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The Role of Vascular Ultrasound in GCA-PMR Spectrum Disease

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Colm Kirby

March 2024

Declaration and Statement of Plagiarism

I declare that this thesis is my own work. Sources used for forming hypotheses are cited in the references section. Full and informed consent was obtained from all study participants.

Colm Kirby

March 2024

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List of abbreviations

AA Axillary Artery (or arteries)

AAUS Axillary Artery Ultrasound

ACR American College of Rheumatology

AUC Area Under Curve

cc Classification Criteria

CRP C-Reactive Protein

CS Compression Sign

cSTA Common Branch of STA

CV Cardiovascular

DMARD Disease-Modifying Anti-Rheumatic Drug

ESR Erythrocyte Sedimentation Rate

EULAR European Alliance of Associations for Rheumatology

fSTA Frontal Branch of STA

GCA Giant Cell Arteritis

HC Halo Count

HS Halo Score

IMT Intima-Media Thickness

IMTmax Maximum Measured Intima-Media Thickness

IQR Interquartile range

Lt Left-sided

LV Large Vessel

Max Maximum value

Min Minimum value

MRA Magnetic Resonance Angiography

MRI Magnetic Resonance Imaging

NPV Negative Predictive Value

OGUS OMERACT GCA US Score

OMERACT Outcome Measures for Arthritis Clinical Trials

PET Positron Emission Tomography

PMR Polymyalgia Rheumatica

PPV Positive Predictive Value

pSTA Parietal Branch of STA

PTPS Pre-Test Probability Score

Rt Right-sided

SA Subclavian Artery

SD Standard deviation

Sens Sensitivity

Spec Specificity

SSA Steroid-Sparing Agent

STA Superficial Temporal Artery (or arteries)

TAB Temporal Artery Biopsy

TAUS Temporal Artery Ultrasound

VA Vertebral Artery

VUS Vascular Ultrasound

Abstract

Background

Timely and accurate identification of 'GCA-PMR Spectrum Disease' and its subsets is important so vascular complications can be averted. Traditional diagnostic and monitoring tools such as Temporal Artery Biopsy (TAB) and serum biomarkers have many shortcomings. Vascular Ultrasound (VUS) is superseding TAB for diagnosis but its role in disease monitoring is unclear. Few studies have evaluated the prevalence and natural history of Subclinical Giant Cell Arteritis (GCA) in Polymyalgia Rheumatica (PMR).

Methods

VUS was performed in newly diagnosed GCA and PMR patients and a subset of patients had TAB and Superficial Temporal Artery (STA) Magnetic Resonance Angiography (MRA). Pre-Test Probability Score (PTPS), classification criteria and VUS quantification scores were applied to the cohort. In those with a positive baseline scan, VUS was repeated at 1, 3, 6 and 12 months. Clinical diagnosis was verified by two rheumatologists and confirmed at 6 months.

Results

In 124 patients with GCA, VUS outperformed TAB and MRA STA for a clinical diagnosis of GCA. Sensitivities (sens), specificities (spec) and 'Area Under Curve' (AUC) were as follows; VUS- 82.76%, 84.68%, 0.85; TAB- 40.4%, 100%, 0.70; MRA- 47.1%, 20.0%, 0.35. PTPS improved the performance of VUS, achieving an AUC 0.91 when used in combination with VUS. When PTPS ≥ 16 and VUS was positive, specificity for GCA diagnosis was 100%. When PTPS < 6 and VUS was

negative, sensitivity for GCA diagnosis was 100%. 2022 ACR/EULAR GCA Classification Criteria had a better sensitivity and AUC than 1990 criteria but were less specific for GCA diagnosis (sensitivities 92.4% and 72.7%, specificities 63.8% and 69.1%, AUCs 0.78 and 0.70, respectively). Intima-Media Thickness (IMT) cut-off points in this cohort differed from the currently accepted normal values. Incorporating IMT measurement into the VUS protocol substantially improved its diagnostic performance. Using the Right Frontal STA as an example; IMTmax <0.15mm had 100% sensitivity for GCA, IMTmax >0.46mm had 100% specificity for GCA. VUS quantification scores (Halo Count (HC), Halo Score (HS) and OMERACT GCA US Score (OGUS)) declined over follow-up and baseline values were more predictive of future adverse events than were all other patient variables. OGUS demonstrated the most sensitivity to change. VUS had 83% sensitivity for detecting Subclinical GCA in PMR, the prevalence of which was 24%, and these patients were likelier to require biologic therapy.

Conclusions

VUS is confirmed as the optimal diagnostic test for GCA and TAB lacks sensitivity for this purpose. PTPS has a role in evaluating suspected GCA when used in combination with VUS. 2022 ACR/EULAR Classification Criteria are more sensitive than 1990 criteria but lack adequate specificity to be used in clinical practice as diagnostic criteria. MRA of STA lacked sensitivity and specificity for GCA. Measuring IMT has a clear role in diagnosing GCA and allows for monitoring of longitudinal trends in sonographic inflammation using VUS quantification scores, of which OGUS appears the best. VUS quantification scores are more predictive of future adverse events than all other patient variables. >20% of newly-diagnosed PMR patients have Subclinical GCA. This appears to be a phenotypically distinct

subset of GCA, can be accurately identified by VUS and these patients are likely to require biologic therapy.

Lay Abstract

Background

Timely and accurate identification of 'GCA-PMR Spectrum Disease' and its subsets is important so blindness and strokes can be avoided. Traditional diagnostic and monitoring tools such as biopsy and laboratory results have many shortcomings. Little is known about VUS as a monitoring tool for GCA. Few studies have evaluated what number of PMR patients actually have underlying GCA.

Methods

VUS was performed on newly diagnosed GCA and PMR patients and a subset of patients had biopsy and arterial MRI performed. New classification criteria, PTPS and VUS quantification scores were applied to the cohort. In those with a positive baseline scan, VUS was repeated at regular intervals over 12 months. Diagnosis of GCA was established by agreement between 2 rheumatologist and was the reference against which we compared all other tests.

Results

In 124 patients, VUS was superior to biopsy and MRI for diagnosing GCA and it performed even better when we incorporated PTPS. 2022 ACR/GCA Classification Criteria are more applicable to GCA than 1990 criteria. VUS quantification scores declined over follow-up and higher baseline values were predictive of future flares of GCA as well as future requirement for additional immunosuppressive

medications. 24% of those presenting with PMR actually had underlying GCA and VUS successfully identified this in 83% of cases. These patients were likelier to require additional immunosuppressive medication.

Conclusions

VUS is the best initial test for confirming GCA diagnosis and detects more positive cases of the disease than TAB. PTPS has a role in evaluating suspected GCA when used in combination with VUS. 2022 ACR/EULAR Classification Criteria detect more positive cases of GCA than 1990 criteria but these criteria can also be fulfilled in patients who do not have GCA, so it is less useful in routine clinical practice. MRA of STA appears to be inaccurate in identifying GCA. Measuring IMT has a role in diagnosing GCA and should be considered a standard aspect of VUS in GCA diagnosis. Additionally, it allows for monitoring of longitudinal trends in VUS signs of inflammation using VUS quantification scores, of which OGUS appears the best. VUS quantification scores are more predictive of future adverse events such as future flares of GCA, than are all other patient variables such as symptoms and laboratory results. >20% of newly-diagnosed PMR patients have Subclinical GCA. These patients have distinctive clinical and biochemical characteristics, can be accurately identified by VUS and these patients are likely to require additional immunosuppressive therapy.

