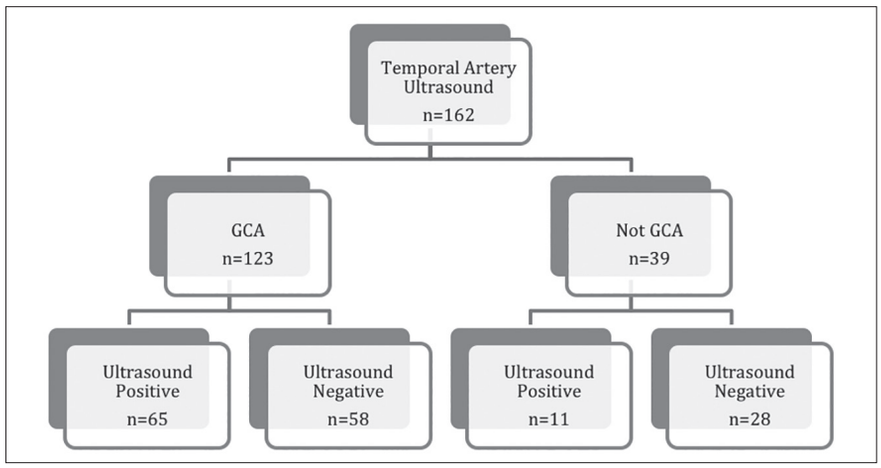

Fig. 1. Temporal artery ultrasound results stratified by clinical diagnosis.

Temporal artery ultrasound

All ultrasounds were performed on a Philips iU22 scanner (Philips Healthcare, Amsterdam, Netherlands) using a high-frequency linear array 12-MHz transducer by one of two consultant radiologists (EJH and RPK). The radiologists were blinded to the clinical diagnosis. The superficial TA was identified at the level of the tragus of the ear and evaluation continued into the parietal and frontal branches on each side. Sonography was performed using both grey-scale and colour-Doppler assessment. The examination was considered positive for temporal arteritis if any segment of the TA demonstrated circumferential hypoechoic mural thickening (the 'halo' sign). The halo sign was recorded as a dichotomous outcome (present or absent), the thickness of the halo was not measured. The compression test was not used in this study.

Temporal artery biopsy

Unilateral TAB was performed by vascular or ophthalmic surgeons on the more symptomatic side. A TAB was considered positive if it contained an inflammatory mononuclear cell infiltrate or multinucleated giant cells. Isolated intimal hyperplasia and fragmentation of the internal elastic lamina were considered negative biopsies.

Data collection and final diagnosis

Demographic and clinical data was collected prospectively on all patients. The timing and dosing of glucocorticoid usage prior to procedure performance was entered prospectively into the database.

Consultant rheumatologist diagnosis at 6 months following initial presentation was considered as the reference standard for the diagnosis of GCA for the purposes of this study. The diagnosis was assessed as a binary outcome, GCA or not. Rheumatologists were not blinded to the results of the TA US or TAB.

Statistical analysis

Descriptive statistics were reported as mean and standard deviation (SD), median and interquartile range (IQR) or number (n) and percentages as appropriate. For between group comparisons Chi-squared tests were used for categorical variables and independent samples t-tests for continuous variables. Sensitivity, specificity, positive and negative predictive values and likelihood ratios were calculated comparing TA US and TAB to the reference standard of rheumatologist's 6-month diagnosis. As positive and negative likeli-

hood ratios are influenced by disease prevalence, we repeated these analyses weighting for the prevalence of GCA in our study population. The results were further stratified by time on glucocorticoids; 0 days, >0 ≤3 days, >3 ≤7 days, >7 ≤14 days, and >14 days. For the purposes of this study long-term low-dose glucocorticoids for polymyalgia rheumatica were not included in the calculations of glucocorticoid dose or duration.

It has been suggested that TA US may replace the need for TAB in some patients with suspected GCA; this could potentially result in cost savings and the avoidance of procedure-related complications (9). We further analysed the performance characteristics of three combination testing strategies; (a) a simultaneous strategy of TA US and TAB in all patients, (b) a sequential strategy of TA US followed by TAB only if the TA US was positive, (c) a sequential strategy of TA US followed by TAB only if the TA US was negative. Univariate analyses were performed to assess demographic and clinical predictors of TA US and TAB results. Multiple logistic regression analyses were performed to model predictors of TA US and TAB results. Variables with $p<0.10$ in the univariate analyses were considered for inclusion in the multiple logistic regression model. Statistical significance was set at $p<0.05$ throughout. All analyses were performed using IBM SPSS Statistics (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, v. 20.0. Armonk, NY: IBM Corp.) and GraphPad Prism v. 6.05 for Windows (GraphPad Software, La Jolla California USA, www.graphpad.com).

