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Original article

The impact of disease extent and severity detected by quantitative ultrasound analysis in the diagnosis and outcome of giant cell arteritis

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Abstract

Objectives. To develop a quantitative score based on colour duplex sonography (CDS) to predict the diagnosis and outcome of GCA.

Methods. We selected patients with positive CDS and confirmed diagnosis of GCA recruited into the TA Biopsy (TAB) *vs* Ultrasound in Diagnosis of GCA (TABUL) study and in a validation, independent cohort. We fitted four CDS models including combinations of the following: number and distribution of halos at the TA branches, average and maximum intima–media thickness of TA and axillary arteries. We fitted four clinical/laboratory models. The combined CDS and clinical models were used to develop a score to predict risk of positive TAB and clinical outcome at 6 months.

Results. We included 135 GCA patients from TABUL (female: 68%, age 73 (8) years) and 72 patients from the independent cohort (female: 46%, age 75 (7) years). The best-fitting CDS model for TAB used maximum intima–media thickness size and bilaterality of TA and axillary arteries' halos. The best-fitting clinical model included raised inflammatory markers, PMR, headache and ischaemic symptoms. By combining CDS and clinical models we derived a score to compute the probability of a positive TAB. Model discrimination was fair (area under the receiver operating characteristic curve 0.77, 95% CI: 0.68, 0.84). No significant association was found for prediction of clinical outcome at 6 months.

Conclusion. A quantitative analysis of CDS and clinical characteristics is useful to identify patients with a positive biopsy, supporting the use of CDS as a surrogate tool to replace TAB. No predictive role was found for worse prognosis.

Key words: GCA, ultrasound, colour duplex sonography, TA biopsy, diagnosis, prognosis

Rheumatology key messages

- Quantitative analysis of ultrasound findings informs on the diagnosis of giant cell arteritis (GCA).
- A computable score provides risk-stratification of a positive temporal artery biopsy diagnostic for GCA.
- Prognostic role of baseline ultrasound quantitative findings in GCA needs to be further addressed.

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CLINICAL SCIENCE

Introduction

An increasing body of evidence supports the role of colour duplex sonography (CDS) as a diagnostic tool for GCA [1–5]. CDS detects inflammatory changes as a homogeneous hypoechoic vessel wall swelling, known as a 'halo-sign' [3, 6]. Ultrasound offers the advantage of being a safe, repeatable and less costly procedure than TA biopsy (TAB), allowing us to assess the temporal arteries (TA) and extra-cranial vessels at the same time [4, 7]. TAB has been the standard diagnostic tool for GCA for several years, but imaging, performed with the correct expertise, is emerging as a more effective and versatile method [3]. The combined examination of TA and axillary arteries (AX) represents the minimum ultrasonographic core assessment of patients with suspected GCA and is known to increase the diagnostic yield in large vessel vasculitis [8]. CDS has been demonstrated to have higher sensitivity compared with TAB, which is still recognized as the gold standard for the diagnosis of GCA [4, 9]. Nevertheless, the role of CDS in the follow-up of patients and its predictive value on outcome are still poorly understood.

Available CDS data across studies are largely qualitative, with a binary (positive/negative) assessment of CDS results. A 'positive' CDS supporting a diagnosis of GCA has been defined, qualitatively, as the presence of a halo at one or more vascular sites [6, 7]. However, the value of specific CDS findings such as halo size (maximum or average thickness), number of TA branches involved, total number of anatomical sites with halo, or the presence of bilateral halos in predicting diagnosis and outcome are still to be defined. Moreover, a standardized, quantitative score to grade the severity and extent of vascular involvement detected by CDS in GCA has not yet been developed.

We therefore analysed data from a large prospective multicentre study including new cases of suspected GCA, the TA Biopsy *vs* Ultrasound in Diagnosis of GCA (TABUL) study [4], to determine the association of ultrasonographic parameters with clinical, histological and outcome findings, and to develop a comprehensive CDS score. We then tested the ultrasonographic models on an independent cohort of patients newly referred for suspected GCA.