Hypothesis and Aims of the Project

Hypotheses:

1. VUS is the best initial diagnostic test for evaluating suspected GCA.
2. Incorporating a PTPS improves the performance of VUS.
3. 2022 ACR/EULAR GCA Classification Criteria are more applicable to real-world GCA cohorts than 1990 criteria.
4. The optimal IMT cut-off points to identify an inflamed vessel in GCA are uncertain.
5. Quantification of changes on VUS adds value to GCA diagnosis and may be a useful biomarker.
6. Subclinical GCA in those presenting with PMR is under-recognised and VUS may help identify a unique disease phenotype.

Aims:

1. To compare VUS with TAB and MRA in an inception GCA cohort and identify which tool performs best in confirming clinically-diagnosed GCA.
2. To externally validate the 2022 ACR/EULAR GCA Classification Criteria and the recently-described Southend PTPS in a prospective GCA cohort.
3. To define the optimal IMT cut-off points in STA and Axillary Arteries (AA) that distinguish a normal from an inflamed vessel.
4. To assess time-to-regression of halo and identify if any correlation exists with future disease trajectory in GCA.
5. To externally validate Halo Count, Halo Score and OGUS, identify clinical variables associated with higher baseline scores and to identify how these scores may help with disease prognostication.
6. To define the prevalence of Subclinical GCA in an inception PMR cohort and to characterise the natural history of Subclinical GCA.

Value of Research

This research highlights the superiority of VUS as the test of choice when evaluating patients with suspected GCA and equally, it shines a light on the limitations of TAB, which is the traditional gold standard diagnostic tool. VUS is less expensive, more readily available and better tolerated by patients than TAB. With growing evidence such as that outlined in this thesis, its' more widespread use should result in a better patient experience, improved patient outcomes and significant cost savings for healthcare providers.

This research also validates updated GCA Classification Criteria and confirms superiority over the previous criteria. Having externally-tested criteria such as these improves the quality of clinical trials and ultimately benefits both academics and patients in developing a better understanding of, and therapeutics for, GCA.

In this thesis, using arterial wall measurements, a framework is presented that allows clinicians to either confirm or refute a diagnosis of GCA on VUS with absolute confidence. This reference point will ultimately allow more patients to be diagnosed and treated earlier and consequently avoid potentially catastrophic events such as stroke and blindness. Additionally, fewer patients will suffer unnecessary treatment-related side effects while clinicians try to rule-out GCA in those with suggestive symptoms in whom the diagnosis is still thought to be unlikely.

This thesis shows that VUS quantification scores decrease over time. Currently, GCA lacks reliable biomarkers which causes uncertainty when monitoring response to prescribed treatments. The data presented here suggests that VUS might fill that void. This will be beneficial to clinicians and patients, resulting in more appropriate therapeutic decisions.

In validating VUS quantification scores, this study has shown associations with adverse disease outcomes such as future flares and future requirements for immunosuppressive therapies. Henceforth, higher baseline scores can identify patients who need more aggressive treatment at an earlier phase of the disease. This should ultimately limit the numbers of patients who develop blindness, strokes and large vessel complications.

This research has shown a higher-than-expected prevalence of Subclinical GCA in those presenting with PMR and a higher requirement for immunosuppressive therapies over the following 12 months. This finding is paradigm-shifting and suggests that all PMR patients should have baseline VUS as part of routine care. Earlier identification and treatment of Subclinical GCA will result in improved patient outcomes.

Outputs

1. Kirby C, Flood R, Mullan R, Murphy G, Kane D,
Evolution of Ultrasound in Giant Cell Arteritis. Front. Med, 03 October 2022 Sec.
Rheumatology
2. Kirby C, Flood R, Landers D, et al.
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Criteria. Annals of the Rheumatic Diseases 2023;82:335.
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8. Cowley S, Kirby C, Harkins P, et al.

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Clinical Phenotype of patients with Subclinical Giant Cell Arteritis in Polymyalgia Rheumatica [abstract]. *Arthritis Rheumatol.* 2023; 75 (suppl 9)

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Chapter 1: Overview of GCA-PMR Spectrum Disease and Current Diagnostic Practices

Abstract

VUS is being increasingly used to diagnose GCA. The traditional diagnostic Gold Standard has been TAB, but this is expensive, invasive, has a false-negative rate as high as 60% and has little impact on clinical decision-making. A non-compressible halo with an enlarged IMT is the sonographic hallmark of GCA. The superficial temporal arteries (STA) and AA are the most consistently inflamed arteries sonographically and imaging protocols for evaluating suspected GCA should include at least these two arterial territories. Studies evaluating VUS in GCA have varied considerably in size and methodology with results showing wide discrepancies in sensitivities (9-100%), specificities (66-100%), positive predictive values (PPV, 36-100%) and negative predictive values (NPV, 33-100%). Bilateral halos increase sensitivity as does the incorporation of pre-test probability, while prior corticosteroid use decreases sensitivity. Quantifying sonographic vasculitis using Halo Counts and Halo Scores can predict disease extent/severity, risk of specific complications and likelihood of treatment response. Regression of the Halo sign has been observed from as little as 2 days to as late as 7 months after initiation of immunosuppressive treatment and occurs at different rates in STA than AA. VUS is more sensitive than TAB and has comparable sensitivity to Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET). It is time-

efficient, cost-effective and allows for the implementation of fast-track GCA clinics which substantially mitigate the risk of irreversible blindness. Algorithms incorporating combinations of imaging modalities can achieve a 100% sensitivity and specificity for a diagnosis of GCA. VUS should be a standard first line investigation in routine clinical care of patients with suspected GCA with TAB reserved only for those having had a normal VUS in the context of a high pre-test probability.

1.1 Background

1.1.1 Giant Cell Arteritis

GCA is a vasculitis of large- and medium-sized vessels with a predilection for the aorta and its major branches (1). It is the commonest idiopathic systemic vasculitis and incidence increases with age, predominantly affecting those aged greater than 70 years (2). Incidence is higher in Northern Europeans with a 1% lifetime risk for women versus 0.5% for men (3). Typical symptoms include headache, visual disturbance, jaw claudication and polymyalgia while examination findings may reveal thickening of the STA, scalp tenderness or large vessel bruits. Laboratory results are usually compatible with a strong acute phase response and typically reveal elevations in Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP) and platelets. The traditional gold standard for diagnosis involves performing a TAB which is costly, invasive, has a high false-negative rate and ultimately has little bearing on clinical decision-making (4-6). GCA is a medical emergency and requires prompt diagnosis and initiation of corticosteroids to prevent the most severe complications of stroke and/or irreversible blindness (7). Visual loss occurs in 30% and is permanent in 10-15% (8). In addition to corticosteroids, conventional Disease-Modifying Anti-Rheumatic Drugs (DMARDs) and biologic agents are mainstays of treatment, particularly in those with complicated or refractory disease trajectories (9, 10). Prognosis is variable and vascular complications are common with a 4-fold increased risk of myocardial infarction and a 2.5-fold increased risk of stroke or aneurysms relative to matched controls (11-13).

1.1.2 Polymyalgia Rheumatica

PMR is a disease characterised by acute onset pain and stiffness in the shoulders and proximal upper limbs, hips and proximal lower limbs (14). Prolonged early morning stiffness is a prominent feature and a high prevalence of constitutional symptoms can often mimic infection or malignancy (15). It predominantly affects those over the age of 70 but appears to exclusively affect those over 50 years old and is more common in females and those of northern European descent (16, 17). The prevalence of PMR is estimated to be between 0.12 and 2.3 cases/1000 individuals aged over 50 years (18). The aetiology of PMR is unclear but various studies have linked disease onset with vaccinations as well as viral infections including COVID-19 (16, 19-21). Clinical examination can be non-specific but may reveal tenderness and limited range of motion in shoulders and hips but crucially, no true muscle weakness exists. Imaging studies have shown that the pathology underlying the symptoms associated with PMR include glenohumeral and hip joint synovitis, biceps tendinitis and bursitis of the subacromial, trochanteric and ischial bursae (22-25). Laboratory results classically show elevations in ESR, CRP and platelets. Unfortunately, there is no single diagnostic test for PMR, rather it is a clinical diagnosis based on presentation, laboratory results and response to treatment. Rapid response (<1 week) to no more than 20 mg/ day of prednisolone is considered to be compatible with the diagnosis (26). In 2012, classification criteria were published for PMR (27). While glucocorticoids are the mainstay of treatment, DMARDs such as methotrexate are frequently required in the event of relapsing disease (28). A number of recent studies have shown promising results for immunotherapies blocking interleukin 6, interleukin 17a and the Janus Kinase

pathway, among others (29-34). The prognosis for PMR is generally good, with a life-expectancy the same as that of matched controls (35).