Table I. Baseline demographics and characteristics of patients.

	GCA	Not GCA	*p*-value
Age, years	71.2 (9.7)	68.3 (11)	0.113
Female	72 (58.5)	26 (66.7)	0.365
Met 1990 ACR criteria for GCA	108 (87.8)	17 (43.6)	<0.001
Biopsy positive	60 (48.8)	1 (2.6)	<0.001
TA Ultrasound positive	65 (52.8)	11 (28.2)	0.007
CT Angiogram positive	26 (21.1)	1 (2.6)	0.007
Cranial-ischaemic complications	25 (20.3)	6 (15.4)	0.494
ESR, mm/hr	60 (31, 80)	40 (11, 69)	0.016
CRP, mg/L	41.3 (5, 103)	11.1 (3, 35)	0.001
Temporal headache	90 (73.2)	28 (71.8)	0.866
Scalp tenderness	64 (52.0)	22 (56.4)	0.633
Temporal artery abnormality	80 (65.0)	15 (38.5)	0.003
Jaw claudication	50 (40.7)	1 (2.6)	<0.001
Visual disturbance	42 (34.1)	15 (38.5)	0.623
Polymyalgia rheumatica	58 (47.2)	12 (30.8)	0.072
Constitutional symptoms	75 (61.0)	13 (33.3)	0.003

Data are expressed as mean (SD) or n (%) as appropriate. ESR and CRP expressed as median (IQR). ACR: American College of Rheumatology; GCA: giant cell arteritis; IQR: interquartile range; TA: temporal artery; CT: computed tomography; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Results

Patient characteristics

From 1st August 2011 to 31st December 2016 291 patients were recruited to the GCA registry with 256 patients having been followed up for at least 6 months following presentation. Of these 169 had both a TA US and TAB performed; of the remaining 87, seven declined TAB and 80 had a TAB prior to the availability of TA US and so where excluded Seven had non-arterial TAB specimens, leaving 162 for final analysis. Consultant rheumatologist diagnosis at 6-months was GCA in 123 (76%), and not GCA in 39 (24%). The baseline characteristics of the included patients stratified by diagnosis are summarised in Table I. Mean (SD) age was 70.5 (10.1) years, 60.5% were female. Patients in the GCA group were significantly more likely to meet the 1990 ACR classification criteria for GCA ($p<0.001$), have a positive TAB ($p<0.001$) or TA US ($p=0.007$), and to have large-vessel vasculitis on CT angiogram ($p=0.007$). Clinically they were more likely to have jaw claudication ($p<0.001$), constitutional symptoms ($p<0.003$), temporal artery abnormalities on exam ($p=0.003$), and an elevated ESR ($p=0.016$) or CRP ($p=0.001$).

Glucocorticoid exposure

Median (IQR) duration of glucocorticoids was 1 day (0, 5) at the time of TA US and 4 days (0, 8) at the time of TAB. Median (IQR) glucocorticoid dose was 15mg (0, 60) at time of TA US and 40mg (0, 60) at the time of TAB. Median (IQR) cumulative glucocorticoid dose was 40mg (0, 370) at the time of TA US and 200mg (0, 645) at the time of TAB. 49.4, 16.7, 15.4, 11.1, and 7.4% of patients had glucocorticoids for 0 days, >0 ≤3 days, >3 ≤7 days, >7 ≤14 days, and >14 days, respectively at the time of TA US. 32.7, 14.8, 23.5, 17.9, and 11.1% of patients had glucocorticoids for 0 days, >0 ≤3 days, >3 ≤7 days, >7 ≤14 days, and >14 days, respectively at the time of TAB.