Methods

Patients were selected among those recruited in the TABUL study [4]. According to the study design, patients with a suspected diagnosis of new-onset GCA had undergone both ultrasound and TAB within 7 days of commencing high-dose glucocorticoids (GC). The detailed methods and results of the TABUL study have been previously described [4]. We selected patients with a positive CDS and a confirmed final diagnosis of GCA. We identified an independent cohort of patients referred to the fast-track GCA clinics of the Rheumatology departments of the University of Oxford and the University of Pavia between March 2016 and November 2017 who had a positive CDS and a confirmed diagnosis of GCA. The two recruiting centres applied the same CDS methodology as TABUL [10].

A positive CDS was defined by the presence of at least one site with a halo at the level of the TA, or at least one AX showing a halo. A halo was defined as a homogeneous, hypoechoic wall thickening, well delineated towards the luminal side, visible on both planes (longitudinal and transverse), most commonly concentric [4, 6, 7]. Among ultrasound abnormalities recorded in the TABUL study, we selected the specific finding of the presence or absence of a halo. Halo thickness was recorded as the maximum thickness, measured in millimetres (mm), of the intima–media complex on the wall distal to the probe on longitudinal planes. Intima–media thickness (IMT) was measured at the site with the maximum size of the intima–media complex. The presence of bilateral halos in the TA was defined as the finding of a bilateral halo in at least one of the branches (common, parietal, frontal) of each TA. Bilateral halo on AX was defined by the involvement of both AX.

To assess the discriminatory ability of the CDS parameters on diagnosis, we included patients with a positive CDS, but in whom a diagnosis of GCA had been excluded. For the association with clinical features (histological findings and outcome) we considered patients with a confirmed diagnosis of GCA, defined by final physician's diagnosis during follow-up visits [4].

Clinical evaluations included details on presenting symptoms, ongoing manifestations on the day of the CDS assessment, physical examination of the TA and information on therapy. Patients provided written informed consent prior to inclusion in the study. Ethical approval was obtained for the study (REC No. 09/H0505/132).

Disease activity was calculated using the BVAS collected at 2-week (for TABUL only) and at 6-month examinations (for both cohorts). The Vasculitis Damage Index and its individual items were considered at the 6-month visit.

Statistical analysis

Data were analysed using Stata 15.1 (StataCorp, College Station, TX, USA). Continuous variables are presented as mean (S.D.) or median values. For categorical variables, absolute and relative frequencies are reported. Differences in the CDS variables according to several clinical, laboratory, histological and outcome characteristics were tested using the Wilcoxon–Mann–Whitney test for continuous variables and the χ^2 test or Fisher's exact test for dichotomous variables.

In order to identify a comprehensive score inclusive of different ultrasonographic parameters that could be combined with clinical and laboratory findings, we fitted the CDS logistic models against two major outcomes: TAB diagnostic for GCA and clinical outcome at 6 months [defined as visual loss, Vasculitis Damage

Index ocular items, GC >10 mg/day of prednisone-equivalent (based on median value for TABUL cohort) at 6 months and/or the need for adjunctive immunosuppressants]. We also fitted clinical logistic models against TAB diagnostic for GCA and clinical outcome at 6 months.

The variables to be included in these models were identified *a priori* based on the available evidence or the hypothesized clinical evidence. We then combined the best CDS and clinical models (according to the Akaike information criterion, the lower the better) to identify independent correlates of a TAB diagnostic for GCA and of clinical outcome at 6 months. The best-fitting CDS and clinical/laboratory models were combined to develop a comprehensive score (the GCA-US score). For model discrimination we computed the model area under the receiver operating characteristic (ROC) curve and its 95% CI. The final model was validated with a 10-fold cross-validation.

We tested the association between the GCA-US score and the clinical outcome at 6 months on the independent cohort.

Results

We included 135 patients recruited in TABUL (female: 92, mean age 73 (8) years) who had a positive CDS and a diagnosis of GCA. In order to assess the discriminatory ability of CDS on diagnosis, we compared these patients with an additional 44 patients (24%) who had a positive CDS showing a halo, but did not have a final diagnosis of GCA. Of the 135 patients, 128 (95%) were recorded as having a halo in at least one site of a TA (either the common trunk, parietal or frontal rami); bilateral halos were present in 71 of these cases (52%). Thirty-seven patients (27%) had AX involvement, of whom 16 (12%) had bilateral halos of the AX. Among the patients with a positive CDS of the AX, only 7 (5%) had exclusive AX involvement.