1.1.3 GCA-PMR Spectrum Disease

There is considerable overlap between GCA and PMR but similarities and differences exist. Both are more common in the elderly and in women, both are associated with a strong acute-phase response and they are both characteristically steroid-responsive. Those with isolated PMR tend to be younger with a less intense acute inflammatory response while GCA is associated with more vascular complications (36). The association between PMR and GCA is strong and well-established and it has been shown repeatedly that approximately 50% of GCA patients have PMR as a feature of their disease (37-40). PMR can precede, coincide with or occur after the onset of GCA, and vice versa. The inextricable link between these two conditions has resulted in the recent description of 'GCA-PMR Spectrum Disease' (41).

Since the early 80s, it has been recognized that up to 53% of GCA cases may present atypically with PMR and Pyrexia of Unknown Origin being particularly common presentations (42, 43). However, early studies evaluating this phenomenon showed low rates of TAB positivity in those presenting with 'pure PMR' (i.e. no cranial symptoms) while other studies suggested prevalence rates varying from 2% to 32% for GCA in those presenting with PMR (44-49). Recent meta-analyses have shown a point-prevalence of GCA at PMR diagnosis, so-called "Subclinical GCA", of 22%-23% with slightly higher rates seen in studies that incorporated PET/CT imaging as part of their diagnostic protocol searching for

underlying GCA (40, 50). In this context, Subclinical GCA refers to those patients who present with Pure PMR but actually have underlying GCA.

The importance of identifying Subclinical GCA in PMR has been emphasized by many studies which show that the prognosis differs to that of 'Isolated PMR' (i.e. Pure PMR with no underlying Subclinical GCA) with more prevalent ocular ischaemic complications, stroke and inflammatory and structural disease of the aorta, with complication rates being reported as high as 50% (12, 51). Phenotypic and laboratory parameters may help in identifying these patients. Those with Subclinical GCA tend to be older, are more likely to have an abnormal STA on exam and have lower haemoglobin and higher acute-phase reactants such as platelets and ESR (36, 52, 53). However, more sensitive tools are needed and given the greater access to ultrasound (US) compared with other imaging modalities, recent research has focused on this area.

1.1.4 GCA classification criteria

In 2022, the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) published updated classification criteria for GCA, replacing the 1990 ACR Classification Criteria which were devised before the prevalent use of advanced vascular imaging tools (54). The 1990 criteria (Table 1.01) were limited by focusing solely on cranial symptoms and also by giving equal weighting to each individual criterion and were shown to have poor sensitivity when applied to modern GCA cohorts (55). In developing the updated criteria, a steering committee comprising of 56 international vasculitis experts identified candidate classification items (>1000) which were then interrogated in a prospective

multicenter observational study of 6991 patients. GCA diagnosis within 2 years of study enrollment was required, while comparator patients with other vasculitides and vasculitis mimics were also recruited. Committee members each examined 50 cases and a diagnosis of GCA was established if 2 reviewers agreed with moderate certainty regarding the diagnosis. 756 GCA cases, confirmed after expert review, were randomly selected for analysis along with 749 comparators.

Criteria
Age ≥ 50
New headache
Temporal artery abnormality (tender, diminished pulsation)
Elevated ESR ≥ 50
Abnormal temporal artery biopsy

Table 1.01: 1990 ACR GCA Classification Criteria. A total score of at least 3/5 had a sensitivity of 93.5% and a specificity of 91.2% for a diagnosis of GCA.

A data-driven process followed to reduce the number of candidate criteria with those having a $<5\%$ prevalence in the study ultimately being excluded, leaving 72 candidate items. Lasso regression of these 72 items identified 27 potential independent predictor variables, each of which was examined in terms of the odds ratio and specificity for GCA. Weighting for each criterion was based on their respective regression coefficient meaning that more discriminatory items factored more heavily. The final classification criteria were validated in an independent cohort of GCA cases with testing being done for study subsets based on clinical phenotype and diagnostic methods employed. The final criteria are outlined in

Table 1.02, with a cut-off >5 in total risk score having a sensitivity of 87%, a specificity of 94.8% and an AUC 0.91 for a diagnosis of GCA. The performance of the criteria for different study subset including biopsy-proven and Large Vessel GCA (LV GCA) are outlined in Table 1.03.

When 1990 ACR Classification Criteria were applied to the data set sensitivity was 80.3%, specificity was 92.5% but sensitivity for LV GCA was particularly poor at 37.1%. These new criteria incorporate modern imaging modalities and perform to a high standard in a large multinational cohort of GCA patients. Importantly, they are classification criteria and not diagnostic criteria, so GCA mimics must be excluded before these criteria can be applied to an individual patient. Although there was a lack of standardization in diagnostic methods across different study sites, these criteria allow for flexibility in application of criteria and are more reflective of real-world practice where no single common diagnostic test is currently used by all clinicians to definitively diagnose or out-rule GCA.

In a study of 133 suspected GCA cases (53 confirmed clinically), the new criteria had an AUC of 0.96 (95% CI 0.92-0.98). Using a cut-off >5 points, sensitivity was 98% but specificity was only 57.5%, with 34 of 80 non-GCA patients being misclassified as having GCA. Applying a cut-off of >6, sensitivity remained high at 96.2% and specificity improved to 71.3% (56). In another retrospective multicenter study of 319 patients (188 GCA cases diagnosed clinically, 131 controls) the 2022 criteria had a sensitivity 92.6%, specificity of 71.8% and an AUC of 0.93 (95% CI 0.90 to 0.96). When the 1990 criteria were applied to this cohort sensitivity fell to 53.2% but specificity increased to 80.2% (57).

Absolute requirements	Age >49	
		Weighting
Clinical Criteria	Morning stiffness shoulders/neck	+2
	Sudden visual loss	+3
	Jaw or tongue claudication	+2
	New temporal headache	+2
	Scalp tenderness	+2
	Abnormal examination of temporal artery	+2
Laboratory, imaging and biopsy criteria	ESR $\geq$ 50 or CRP $\geq$ 10	+3
	Positive TAB or US	+5
	Bilateral AA involvement	+2
	FDG-PET activity in aorta	+2

Table 1.02: 2022 ACR/EULAR GCA Classification Criteria. Score >5 has a sensitivity of 87% and a specificity of 94.8% for a diagnosis of GCA (54).

Only one other published study has sought to validate the new criteria. In a cohort of 136 patients with GCA confirmed on either biopsy or imaging, the 2022 criteria had a sensitivity of 92.6% (higher for cranial than for extracranial GCA) and a specificity of 85.2%. When applying 1990 criteria, specificity was similar but sensitivity fell to 66.1% (58).

Subset	Sample Size (GCA)	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
Development data set	1054 (518)	84.8% (81.4 - 87.7)	95.0% (92.8 - 96.7)	0.90 (0.88 - 0.92)
Validation data set	451 (238)	87.0% (82.0 - 91.0)	94.8% (91.0 - 97.4)	0.91 (0.88 - 0.94)
Biopsy-proven GCA	1104 (355)	100% (99.0 - 100.0)	94.9% (93.1 - 96.4)	0.97 (0.97 - 0.98)
Large-vessel GCA	873 (124)	55.7% (46.5 - 64.6)	94.9% (93.1 - 96.4)	0.75 (0.71 - 0.80)

Table 1.03: Performance of 2022 EULAR/ACR GCA Classification Criteria in different study subsets (54).