Temporal artery ultrasound

TA US was positive in 76 (46.9%) patients (Fig. 1). Of the 123 patients with GCA, TA US was positive in 65, yielding a sensitivity of 52.8% (95%CI 43.7, 61.9). Of the 39 patients without GCA, TA US was negative in 28, yielding a specificity of 71.8% (95%CI 54.9, 84.5). The area under the ROC curve (AUROC) was 0.62. The positive predictive value (PPV) of TA US was 85.5% (95% CI 75.2, 92.2). The negative predictive value (NPV) of TA US was 32.6% (95%CI 23.1, 43.6). The positive (PLR) and negative likelihood ratios (NLR) were 1.87 (95%CI 1.11, 3.18) and 0.66 (95%CI 0.53, 0.81), respectively. Weighting for prevalence resulted in a PLR and NLR of 5.91 (95%CI 3.39, 11.29) and 2.07 (95%CI 1.71, 2.52), respectively. No definitive effect of prior glucocorticoid duration on TA US results was evident, Table II.

Temporal artery biopsy

Histological findings consistent with GCA were present in 61 (37.7%) TABs (Fig. 1). Of the 123 patients with GCA,

TAB was positive in 60, yielding a sensitivity of 48.8% (95%CI 39.7, 57.9). Of the 39 patients without GCA, TAB was negative in 38, yielding a specificity of 97.4% (95%CI 84.9, 99.9). The AUROC was 0.73. The PPV of TAB was 98.4% (95%CI 90.0, 99.9). The NPV of TAB was 37.6% (95%CI 28.3, 47.9). The PLR and NLR were 19.02 (95%CI 2.73, 132.80) and 0.53 (95%CI 0.44, 0.63), respectively. Weighting for prevalence resulted in a PLR and NLR of 60.00 (95%CI 8.59, 419.24) and 1.66 (95%CI 1.38, 1.99), respectively. Time on glucocorticoids prior to TAB did not significantly impact the results, Table II.

Table II. Performance characteristics of ultrasound and biopsy stratified by glucocorticoid duration.

Procedure, glucocorticoid duration	Sensitivity	Specificity	PPV	NPV	PLR	NLR	PLR(W)	NPR(W)
Ultrasound, all	52.8	71.8	85.6	32.6	1.87	0.66	5.91	2.07
Ultrasound, 0 days	51.9	76.9	82.4	43.5	2.25	0.63	4.67	1.30
Ultrasound, >0 ≤3 days	46.2	100	100	6.0	Infinity	0.54	Infinity	14.00
Ultrasound, >3 ≤7 days	60.0	40.0	80.0	20.0	1.00	1.00	4.00	4.00
Ultrasound, >7 ≤14 days	64.3	50.0	81.8	28.6	1.29	0.71	4.50	2.50
Ultrasound, >14 days	44.4	100	100	37.5	Infinity	0.56	Infinity	1.67
Biopsy, all	48.8	97.4	98.0	37.6	19.02	0.53	60.00	1.66
Biopsy, 0 days	46.9	100	100	55.3	Infinity	0.53	Infinity	0.81
Biopsy, >0 ≤3 days	66.7	83.3	92.3	45.5	4.00	0.40	12.00	1.20
Biopsy, >3 ≤7 days	47.1	100	100	18.2	Infinity	0.53	Infinity	4.50
Biopsy, >7 ≤14 days	47.8	100	100	33.3	Infinity	0.52	Infinity	2.00
Biopsy, >14 days	37.5	100	100	17.0	Infinity	0.63	Infinity	5.00

PPV: positive predictive value; NPV: negative predictive value; PLR: positive likelihood ratio; NPR: negative likelihood ratio; PLR(W): positive likelihood ratio weighted by prevalence; NLR(W): negative likelihood ratio weighted by prevalence.

Table III. Performance caracteristics of single, sequential and simultaneous testing strategies.

Strategy	Sensitivity	Specificity	PPV	NPV	PLR	NLR	PLR(W)	NLR(W)
Ultrasound alone	52.8	71.8	85.6	32.6	1.87	0.66	5.91	2.07
Biopsy alone	48.8	97.4	98.0	37.6	19.02	0.53	60.00	1.66
Sequential (US pos)	22.8	97.4	96.6	28.6	8.88	0.79	28.00	2.50
Sequential (US neg)	78.9	71.8	89.8	51.9	2.80	0.29	8.82	0.93
Simultaneous	78.9	71.8	89.8	51.9	2.80	0.29	8.82	0.93

PPV: positive predictive value; NPV: negative predictive value; PLR: positive likelihood ratio; NPR: negative likelihood ratio; PLR(W): positive likelihood ratio weighted by prevalence; NLR(W): negative likelihood ratio weighted by prevalence.