The independent cohort consisted of 72 patients (female: 33; mean age 75 (7) years) with a confirmed clinical diagnosis of GCA and a positive CDS. Five subjects with a positive CDS were diagnosed as not having GCA. Sixty-three patients (87%) had at least one site with a halo at the TA (bilateral in 54% of cases). Twenty-four patients (33%) had AX involvement (bilateral in 8%). Only 6 patients had isolated AX involvement (8%).

Detailed frequencies of CDS findings and halo characteristics in each cohort are presented in Table 1. The distribution of patients according to the number of sites with halos for each cohort is presented in Supplementary Fig. S1, available at *Rheumatology* online. One vascular site showing a halo was recorded for 28% of patients in TABUL and 35% in the independent cohort. Two sites with a halo were recorded in 21% and 29% of patients, respectively. Only a minority of patients showed active involvement in more than six vascular sites (4.4% in TABUL and 0% in the independent cohort).

The clinical characteristics of the populations included in the analysis are presented in Table 2. Patients were more frequently female in TABUL compared with the independent cohort (68% *vs* 46%; $P = 0.002$); there were no significant differences in age between the two cohorts. The mean duration of GC treatment prior to CDS assessment was significantly longer in the independent cohort (14.5 (15.5) *vs* 1.9 (1.8) days; $P < 0.001$); however, GC had been prescribed significantly more frequently to patients enrolled in TABUL compared with the independent cohort (74% *vs* 53%; $P = 0.003$). Clinical presentation differed in terms of frequency of systemic symptoms (58% of cases in TABUL *vs* 19% in the independent cohort; $P < 0.001$) and PMR features, less frequently reported in TABUL patients (18% *vs* 44%; $P = 0.0001$). There were no significant differences regarding ischaemic symptoms at presentation or rate of permanent visual loss between the two cohorts.

The complete descriptive analyses of CDS findings (number of sites with halo and halo size) according to clinical diagnosis, specific TAB findings and clinical presentation are described in Supplementary Tables S1 and S2, available at *Rheumatology* online, for TABUL cohort and Supplementary Tables S3 and S4, available at *Rheumatology* online, for the independent cohort.

Ultrasound and clinical models (TABUL cohort)

The association of the four ultrasound models was tested against two main outcomes: the biopsy outcome (TAB diagnostic for GCA), $n = 76$ patients (56%), and the clinical outcome (composite prognostic measure at 6 months from diagnosis), $n = 55$ patients (41%) (Table 3). There was a significant association between total number of halos, halo thickness at the level of the TA and bilateral TA halos with the biopsy outcome. The best model (with the lowest Akaike information criterion) for a positive TAB included a combination of the following variables: maximum IMT at the TA >0.70 mm, bilateral TA halos, maximum AX IMT >1.30 mm and bilateral AX halos (model 4 CDS).

The association of the four clinical models was tested against the same two main outcomes. The best model (with the lowest Akaike information criterion) included the number of ischaemic symptoms at presentation, PMR symptoms and elevated ESR/CRP values (model 3 clinical). None of the clinical models reached statistical significance in predicting the biopsy outcome, although a significant association of elevated ESR/CRP values with the biopsy outcome was reported. None of the clinical models predicted the clinical outcome at 6 months, with only systemic symptoms showing significant association with the 6-month outcome (Table 4).

GCA-US score

By combining the best-fitting CDS and clinical models (Table 4) we derived a simple score to compute the probability of a positive biopsy. The final model area under the ROC curve was 0.77 (95% CI: 0.68, 0.84);

Table 1 Frequencies of ultrasound findings and halo characteristics considered for the analysis in the two cohorts