1.1.5 Temporal Artery Biopsy

Despite the increasing use of VUS in recent years, TAB is the traditional gold standard for diagnosis and still has high value as a diagnostic test considering its specificity of 100%. TAB has many shortcomings which make it an undesirable test to rely upon when assessing suspected cases of GCA. Not only is it costly and invasive, but it has been shown to have a false negative rate as high as 60% with inadequate tissue sampling, skip lesions and pre-operative steroid use all contributing factors (5). Additionally, its impact on clinical decision-making is questionable. In routine clinical practice, most patients with suspected GCA are treated empirically for the disease whilst a confirmatory test is awaited, often a

TAB. A growing body of evidence suggests that TAB result ultimately has little bearing on whether or not treatment is continued (6).

Alberts et al performed a retrospective analysis of the clinical decisions made after a negative TAB versus those made after a negative TAUS. This cohort included 290 patients in whom GCA was suspected, with a subsequent negative diagnostic test, 147 of whom had a negative bilateral TAUS and 143 of whom had a negative unilateral TAB. Interestingly, there was no between-group difference in the number of patients who had steroids discontinued, despite further stratification accounting for the pre-test probability of having GCA, and no between-group differences were noted in adverse outcomes (including blindness) or number of alternative diagnoses considered. These findings suggested that TAUS was serving the same purpose as TAB but without the associated procedural risks (6). In another retrospective cohort of 264 patients who underwent TAB, of which only 8% were positive, 41% of those with negative biopsies had corticosteroid therapy continued anyway (59). To complement these findings, *Bowling et al* reported that while only 13.2% of 129 TABs were positive, 87.3% of biopsy-negative patients continued prednisolone therapy for GCA on clinical grounds, while other studies have confirmed the relatively high cost (\$452 vs \$170) and comparatively low yield of TAB compared with TAUS (60, 61).

Thus, the studies above suggest that not only are most TABs that are performed negative, but negative TABs have little impact on clinical decision-making. Importantly, it has been shown that incorporating TAUS into the workup for suspected GCA increases the positive yield from TAB from 8.5% to 24% with an associated 38% reduction in the number of TABs being performed (62).

Author	Year	Sample Size	Key findings
Alberts (6)	2007	290 (147 TAUS, 143 TAB)	No between-group difference in steroid discontinuation
Cristaudo (61)	2016	50 TAB	38/50 fulfilled ACR classification criteria, 2/50 TABs positive
Bowling (60)	2017	129 TAB	87.3% of TAB-negative patients continued prednisolone
Deyholos (59)	2020	264 TAB	41% of TAB-negative patients continued prednisolone

Table 1.04: Studies evaluating the impact of TAB on therapeutic decisions.

1.1.6 Vascular Ultrasound in PMR and GCA

In recent years, the use of VUS in assessing cases of suspected GCA has increased considerably. The definitions of what constitutes vasculitis on US are still evolving as is our understanding of its true place not only in the diagnosis, but also in the long-term monitoring of GCA. A non-compressible ‘Halo’ sign in a vessel with an enlarged IMT implies Superficial Temporal Artery (STA) vasculitis while the Halo and ‘Slope’ signs signify the presence of Axillary Artery (AA) vasculitis (63-66). Early VUS studies appeared to show low little or no Subclinical GCA in those presenting with pure PMR however the technology available at the time was less sophisticated than it is now (47, 67). More recent studies using contemporary technology and standardized scanning protocols suggest that over 20% of new PMR patients have Subclinical GCA as defined by VUS (68, 69).

1.1.7 MRI in diagnosing GCA

The role of MRI in evaluating large arteries in suspected cases of GCA is well-established, both in terms of initial diagnosis and more recently in disease-monitoring (70, 71). Its high resolution allows us to accurately and non-invasively delineate oedema and depict vessel wall thickness (72). However, much less is known about the role of MRI with/without angiography (MRA) in visualising STA in those with suspected GCA, or indeed in the monitoring of patients with confirmed GCA. Much of our understanding of the use of STA MRA comes from case reports, with a dearth of large-scale studies published to date.

1.2 Defining the presence of Vasculitis on Ultrasound

1.2.1 Historical predecessors of Ultrasound in GCA

The first report of dedicated temporal artery imaging comes from Aberdeen in 1969 when *Gillanders* described a novel but invasive technique for STA arteriography in a series of 15 patients (73). This procedure involved the operator cannulating the STA and injecting a contrast medium (hypaque) prior to performing X-Ray.

Although it was deemed to have some diagnostic purpose, its primary value was in identifying the most appropriate site for TAB and its use continued until 1980 when a study of 33 patients highlighted its' weak diagnostic potential relative to TAB (74).

The first documented use of VUS in assessing GCA came in 1978 but early studies

demonstrated varying sensitivities of 40% - 90% (75-78). In 1984, *Vinickier et al* demonstrated stenosis involving the facial, occipital, ophthalmic and temporal arteries in a series of GCA patients which they later confirmed in a larger cohort, revealing a sensitivity of 80% for changes in the STA and facial arteries (79, 80). Most of the early uses of VUS in GCA involved velocimetry, often specifically examining the blood flow to the orbit and owing to the technology at the time, little or no information on the morphology of the vessel wall was attainable (81).

1.2.2 Halo Sign

In 1995 *Schmidt* first described, what still remains to this day, the cardinal sonographic hallmark of vasculitis- 'The Halo Sign' (63). It describes a sonographically hypoechoic ring of inflamed, oedematous vessel wall, surrounding the lumen of an artery. In a prospective study of 30 patients with clinically diagnosed GCA, confirmed by 2 independent rheumatologists, 22/30 had a Halo sign identified in their STA, bilaterally in 17, and the rate of agreement between the two sonographers was 100%. No Halo sign was identified in the 82 patients who had GCA excluded on clinical grounds (82).

1.2.3 Compression Sign

In 2012, a new sonographic hallmark of vasculitis was reported: 'The Compression Sign' (CS). In a prospective study of 80 suspected cases of GCA (43 ultimately diagnosed as GCA based on ACR criteria), all participants had bilateral TAUS performed, examining for the presence of Halo sign and/or Compression sign. The Compression sign was defined as persistent visibility of the STA despite

transducer-imposed arterial compression (i.e. persistent contrasting echogenicity between vessel wall and surrounding tissue). Three physician-sonographers were involved in scanning and were blinded to the clinical details of the case.

Interestingly, the Halo sign and Compression sign were both observed in 34/43 GCA patients and both signs were absent in all patients in the non-GCA group, showing a sensitivity and specificity of 79% and 100% respectively for both signs in diagnosing GCA (83, 84).

In 2018, the Outcome Measures for Arthritis Clinical Trials (OMERACT) Large Vessel Vasculitis (LVV) US working group defined the Halo and Compression Signs as the most significant sonographic abnormalities of GCA with inter-rater agreements of 91-99% and mean kappa values of 0.83-0.98 for both inter-rater and intra-rater reliabilities. The group defined the Halo Sign as “homogenous, hypoechoic wall thickening, well delineated towards the luminal side, visible both in longitudinal and transverse planes, most commonly concentric in transverse scans”. The Compression Sign was defined as being assessed “by applying pressure via the transducer until the lumen of the temporal artery occludes and no arterial pulsation remains visible” (64). A recent cross-sectional study of 20 patients with GCA showed a kappa coefficient for agreement of the 2 signs of 0.67 (95% confident interval: 0.54-0.85). When combined, both signs had better sensitivity than either sign in isolation, for a diagnosis of GCA (85).