Sequential and simultaneous testing strategies

The sensitivity of a simultaneous testing strategy of performing a TA US and TAB in all patients was 78.9% (95%CI 70.1, 85.5) and the specificity was 71.8% (95%CI 54.9, 84.5). The PPV was 89.8% (95% CI 82.1, 94.6). The NPV was 51.9% (95%CI 38.0, 65.5). The PLR and NLR were 2.80 (95%CI 1.68, 4.65) and 0.29 (95%CI 0.21, 0.42), respectively. Weighting for prevalence resulted in a PLR and NLR of 8.82 (95%CI 5.02, 15.49) and 0.93 (95%CI 0.68, 1.27), respectively. The AUROC was 0.75.

A sequential strategy of TA US followed by TAB only in the case of a negative TA US result was assessed. 97 of the 123 patients ultimately diagnosed with GCA had either a positive TA US or a negative TA US followed by a positive TAB. 28 of the 39 patients ultimately diagnosed with an alternative condition had a negative TA US followed by a negative TAB. The sensitivity and specificity of this strategy were 78.9% (95%CI 70.1, 85.5) and 71.8% (95%CI 54.9, 84.5), respectively. The PPV was 89.8% (95% CI 82.1, 94.6). The NPV was 51.9% (95%CI 38.0, 65.5). The PLR and NLR were 2.80 (95%CI 1.68, 4.65) and 0.29 (95%CI 0.21, 0.42), respectively. Weighting for prevalence resulted in a PLR and NLR of 8.82 (95%CI 5.02, 15.49) and 0.93 (95%CI 0.68, 1.27), respectively. The AUROC was 0.75.

A second sequential strategy of TA US followed by TAB only in the case of a positive TA US result was assessed. The sensitivity of this strategy was 22.8% (95%CI 15.9, 31.4) and specificity 97.4% (95%CI 84.9, 99.9). The PPV was 96.6% (95% CI 80.1, 99.8). The NPV was 28.6% (95%CI 21.2, 37.2). The PLR and NLR were 8.88 (95%CI 1.25, 63.15) and 0.79 (95%CI 0.72, 0.87), respectively. Weighting for prevalence resulted in a PLR and NLR of 28.00 (95%CI 4.08, 192.35) and 2.50 (95%CI 2.16, 2.89), respectively. The AUROC was 0.60.

Patients with positive temporal artery ultrasound ultimately given alternative diagnosis

Eleven patients with positive TA US were ultimately given a diagnosis other than GCA; one of the patients also had a positive TAB (mononuclear infiltrate, no giant cells). The final diagnoses covered a broad spectrum from polyarteritis nodosa to malignancies, and migraine. Full details of this patient group are shown in Table IV. Five of these TA US were positive bilaterally and six unilaterally. The final diagnoses in the five patients with bilateral positive TA US were multiple myeloma, prolapsed cervical disc and lower respiratory tract infection, migraine and urinary tract infection, polyarteritis nodosa, and migraine and pulmonary carcinoid.

Univariate analyses

Simple logistic regression analyses were performed to assess predictors of positive TA US and TAB. Male sex (OR 5.12; 95%CI 2.58, 10.15; $p<0.001$), was the only significant predictor of a positive TA US. Jaw claudication (OR 3.69; 95%CI 1.84, 7.39; $p<0.001$), ESR (OR 1.02; 95%CI 1.01, 1.03; $p<0.001$), CRP (OR 1.01; 95%CI 1.00, 1.01; $p<0.001$), the presence of poly-

Table IV. Characteristics of non-GCA patients with positive temporal artery ultrasound.