CDS variable	Detailed description	Frequency and halo size	
		TABUL	Independent cohort
Overall number of sites with halo	Number of sites with halo in TA + number of sites with halo in AX	128 patients with halo in TA + 37 with halo in AX; min 0, max 8 sites	63 patients with halo in TA + 24 with halo in AX; min 0, max 6 sites
Number of halos in TA	Sum of sites with halo in TA	128 patients with halo in TA; min 0, max 6 sites	63 patients with halo in TA; min 0, max 6 sites
Average halo thickness in TA	Average halo thickness among sites with halo in TA	Data available for 125 patients; average 0.6 (0.28) mm	Data available for 63 patients; average 0.56 (0.13) mm
Average halo thickness in AX	Average halo thickness among sites with halo in AX	Data available for 37 patients; average 1.3 (0.85) mm	Data available for 24 patients; average 1.38 (0.3) mm
Maximum halo thickness in TA	Maximum halo thickness among sites with halo in TA	Data available for 125 patients; min 0.1, max 3.2 mm	Data available for 63 patients; min 0.3, max 1.4 mm
Maximum halo thickness in AX	Maximum halo thickness among sites with halo in AX	Data available for 37 patients; min 0.6 mm, max 6.7 mm	Data available for 37 patients; min 1.0 mm, max 2.4 mm
Bilateral halo in TA	Defined as the presence of a bilateral halo on any branch of the TA	71 of 135 patients (52%)	39 of 72 patients (54%)
Bilateral halo in AX	Defined as the presence of a halo on both AX arteries	16 of 135 patients (12%)	6 of 72 patients (8%)

AX: axillary artery; CDS: colour duplex sonography; TABUL: TA Biopsy *vs* Ultrasound in Diagnosis of GCA.

after 10-fold cross-validation it became 0.66 (95% CI: 0.55, 0.76).

The score can be easily computed using the algorithm shown in Fig. 1 (left panel) and the expected probability of positive biopsy is derived from Fig. 1 (right panel). Two simulated cases are reported.

Application of the ultrasound and clinical models on the independent cohort

The CDS and clinical models were used to assess the association with the clinical outcome at 6 months in the independent cohort confirming the lack of association (Supplementary Tables S5 and S6, available at *Rheumatology* online).

To overcome the lack of TAB data in the independent cohort, we tested whether the predictive probability of a positive biopsy (given the clinical and CDS information) was different between the two cohorts by applying the GCA-US score, and found that there was no difference in the probability of having a positive TAB if the patients from the independent cohort had undergone a biopsy (mean probability of a positive TAB in TABUL 0.64 (0.22) compared with 0.61 (0.21) in the independent cohort; $P = 0.254$).

Given the absence of TAB data in this cohort, we could not formally validate the GCA-US score on an independent cohort.

Discussion

To the best of our knowledge, this was the first study to assess the role of quantitative information on the localization and degree of vascular involvement detected by CDS in patients with GCA. Our study demonstrates that a comprehensive analysis of specific CDS quantitative findings rather than a simple binary (positive/negative) approach can add value to the diagnostic role of ultrasound in the assessment of GCA.

In this study we identified the best CDS and clinical characteristics to identify patients with a positive TAB; these were combined in a comprehensive GCA-US score to assess the probability of a positive biopsy. However, the same models were not able to discriminate the clinical outcome at 6 months.

The gold standard for the diagnosis of GCA is still represented by characteristic histological findings on TAB [11]; however, the unsatisfactory sensitivity of this test prompted the search for more reliable, rapid and less invasive diagnostic tools. TABUL was the first study to systematically compare the role of CDS *vs* TAB in a prospective, multicentre cohort study [4]. The TABUL study demonstrated that ultrasound has a higher sensitivity (but lower specificity) compared with TAB. CDS was indeed more likely than TAB to provide evidence for a diagnosis of GCA, with a fair level of agreement between the two tests (30% discordance). Our study analysed this association in further detail by

TABLE 2 General characteristics of the two cohorts with newly suspected and clinically proven GCA patients