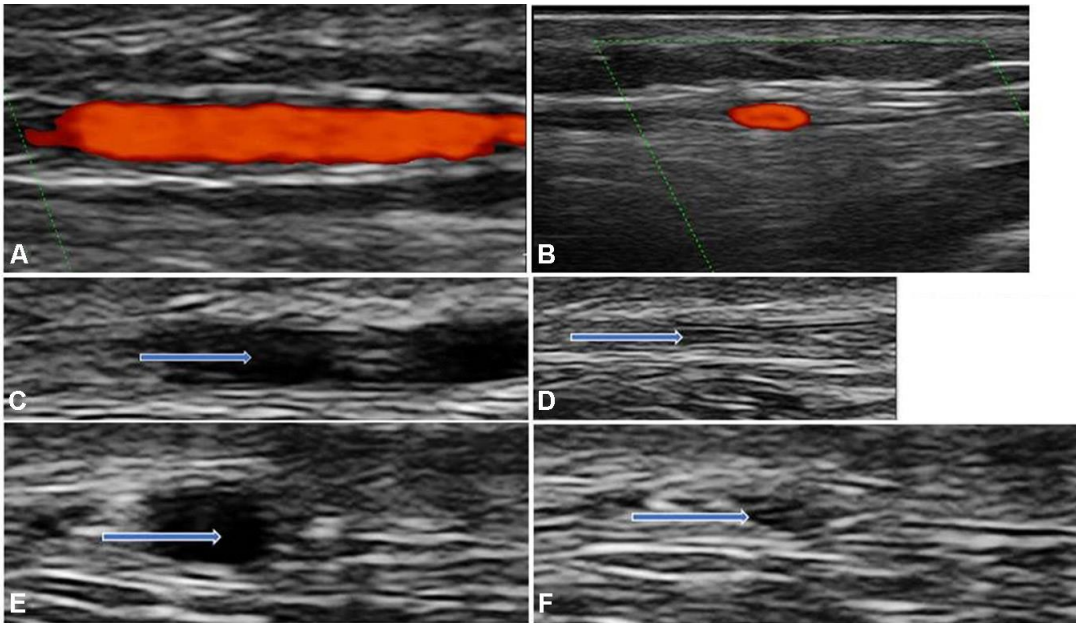


Figure 1.01: Normal Superficial Temporal Artery Ultrasound. A- Longitudinal view. B- Transverse view. C- Longitudinal view before compression. D- Longitudinal view with compression. E- Transverse view before compression. F- Transverse view with compression (64).

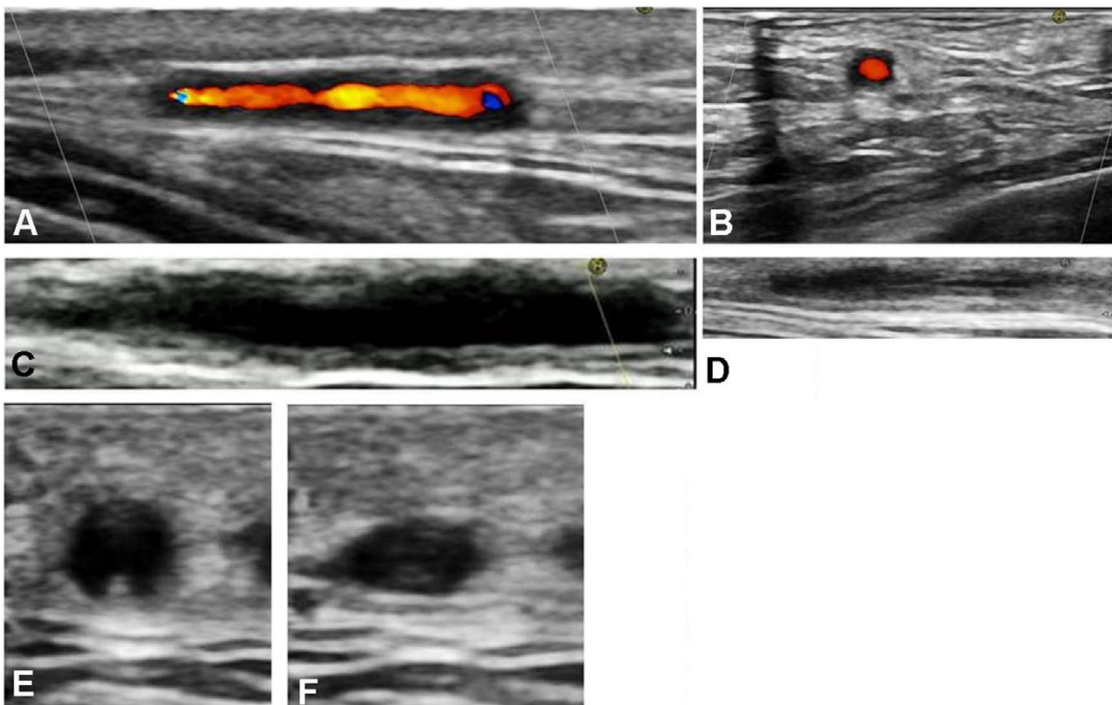


Figure 1.02: Abnormal Superficial Temporal Artery Ultrasound. A- Longitudinal view with halo sign. B- Transverse view with halo sign. C- Longitudinal view before compression. D- Longitudinal view with compression sign. E- Transverse view before compression. F- Transverse view with compression sign (64).

1.2.4 Slope Sign

More recently, the 'Slope Sign' of AA vasculitis has been described. This sign describes a long, thickened segment of inflamed arterial wall that slides down to a normal intima-media structure (double line). In 214 patients referred to a fast-track GCA clinic, 81 were diagnosed with GCA, 23 of whom had axillary vasculitis. The slope sign was observed in all patients with AA vasculitis (65, 66).

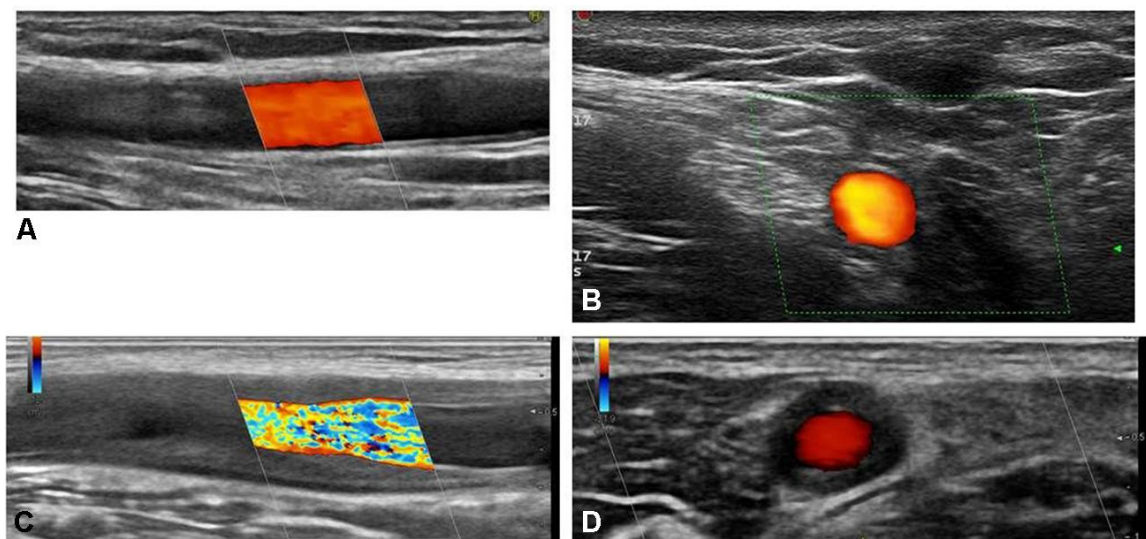


Figure 1.03: Axillary artery US. A- Longitudinal view (normal). B- Transverse view (normal). C- Longitudinal view with Halo sign. D- Transverse view with Halo sign (64).