Case No.	Age	Gender	Diagnosis	Biopsy	Historical disease features	ESR	CRP	Other imaging
1	66	Male	Malignant otitis externa	Intimal hyperplasia	Headache, scalp tenderness	69	23	CT brain: malignant otitis externa
2	77	Male	Multiple myeloma	Amyloid	Fever, weight loss, anorexia	43	1	None
3	57	Male	PAN	Vessel recanalisation and wall scaring	Headache, scalp tenderness, visual blurring, calf myalgia, abdominal warmth	32	53	Mesenteric angiogram: medium-vessel vasculitis with microaneurysms
4	71	Male	Metastatic Neuroendocrine Tumour	Normal	Headache, fever, anorexia, weight loss	58	180	None
5	79	Female	Migraine	Normal	Headache, scalp tenderness, visual blurring, jaw claudication	74	9	None
6	67	Male	PAN	Mononuclear infiltrate, fragmentation of IEL	Headache, scalp tenderness, fever, anorexia, weight loss, myalgia	94	167	MRI -myositis and fasciitis bilateral thigh muscles
7	60	Female	Migraine	Normal	Headache, scalp tenderness	4	4	None
8	64	Male	Greater occipital neuralgia	Normal	Headache, scalp tenderness	10	11	None
9	78	Male	Prolapsed cervical disc, LRTI	Calcification IEL	Neck pain, lower limb weakness and numbness, anorexia, weight loss	74	268	CT angiogram: NAD MRI cervical spine: disc prolapse
10	52	Male	Migraine, Urinary Tract Infection	Normal	Headache, scalp tenderness, visual blurring	24	5	CT brain: post-traumatic encephalomalacia
11	74	Female	Migraine, Atherosclerosis, Pulmonary Carcinoid	Normal	Headache	75	3	CT thorax: pulmonary nodule, confirmed as carcinoid on biopsy

ESR: erythrocyte sedimentation rate; CRP: C reactive protein; CT: computed tomography; PAN: polyarteritis nodosa; PMR: polymyalgia rheumatica; IEL: internal elastic lamina; MRI: magnetic resonance imaging; LRTI: lower respiratory tract infection.

myalgic (OR 2.04; 95%CI 1.07, 3.89; p=0.031) or constitutional symptoms (OR 3.35; 95%CI 1.69, 6.65; p=0.001), and documented large-vessel vasculitis (OR 2.42; 95%CI 1.05, 5.59; p=0.039) were significant predictors of a positive TAB.

Multiple logistic regression analyses

Our results were used to construct a model to predict the occurrence of a positive TA US based on male sex, scalp tenderness, and TA abnormality on clinical examination. The logistic regression model was statistically significant, $\chi2(3)=29.619$, $p<0.001$. The model explained 22.3% (Nagelkerke R Square) of the variance in TA US positivity and correctly classified 69.1% of cases. The only factor independently predictive of a positive TA US was male sex (OR 5.53, 95% CI 2.72 to 11.22, $p<0.001$) (Table II). The Hosmer and Lemeshow test demonstrated goodness-of-fit of the model, $\chi2(6)=9.299$, $p=0.157$.

Our results were also used to construct a model to predict the occurrence of a positive TAB based on age, jaw claudication, ESR, CRP, presence of polymyalgic symptoms, presence of constitutional symptoms, daily glucocorticoid dose prior to biopsy, and documented large-vessel vasculitis. ESR and CRP were both included in the model as they did not demonstrate significant collinearity (R=0.493). The logistic regression model was statistically significant, $\chi2(8)=36.752$, $p<0.001$. The model explained 27.6% (Nagelkerke R Square) of the variance in biopsy positivity and correctly classified 72.8% of cases. The only factor independently predictive of a positive TAB was jaw claudication (OR 2.40, 95% CI 1.11, 5.21, p=0.027). The Hosmer and Lemeshow test demonstrated goodness-of-fit of the model, $\chi2(8)=13.225$, p=0.104.

Discussion

The sensitivity and specificity of TA US in our study were 52.8% and 71.8%, respectively. The simultaneous performance of TAB and TA US significantly increased the sensitivity of the testing strategy to 78.9% with no change in specificity. A strategy of performing an

initial TA US followed by a TAB only if the TA US is negative appeared to be the most efficient strategy with identical performance compared to simultaneous performance of the two tests. In contrast to some previous studies we did not find any appreciable effects of glucocorticoid duration on the results of TA US or TAB (32, 33). Male sex was the only significant predictor of a positive TA US in the multiple regression analysis, while jaw claudication was the only significant predictor of a positive TAB. Our overall results demonstrate that the use of TA US as a screening test is not appropriate. It should be used only as part of the diagnostic formulation by physicians experienced in the assessment of patients with suspected GCA.