	Patients with GCA with positive CDS		
	TABUL ($n = 135$)	Independent cohort ($n = 72$)	*P*-value
Female, *n* (%)	92 (68)	33 (46)	0.002
Age, mean (S.D.), years	73 (8)	75 (7)	0.086
High-dose GC prior to CDS, *n* (%)	100 (74)	38 (53)	0.003
Number of days on GC on the day of CDS scan, mean (S.D.)	1.9 (1.8)	14.5 (15.5)	<0.001
TAB findings, *n* (%)			
TAB diagnostic for GCA	76 (56)	NA[a]	
Media infiltrate	20 (15)	NA	
Transmural infiltrate	26 (19)	NA	
Small vessel or adventitia	18 (13)	NA	
Laboratory findings/symptoms, *n* (%)			
Elevated ESR/CRP[b]	131 (97)[c]	70 (97)[c]	1
General symptoms pre-GC	96 (71)	29 (40)	<0.001
Headache pre-GC	93 (69)	57 (79)	0.126
Jaw claudication pre-GC	62 (46)	37 (51)	0.494
Visual symptoms pre-GC	57 (42)	40 (56)	0.055
PMR pre-GC	25 (18)	32 (44)	0.0001
General symptoms current on day of CDS	78 (58)	14 (19)	<0.001
Headache current on day of CDS	69 (51)	35 (49)	0.784
Jaw claudication current on day of CDS	39 (29)	19 (26)	0.647
Visual symptoms current on day of CDS	30 (22)	18 (25)	0.626
PMR current on day of CDS	24 (18)	20 (28)	0.096
Any visual loss[d]	22 (16)	18 (25)	0.117
Ischaemic symptoms at presentation (jaw/tongue claudication, amaurosis fugax, double vision, stroke)	81 (60)	50 (69)	0.226
Number of ischaemic symptoms at presentation, *n* (%)			0.205
0	54 (40)	22 (31)	
1	39 (29)	29 (40)	
2	37 (27)	16 (22)	
3	5 (4)	5 (7)	
BVAS 6 months, *n* (%)			
BVAS ocular	11 (8)	7 (10)	0.627
BVAS nervous	11 (8)	19 (26)	0.0004
BVAS = 0	93 (69)	39 (54)	0.033
BVAS ≥1	28 (21)	26 (36)	0.019
BVAS ≥5	12 (9)	3 (4)	0.187
BVAS ≥10	2 (1)	0	NA
VDI 6 months, *n* (%)			
VDI = 0	77 (57)	36 (50)	0.336
VDI = 1	29 (21)	17 (24)	0.621
VDI = 2	10 (7)	3 (4)	0.386
VDI = 3	1 (0.7)	3 (4)	0.093
VDI = 4	3 (2)	2 (3)	0.652
VDI = 5	1 (0.7)	1 (1)	0.818
VDI diplopia	12 (9)	12 (17)	0.089
VDI blindness	13 (10)	12 (17)	0.147
GC >10 mg/day at 6 months	39 (29)	25 (35)	0.375
Adjunctive immunosuppressive drug at 6 months[e]	12 (9)	34 (47)	<0.001

[a]In the independent cohort of patients with GCA, only one TAB was performed (and without any artery obtained in the specimen). [b]Elevated ESR/CRP: ESR >15 mm/h and or CRP >5 mg/L. [c]Data not available for two patients. [d]Any visual loss defined as: permanent visual loss in at least one eye and/or evidence of anterior ischaemic optic neuropathy due to GCA. [e]TABUL: methotrexate ($n = 10$); leflunomide ($n = 2$). Independent cohort: methotrexate ($n = 32$); leflunomide ($n = 1$); IL-6 inhibitor ($n = 1$). CDS: colour duplex sonography; GC: glucocorticoids; NA: not available; TAB: TA biopsy; TABUL: TA Biopsy *vs* Ultrasound in Diagnosis of GCA; VDI: Vasculitis Damage Index.

Table 3 Association between the ultrasound combined models and the biopsy and clinical outcome—TABUL cohort