1.2.5 Normal Intima-Media Thickness measurements

In 2017, normal cut-off values for the IMT of arteries involved in GCA were first published. IMT measurements of the STA, facial arteries and AA in 40 new GCA

cases and 40 controls were obtained, with the gold standard being a clinical diagnosis of GCA. The cut-off values with sensitivities and specificities of the various arterial segments for a diagnosis of GCA are outlined in Table 1.05, with similar results later being found in a larger study of 248 patients (86, 87). A recent study looked at 101 patients aged > 50 years, without a diagnosis of GCA or PMR, but with varying degrees of perceived cardiovascular (CV) risk. US of STA and AA were performed on all and notably, in those deemed to have high/very high CV risk, mean IMT was greater than in those with moderate/ low risk both in STA and AA. IMT was greater than standard normal cut-off values in at least one artery in 10.1% of patients, 80% of whom had very high/ high CV risk (88).

Arterial Branch	IMT Cut-off (mm)	Sensitivity	Specificity
Common Branch of STA	0.42	100%	100%
Frontal Branch of STA	0.34	100%	100%
Parietal Branch of STA	0.29	97.2%	98.7%
Axillary Artery	1.0	100%	100%

Table 1.05: IMT cut-off values for defining a vasculitic artery, with sensitivities and specificities for a clinical diagnosis of GCA (86).

1.2.6 Distribution of Pathology on Ultrasound in GCA

Up until 2002, the frequency and location of peripheral arterial sonographic changes in GCA was unknown. In 10/33 GCA patients in one study, a Halo could be demonstrated in peripheral arteries but importantly, sonographic vasculitis was consistently present in STA and/or AA if also present elsewhere (89). Additionally,

it has been demonstrated that performing Axillary Artery Ultrasound (AAUS) increases the diagnostic yield for large-vessel GCA with a detection-rate of 98% versus 62% for Temporal Artery Ultrasound (TAUS) alone, while asymptomatic abdominal aortic aneurysms may be detected in 33% of biopsy-proven GCA cases on VUS despite no clinical evidence of same (90-93). Other studies have consistently shown varying degrees of involvement of vertebral (VA), carotid and femero-popliteal arteries while the addition of occipital and facial arteries appears to only marginally increase the yield from VUS (94-98).

Author	Year	Sample Size	Key findings
Schmidt (63)	1995	10	Halo: Sen, Spec, PPV, NPV of 100%
Schmidt (82)	1997	30	Halo: Sen 73% (versus 84% for TAB), Spec 100%, PPV 100%, NPV 91%
Aschwanden (83)	2013	43	Halo and CS independently had Sen 79%, Spec 100%, PPV 100%, NPV 80%. TAB: Sen 53%, Spec 100%, PPV 100%, NPV 45%
De Miguel (99)	2018	40	STA IMT cut-off >0.34mm in more than one branch improves specificity of halo
Milchert (65)	2019	23	Slope sign present in 23/23 patients with AA vasculitis
Fernandez-Fernandez (100)	2020	291	14/305 false positive Halos
Ješe (87)	2021	248	Halo with CS seen in 244. Best IMT Cut-offs: ≥ 0.4 mm for STA, facial and occipital arteries, ≥ 0.7 mm for VA, ≥ 1 mm for carotid, subclavian artery (SA) and AA
Czihal (101)	2021	30	STA cut-off value of ≥ 0.7 mm: sen 100%, spec 84.5%. Sen reduced in males >70 years. Combined STA/AA IMT cut-off ≥ 0.7 mm/1.2 mm: Sen 91.4%
Martire (88)	2021	101	IMT > normal cut-off in 10.1%, 80% of whom had very high/ high CV risk

Table 1.06: Studies informing the sonographic definition of vasculitis.

In a cohort of 92 patients with GCA, the sensitivity of VUS increased from 69.6% to 84.8% by performing AAUS in addition to TAUS, as opposed to TAUS alone while no false positive AAUS were reported (102). In another cohort of 168 patients with suspected GCA, addition of SA US (with a cut-off IMT of 1.5mm) did not improve the sensitivity over and above that of TAUS and AAUS, while using lower cut-offs yielded many false-positive results (103). In 72 patients with US-confirmed GCA in Spain, 24 (33.3%) had LVV on PET-CT, only 2 of whom had negative US imaging of large vessels, suggesting that those with no evidence of LV GCA on VUS (carotid, SA, axillary) are at low risk for having aortitis (104). One recent study of 133 patients who fulfilled 1990 ACR classification criteria and had a positive baseline VUS compared limited (AA only) versus extended (carotid, VA, SA and AA) large vessel imaging in addition to TAUS. In using the limited VUS protocol, 5 cases of GCA would have been missed but average examination time doubled (105). A recent editorial by *Wolfgang Schmidt* highlights important points to consider when determining the VUS scanning protocol to be used and suggests that while combined TAUS and AAUS is the most efficient with a high degree of sensitivity, if negative, then other symptomatic sites should also be interrogated (106).

Thus, the literature to date suggests that not only is there widespread involvement of large vessels, but the abdominal aorta and lower limb arteries are often sub-clinically involved. Additionally, numerous studies highlight that AAUS increases the diagnostic yield when added to TAUS but importantly, STA and AA are the most consistently inflamed arteries sonographically. Therefore, any VUS protocol for assessing suspected GCA should, as a minimum, interrogate these two arterial territories.

Author	Year	Sample Size	Key findings
Schmidt (89)	2002	33	10/33 had peripheral arterial involvement, 2/10 symptomatic. Sonographic vasculitis present in STA and/or AA if also present elsewhere.
Agard (91)	2007	30	10/30 had periaortic halo on abdominal US.
Schmidt (90)	2008	53	AA involvement 98%, SA 61%, brachial 21%.
Agard (107)	2009	20	VUS suggestive of aortitis in 8 cases, 7/8 had a halo, 3/8 had aneurysm, all asymptomatic.
Aschwanden (108)	2010	38	21/38 GCA patients had abnormal VUS, LVV in 12/21 cases.
Garcia-Garcia (109)	2011	1237	5/1237 stroke patients had VA vasculitis on US, all had posterior circulation syndrome.
Ghinoi (110)	2012	62	LVV in 29% cases on VUS.
Czihal (95)	2012	112	LVV 53.6%: AA 48.2%, Femoro-popliteal 53%.
Ješe (96)	2017	93	Addition of facial and occipital artery US identified only 4.3% more GCA patients.
Gehlen (94)	2018	35	VA vasculitis in 22% (only half had posterior circulatory symptoms). All had evidence of STA or SA involvement also.
Zachrisson (98)	2018	29	8/29 patients with sonographic signs of LVV had a diagnosis other than LVV.
Hop (111)	2020	41	Addition of AAUS to TAUS improved sensitivity from 52% to 71%.
Nielsen (93)	2020	46	Addition of LV US to TAUS improved sensitivity from 71% to 97%.
Prearo (102)	2022	92	Addition of AAUS to TAUS improved sensitivity from 69.6% to 84.8%.
Oshinsky (103)	2023	168	Addition of SA US did not improve the sensitivity of VUS.
Molina-Collada (104)	2023	72	24 had LVV on PET, only 2 of whom had negative US imaging of LV.
Bull Haaversen (105)	2023	133	Using limited versus extended US protocol, 5 cases of GCA would have been missed but average examination time doubled.
Nakajima (112)	2023	2893	Addition of AAUS to TAUS improved sensitivity.

Table 1.07: Studies informing the optimal VUS protocol for GCA.