Our study differs from previous studies in this area in several ways and fills an important gap in the current literature. This is the first prospective study performed in a real-world setting assessing radiologist-performed TA US compared with physician diagnosis at 6 months. A number of previous studies of TA US have used TAB as a reference standard for the diagnosis of GCA (20, 23, 34-36). As our study and others have shown, TAB has a low sensitivity for the diagnosis of GCA and is therefore not suitable for use as a reference standard (9). Others have used the 1990 ACR classification criteria for GCA as the reference standard for diagnosis (16, 22, 23, 37). The ACR criteria are classification criteria and have been shown to perform poorly when utilised as diagnostic criteria (38). Several previous studies utilised rapid access pathways resulting in the inclusion only of patients extremely early in their disease course, frequently prior to glucocorticoid treatment (6, 9, 20, 22-24, 36). In reality, as patients vary widely in the duration of symptoms and glucocorticoid treatment at the time of presentation, the performance of TA US across the spectrum of clinical presentations requires evaluation. Several previous studies were performed at specialist centres with highly trained clinician ultrasonographers focused exclusively on TA US (6, 9, 16, 35, 36). In many centres the performance of TA US will be the responsibility of radiologists involved in multiple competing roles. Previous retrospective assessments of the utility of TA US have the inherent limitations of studies based on retrospective chart reviews (19, 25, 26, 35, 36, 39).

The sensitivity of 52.8% and specificity of 71.8% identified for TA US in our study are congruent with the majority of previous studies in this area. Several studies have assessed the use of TA US with varying methodology, populations, and results, with sensitivity ranging from 10–100% and specificity from 61–100% (6, 9, 16, 18-26). Two meta-analyses of TA US studies in GCA reported sensitivities of 55–69% and specificity of 82–94% for the halo sign compared to either TAB or the ACR classification criteria (27, 28). The recently reported TABUL prospective multicentre cohort study reported a sensitivity of 54% and specificity of 81% (9). The suggestion from the majority of previous studies has been that commencement of glucocorticoids results in rapid resolution of the US appearances of GCA (16, 31-33). This has led to advocacy for the necessity of the rapid performance of TA US in suspected GCA. Persistent US detected inflammatory changes have also been demonstrated in some patients however (29, 30). Our study did not demonstrate any significant effect of glucocorticoid duration on TA US results. Although a limited number of our patients had received glucocorticoids for more than 14 days, it would appear that the US signal is durable in our population at least up to this time. Clearly, sequential ultrasound scanning of individual patients over time would assess this issue more robustly, but was beyond the scope of the current study.

This is the first study to assess predictors of a positive TA US in a multiple logistic regression model. Interestingly we found that male sex was the strongest predictor of a positive TA US with an odds ratio of 5.5 ($p<0.001$). Our study does not provide evidence as to why sex should be such a strong predictor of TA US positivity. Hypotheses include pathophysiological differences in the disease between men and women, a lower frequency of cranial mimics of GCA in the male population, or that there is generally greater difficulty in scanning the TA beyond the hairline in women which can make a substantial portion of the vessel not assessable. Jaw claudication emerged as the only independent predictor of a positive TAB in the multiple regression model; the importance of jaw claudication in this regard is consistent with previous reports on predictors of both a positive TAB and a diagnosis of GCA (40-42).

There are several potential limitations to this work. We used physician diagnosis at 6 months as the reference standard diagnosis. This is not a perfect reference standard, however it is coherent to the methodology used in the TABUL study and is superior to the use of either TAB or the ACR classification criteria given their acknowledged limitations in this regard (9). Treating physicians were not blinded to the results of TA US or TAB, therefore the knowledge of the results of these tests may have biased the final diagnosis reached. We have not evaluated other potential ultrasound findings such as the thickness of the temporal artery “halo” or the compression test and therefore based on our data cannot comment on their utility. Of the 256 patients in the registry only 162 had both TA US and TAB, this introduces the potential for selection bias, however the reasons for exclusion, especially TAB being performed prior to ultrasound, are unlikely to affect the target population. While no significant negative effect of avoidance of TAB in cases of positive TA US was demonstrated in this study, potential concerns remain over the adequate exclusion of uncommon GCA mimics in the absence of histological results. The clinical decision to proceed to biopsy in patients with positive TA US should be made by clinicians experienced in the assessment and management of patients with suspected GCA.

In conclusion, our prospective study supports the diagnostic utility of and identifies potential pitfalls in the use of radiologist-performed TA US for assessment of an unselected spectrum of patients presenting with suspected GCA in routine clinical practice.

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