Ultrasound models	Biopsy outcome (TAB diagnostic for GCA)				Clinical outcome (visual loss + more intensive treatment at 6 months)				
	OR	95% CI	AIC	*P*-value		OR	95% CI	AIC	*P*-value
Model 1 CDS			162.39	0.008	Model 1 CDS			172.49	0.406
Total halos	1.36	1.09, 1.69		0.007	Total halos	0.97	0.80, 1.18		0.788
Average TA IMT > 0.60 mm	2.26	1.02, 5.02		0.044	Average TA IMT > 0.60 mm	0.97	0.45, 2.07		0.932
Average AX IMT > 1.20 mm	1.15	0.47, 2.82		0.762	Average AX IMT > 1.20 mm	1.53	0.45, 3.58		0.325
Model 2 CDS			161.48	0.079	Model 2 CDS			170.53	0.790
Maximum TA IMT > 0.70 mm	4.43	2.01, 9.78		<0.001	Maximum TA IMT > 0.70 mm	1.09	0.53, 2.26		0.378
Maximum AX IMT > 1.30 mm	1.34	0.57, 3.16		0.508	Maximum AX IMT > 1.30 mm	1.48	0.66, 3.35		0.342
Model 3 CDS			156.83	0.597	Model 3 CDS			173.91	0.118
Average TA IMT > 0.60 mm	2.81	1.25, 6.33		0.013	Average TA IMT > 0.60 mm	0.90	0.43, 1.87		0.773
Bilateral TA	4.61	2.06, 10.32		<0.001	Bilateral TA	1.10	0.52, 2.33		0.796
Average AX IMT > 1.20 mm	1.72	0.57, 5.23		0.339	Average AX IMT > 1.20 mm	1.18	0.40, 3.44		0.764
Bilateral AX	1.31	0.27, 6.46		0.736	Bilateral AX	1.67	0.40, 7.06		0.485
Model 4 CDS			155.91	0.351	Model 4 CDS			173.99	0.620
Maximum TA IMT > 0.70 mm	3.16	1.36, 7.34		0.007	Maximum TA IMT > 0.70 mm	1.00	0.46, 2.19		0.994
Bilateral TA	3.53	1.56, 7.98		0.003	Bilateral TA	1.09	0.50, 2.39		0.823
Maximum AX IMT > 1.30 mm	1.54	0.52, 4.60		0.440	Maximum AX IMT > 1.30 mm	1.20	0.41, 3.48		0.737
Bilateral AX	1.15	0.23, 5.72		0.868	Bilateral AX	1.63	0.38, 6.98		0.510

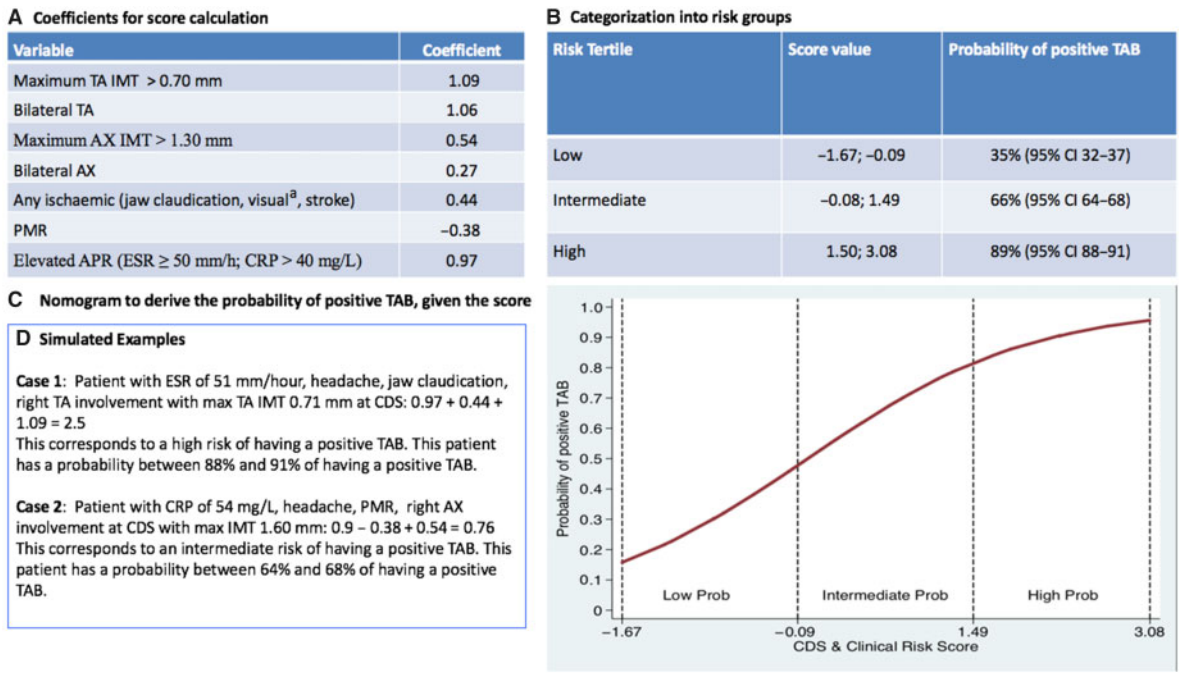
AIC: Akaike information criterion; AX: axillary arteries; CDS: colour duplex sonography; IMT: intima–media thickness; TAB: TA biopsy; TABUL: TA Biopsy *vs* Ultrasound in Diagnosis of GCA.