1.2.7 Summary

While early sonographic definitions of vasculitis included the presence of vessel stenosis and occlusions, the conventional standard is to diagnose vasculitis based on the presence of a Halo Sign, a non-compressible artery (Compression Sign) with an enlarged IMT. The precision of these definitions remains a constant process of refinement and further research is needed in this field to further specify normal/abnormal IMT values. Additionally, false-positive ultrasounds can occur, as demonstrated in a cohort of 305 patients in whom TAUS confirmed the presence of a Halo sign, but 14 of whom ultimately had a variety of diagnoses other than GCA. CV risk profile, age and sex are potentially important factors contributing to false positive VUS and should be considered when interpreting IMT measurements, although this is not currently part of routine practice (88, 99-101).

1.3 VUS and TAB in Diagnosing and Monitoring GCA

1.3.1 VUS versus TAB in GCA Diagnosis

Many studies have interrogated VUS as a diagnostic tool in GCA over the past two decades but have varied considerably in size and methodology with results showing wide discrepancies in sensitivity (9-100%), specificity (66-100%), positive predictive value (36-100%) and negative predictive value (33-100%) for a clinical or histological diagnosis of GCA (113-118). In 2005, *Karassa et al* undertook the first meta-analysis including all studies of >4 patients, which investigated the sensitivity and specificity of TAUS in GCA, using TAB or ACR classification criteria as the gold standard. 23 studies of 2036 patients demonstrated a weighted sensitivity and specificity of the Halo sign of 69% and 82% respectively, compared with biopsy, and 55% and 94% respectively, compared with ACR classification criteria. The studies included were mostly small with heterogeneous methodologies but they did show that in the presence of a low pre-test probability of GCA, a negative ultrasound can help out-rule the diagnosis (119).

A second meta-analysis was published in 2010 specifically examining the Halo sign and included 8 studies of 575 patients (204 with GCA). Unilateral Halo sign achieved an overall sensitivity and specificity of 68% and 91% respectively for GCA. The odds of having GCA in patients with a Halo sign versus in those without (pooled diagnostic odds ratio) was 34 (120). A systematic review by *Ball* evaluated studies comparing TAUS and TAB and included 17 homogeneous studies of 998 patients. When the sonographic Halo was compared with TAB, the sensitivity was 75% and the specificity was 83%, leading the authors to conclude that TAUS was

relatively accurate for diagnosing GCA and had promise as a first-line investigation, perhaps with TAB being reserved only for those with a normal TAUS (121).

The seminal TABUL study was published in 2016 and showed that VUS was more sensitive and cost effective than TAB in investigating suspected GCA and importantly, the sensitivity of TAB was only 39% versus previously published figures of >80%. In this prospective, multicentre study of 381 patients (257 with a reference standard clinical diagnosis of GCA, 124 without), all patients underwent VUS followed by TAB within 7 days of commencing treatment for GCA. 101 patients and 162 patients had positive TAB and VUS respectively, with concordant results in 70% (kappa value 0.35). The sensitivities and specificities of biopsy and ultrasound were 39% and 100%, and 54% and 81%, respectively. Positive biopsy rate fell after 3 days of high-dose glucocorticoids whereas VUS abnormalities regressed within 4 days, a finding which concurred with those of a number of other studies highlighting the prompt regression of the Halo sign in those on corticosteroids (82, 122, 123). Of note, the authors demonstrated that a strategy of combining clinical assessment with VUS results was substantially cheaper (£485 per patient) than combining clinical assessment with biopsy (5). In 2018, EULAR published guidelines on the use of imaging in LVV. Informing these guidelines was a systematic review performed by *Duftner et al.* TAUS (8 studies, 605 patients) yielded a pooled sensitivity of 77% and specificity of 96% for a clinical diagnosis of GCA (2). Another meta-analysis published in 2019 reported a sensitivity for Halo of 68% and specificity of 81% when compared to positive TAB, based on 20 studies (124).

A comprehensive summary of all studies relating to VUS in the evaluation of suspected GCA is tabulated in Appendices 1.1-1.3. Most of the conflicting results in

the literature to date likely relate to heterogeneous methodologies, variances in sonographer technique and/or advances in ultrasound technology. The ever-expanding literature in this field has also shown us that the presence of bilateral halos increases sensitivity of VUS as does the incorporation of pre-test probability, while duration of prior corticosteroid use correlates inversely with likelihood of having a positive scan (125).

1.3.2 VUS in predicting GCA phenotype and prognosis

A number of studies over the past 15 years have investigated how specific patterns of sonographic changes might correlate with clinical features and even help predict disease course. *Gribbons et al* showed that vascular imaging “identifies clinical subsets of patients based on involvement of temporal and extracranial arteries.” 942 patients, recruited from 72 sites, were divided into 4 subsets based on STA abnormalities (histologic or sonographic) and/or evidence of sonographic LVV. 51% of patients had an STA abnormality without evidence of LVV and this subset had a high burden of cranial ischaemia while 26% of patients had normal STA and no evidence of LVV and this group had a high rate of cranial ischaemia and musculoskeletal symptoms.

Author	Year	Sample Size	Reference Standard	US Definition of Vasculitis	Sens	Spec
Karassa (119)	2005	2036	CD	Halo	55%	94%
			TAB	Halo	69%	82%
Arida (120)	2010	575	CD	Unilateral Halo	68%	91%
Ball (121)	2010	998	TAB	Halo/stenosis/occlusion	75%	83%
Duftner (2)	2018	605	CD	Halo	77%	96%
			CD	MRI Cranial Arteries	73%	88%
			CD/ TAB	PET-CT	67- 77%	66- 100%
Rinagel (124)	2019	1062	TAB	Halo	68%	81%
Nakajima (112)	2023	2893	CD	Halo	76%	93%

Table 1.08: Meta-analyses and systematic reviews relating to VUS in GCA. CD= Clinical Diagnosis.

The 12% of patients with normal STA and positive LVV imaging for vasculitis had a high prevalence of upper limb vascular abnormalities but few visual complications. 11% had abnormal STA and LVV on imaging and these patients had a high

prevalence of cranial ischaemia and elevated inflammatory markers (126). Other studies have confirmed that STA involvement without AA involvement is predictive of ocular disease with a stronger association being seen for those with bilateral Halos, while involvement of AA irrespective of STA involvement appears to confer ocular protection (95, 126-131). Involvement of both STA and AA is associated with a significantly higher risk of relapse and a more frequent requirement for steroid-sparing agents (SSA) relative to those patients with either isolated cranial or isolated upper limb GCA. A similar association was observed for higher baseline Halo Count and Halo Score (132, 133). In a study of 67 patients with AA vasculitis on US and 34 patients with cranial GCA, those with AA involvement had a longer median interval until discontinuation of steroid treatment (42 months versus 30 months) and numerically higher median cumulative steroid dose (134).

Therefore, available evidence suggests that the presence and distribution of Halos as well as their size and frequency, are associated with disease extent and severity in GCA.

Author	Year	Sample Size	Key findings
Schmidt (130)	2003	36	Positive correlation between bilateral halo and ocular involvement.
Pfadenhauer (135)	2007	132	More sonographic abnormalities in the STA (81% vs 62%) and periorbital (32% vs 5%) arteries seen in GCA patients with, as opposed to without, neuro-ophthalmic complications .
Schmidt (128)	2009	222	Greater number of patients without UL vasculitis had ocular involvement (34% vs 18%).
Czihal (95)	2012	110	Extracranial GCA: younger, fewer visual complications, longer time to diagnosis, often did not fulfil ACR criteria.
Czihal (132)	2015	43	Involvement of both STA and SA/AA associated with more recurrent disease.
Ješe (96)	2017	93	Facial artery vasculitis correlated strongly with jaw claudication and visual manifestations.
Monti (136)	2018	118	Only newly diagnosed or flaring patients had a sonographic halo in ≥ 4 sites.
Van der Geest (127)	2020	67	Higher HC/HS: associated with greater degrees of systemic inflammation and a higher risk of ocular complications.
Gribbons (126)	2020	942	STA abnormality associated cranial ischaemia, LV abnormalities associated with UL ischaemia.
Ponte (131)	2020	226	STA Halo: more prevalent visual symptoms and jaw claudication.
Soares (123)	2021	91	STA Halo: associated with older age, systemic features and biochemical inflammation.
Ponte (133)	2021	49	STA HC/HS (and not AA Halo): correlate with ESR/CRP, cumulative steroid dose and lower likelihood of achieving remission.