Table 4 Association between the clinical combined models and the biopsy and clinical outcome—TABUL cohort

Clinical models	Biopsy outcome (TAB diagnostic for GCA)				Clinical outcome (visual loss + more intensive treatment at 6 months)				
	OR	95% CI	AIC	*P*-value		OR	95% CI	AIC	*P*-value
Model 1 clinical			148.77	0.707	Model 1 clinical			147.85	0.688
Any ischaemic symptoms[a]	1.30	0.56, 3.05		0.542	Any ischaemic symptoms[a]	2.27	0.97, 5.31		0.059
PMR	0.62	0.23, 1.68		0.342	PMR	1.21	0.45, 3.25		0.707
Elevated ESR/CRP[b]	2.96	1.32, 6.66		0.009	Elevated ESR/CRP[b]	0.50	0.22, 1.12		0.093
Model 2 clinical			149.14	0.824	Model 2 clinical			147.36	0.599
Systemic symptoms[c]	0.97	0.37, 2.52		0.951	Systemic symptoms[c]	2.69	1.01, 7.17		0.048
PMR	0.66	0.24, 1.85		0.434	PMR	1.06	0.39, 2.91		0.907
Elevated ESR/CRP[b]	2.81	1.26, 6.30		0.012	Elevated ESR/CRP[b]	0.47	0.21, 1.06		0.070
Model 3 clinical			147.59	0.189	Model 3 clinical			148.59	0.543
Number of ischaemic symptoms[a]	1.33	0.84, 2.11		0.219	Number of ischaemic symptoms[a]	1.46	0.94, 2.27		0.091
PMR	0.57	0.21, 1.58		0.278	PMR	1.20	0.44, 3.24		0.719
Elevated ESR/CRP[b]	3.02	1.34, 6.78		0.008	Elevated ESR/CRP[b]	0.46	0.21, 1.03		0.059
Model 4 clinical			149.09	0.551	Model 4 clinical			147.86	0.697
Headache	0.90	0.36, 2.21		0.815	Headache	2.37	0.96, 5.87		0.061
PMR	0.68	0.25, 1.84		0.442	PMR	1.17	0.43, 3.15		0.762
Elevated ESR/CRP[b]	2.79	1.25, 6.21		0.012	Elevated ESR/CRP[b]	0.46	0.21, 1.04		0.062

[a]Ischaemic symptoms: presentation with jaw or tongue claudication, amaurosis fugax, double vision, stroke. [b]ESR ≥50 mm/h and/or CRP >40 mg/L. [c]Systemic symptoms: fever, weight loss, night sweats. AIC: Akaike information criterion; TAB: TA biopsy; TABUL: TA Biopsy *vs* Ultrasound in Diagnosis of GCA.

Fig. 1 GCA-US score



Combination of ultrasonographic and clinical models to stratify patients according to the risk of having a positive TA biopsy. [a]Visual: double vision, amaurosis fugax. APR: acute phase reactants; AX: axillary artery; IMT: intima–media thickness; TA: temporal artery.

exploring the role of specific CDS findings and not just the presence/absence of a halo. We demonstrated that several CDS parameters representing the extent of vascular involvement (total number of sites with halo, number of halos at the TA, bilateral TA halos) and the degree of vessel wall inflammation (maximum IMT at the TA) are strongly associated with a TAB consistent with GCA. The increase in specificity up to 100% in the presence of bilateral TA halos has been previously reported [12]; however, the association in terms of number and size of halos is new. Our findings suggest that having more widespread vessel involvement with a higher number of sites with halos and having a more prominent halo at the level of the TA correlate with the histological diagnosis of GCA. An increasing interest in the IMT size and its potential role in the diagnosis and/or monitoring of disease is emerging. Recently, cut-off values to distinguish IMT of patients with GCA from matched controls without vasculitis have been formally addressed in a prospective study demonstrating that halo thickness can be useful in distinguishing pathological cases from normal findings [13]. IMT of TA and AX has been analysed to identify the cut-off value ensuring the best diagnostic performance (using clinical diagnosis as the reference standard) finding IMT sizes in line with the values used in our study ($\geq$0.7 mm for TA and $\geq$1.2 mm for AX) [14].

All this evidence clarifies the association between CDS and TAB and supports what is becoming more common practice in centres with expertise in vasculitis imaging; that is to avoid TAB in patients with a clinically suggestive picture and a positive ultrasound [3]. Based on the association of the ultrasound models and several clinical and laboratory findings, we have identified a comprehensive score that best fitted with the outcome of a positive TAB. The comprehensive GCA-US score, by combining the maximum IMT size and bilaterality of halos at the level of the TA and AX with relevant clinical or laboratory variables (raised inflammatory markers, headache, ischaemic symptoms, PMR) provides a computable estimate of the probability of a positive histology, supporting the use of CDS as a surrogate diagnostic tool to replace TAB.

In the management of GCA we are in urgent need of clinical, laboratory or imaging biomarkers that would predict, at baseline, the subsequent outcome of disease. In our study, we did not identify any baseline CDS or clinical parameter that could predict a worse outcome at 6 months (visual sequelae and/or the need for more intensive treatment). In line with our findings, Schmidt *et al.* [15] had previously assessed a large cohort of consecutive patients with GCA and found no statistically significant association between number of pathological TA segments, presence of stenoses or bilateral findings and ophthalmic complications. We did not confirm the findings from Czihal *et al.* [16] who had reported a poorer response to treatment after a mean follow-up of over 2 years in 43 GCA patients with extra-cranial large vessel involvement. The shorter follow-up in our two cohorts might explain the different results. It is possible that the long-term consequence of higher degree of disease extent at baseline only becomes apparent after a longer follow-up, once the dose of GC has been significantly reduced. Nonetheless, these results might also suggest that CDS findings do not fully capture the complexity and severity of disease and, until further evidence is collected, underscore the need to always correlate imaging findings with the clinical picture and clinician's judgement.

Our study has some limitations. Some baseline characteristics of the two cohorts (TABUL and independent cohort) are different, particularly concerning the frequency of female patients and the number of days on GC treatment at the time of CDS assessment. However, the independent cohort reflects common clinical practice and represents the setting in which to apply the evidence gathered from standardized clinical studies. The need for more intensive treatment at the end of follow-up as a measure of worse prognosis can be considered a reliable indicator of a higher GC-dependent disease or more relapsing disease, but may also be biased by the treating physician's practice; nevertheless, the inclusion of patients enrolled in TABUL and of an independent cohort applying the same methodology should have limited too much variability. Finally, the short-term follow-up (6 months) might have precluded the recognition of some potential associations between ultrasound findings and long-term outcome, which will need to be addressed by further studies. This might limit prognostic ability of our tool based on a combined end point of ischaemic complications or need for intensified treatment. Finally, it is important to remember that TABUL data were acquired before definitions of cut-off data on IMT normal values were published. Minimum TABUL requirements were the use of a linear probe with grey-scale frequency of at least 10 MHz. Nevertheless, replication of the data in the more recent independent cohort with higher frequency probes (18 MHz) reached the same conclusions as those of the TABUL data.

Conclusions

In conclusion, we have demonstrated that the quantitative analysis of CDS findings (bilaterality of halos, IMT size) provides important information that can be used to support the diagnosis of patients with GCA. A simple score combining ultrasonographic and clinical information allows for a predictable risk assessment of the probability of having a positive TAB and supports the role of CDS in the diagnosis of GCA. The prognostic role of quantitative CDS findings needs to be addressed by long-term studies.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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