Table 1.09: Studies of VUS contributing to GCA phenotyping and prognostication.

1.3.3 Monitoring GCA disease activity using Ultrasound

Early studies evaluating the role of VUS in GCA disease-monitoring seemed to agree that Halo regression occurred within 3-4 weeks of initiating treatment (82, 89, 114, 118, 137, 138). Later studies however, presumably due to improvements in US technology, identified halo persistence as late as 6 months after commencing immunosuppressive treatment (108, 139, 140). *Habib* looked at 32 cases of suspected GCA and 30 age- and sex-matched controls. Bilateral US of STA were performed in all patients with subsequent unilateral TAB (controls were not biopsied). In those with abnormal VUS, follow-up imaging was performed at 2, 4, 8 and 12 weeks. The mean number of days for disappearance of Halo after initiation of treatment was 21 days, much shorter than the mean of 11 weeks seen in another cohort of 38 patients (141, 142). It is notable that Halo regression appears to occur more quickly in STA than AA, in those with relapsing versus new-onset disease, in those who achieve clinical remission earlier, and in those with fewer STA branches affected at baseline (136, 142, 143). It has also been demonstrated however, that there is no difference in relapse rate/steroid consumption between those with and without wall-thickening regression (144).

In 2021, a prospective study evaluated the role of VUS in monitoring GCA in a cohort of 49 patients. The number of arterial segments with Halo and the maximal IMT were measured at weeks 1, 3, 6, 12 and 24 and showed significant differences at all time points in STA and after 6 weeks in AA. Higher Halo numbers/thickness correlated with inflammatory markers, cumulative steroid dose and lower likelihood of achieving remission with no such associations seen for AA Halo. In cases of

relapse, 16/17 cases had increased Halo IMT compared to the last measured value (133).

The role of corticosteroid treatment on longitudinal STA sonographic changes is not insignificant. *Ponte et al* showed a consistent reduction in Halo size in STA over 7 days of corticosteroid treatment in 226 GCA patients (131). In another cohort of 18 patients, VUS was used to evaluate a steroid treatment protocol consisting of ultra-short course of glucocorticoids followed by Tocilizumab monotherapy. After a 3-day pulse of steroids, IMT decreased sharply in STA and AA, followed by a return to baseline by 4 weeks. A slow and steady reduction in IMT was witnessed thereafter on Tocilizumab monotherapy (122). One recent study evaluated the sensitivity to change of VUS scores in monitoring GCA. In a cohort of 44 GCA patients with positive baseline VUS, follow-up scans were performed at weeks 8, 24 and 64. A number of quantification scoring systems were applied to the dataset. Sensitivity to change was noted in all by week 8 and although LVs responded poorly, all STA-based scores showed moderate-strong correlation with disease activity markers (145).

Thus, no reliable conclusions can be drawn regarding the use of VUS in monitoring GCA based on available data. While it has been demonstrated that Halo IMT is larger in those flaring during follow-up, regression of the halo sign has been observed from as little as 2 days to as much as 7 months after initiation of immunosuppressive treatment. Further research is therefore necessary in this area, particularly given the recent advances in the resolution of contemporary US systems, standardisation of US training by EULAR and EFSUMB, and recent OMERACT advances on US definitions of vasculitis and standardised scanning

protocols, all of which will allow for more detailed analysis of longitudinal IMT changes within individual patients.

Author	Year	Sample Size	Sonographic changes at follow-up
Schmidt (82)	1997	30	Halo disappearance at a mean of 16 days after initiation of corticosteroids.
Lawerys (114)	1997	6	Peak systolic flow velocity improved in follow-up imaging in all 6 patients.
Schmidt (89)	2002	33	Halo disappearance mostly seen by 21 days.
Schmid (137)	2002	12	1/6 patients still had Halo visible after 3 months of therapy.
Karahaliou (118)	2006	22	Halo resolved in 50% by 2 weeks, and in the other 50% by 4 weeks.
Perez-Lopez (139)	2009	30	Halo seen in 50% of patients after 6 months (all in remission).
Suelves (146)	2010	10	2 early relapses detected by scheduling repeat VUS at 3 weeks and 3 months.
Aschwanden (108)	2010	12	9/12 had signs of inflammation after 6 months despite clinical and biochemical remission.
Habib (141)	2012	16	Mean time to Halo disappearance of 3 weeks.
De Miguel (142)	2012	30	Mean time to Halo disappearance of 11 weeks.
Santoro (138)	2013	1	Halo disappearance: 2 days after initiation of corticosteroids.
Hafner (147)	2014	41	Mean carotid IMT: baseline 1.0mm, 6-months 0.82mm.
Diamantopoulos (140)	2014	1	Persistence of Halo 7 months after diagnosis, despite remission.
Martins (148)	2016	1	Resolution of Halo correlated with improved symptoms, ESR, CRP.
Monti (136)	2018	118	Follow-up imaging in 89 asymptomatic cases: 21% positive. Follow-up imaging in 29 symptomatic cases: 37% positive.
Aschwanden (144)	2019	42	No difference in relapse rate/steroid consumption between those with (45% LV, 85% STA) and without wall-thickening regression.
Ford (143)	2020	42	9/42 had persistent vasculitis on VUS at median 5.1 months follow-up.
Ponte (131)	2020	226	Regression of Halo in STA but not AA during the first 7 days of treatment.
Ponte (133)	2021	49	In cases of relapse, 16/17 had increased Halo IMT compared to last measured value.
Seitz (122)	2021	18	After a 3-day pulse of steroids IMT decreased sharply in STA and AA, followed by a return to baseline by 4 weeks.
Nielsen (145)	2023	44	Quantification of VUS changes may correlate with other disease activity markers.

Table 1.10: Studies of VUS in monitoring GCA disease activity.

1.3.4 Vascular Ultrasound in Polymyalgia Rheumatica

The association between GCA and PMR is long-established but VUS studies found no significant link sonographically until 2000. In a prospective series of 22 PMR patients, none of whom had symptoms suggestive of GCA, but all of whom had a TAUS performed prior to TAB (48), US demonstrated an STA halo in 7/22 patients, and 5 of these 7 patients subsequently had biopsy-confirmed GCA. Halo sign had 100% sensitivity and 88% specificity with respect to histologically-diagnosed GCA. *Schmidt et al* suggested a lower prevalence in a cohort of 102 pure PMR patients around this time (47). More recently, *Schäfer et al* reported results of their study on 50 PMR patients, all of whom had VUS performed. Strikingly, 54% had sonographic evidence of GCA, suggesting that all PMR patients should have VUS performed at baseline where feasible.

In 2022, an international multi-centre cross-sectional study of 346 patients with pure PMR was undertaken in which all patients underwent US of STA, carotid, SA and AA. 79 patients (22.8%) were deemed to have underlying GCA, as evidenced by at least 1 Halo. These patients were older, had more prolonged morning stiffness and more hip pain than those PMR patients without sonographic GCA and the vasculitis had a predilection for extracranial arteries (68). The findings of this study were replicated in only one other cohort since and more studies are needed to support these observations (69).

Author	Year	Sample Size	Results
Kraft (67)	1996	8 PMR	0% had Halo.
Lauwerys (114)	1997	21 PMR	Hypoechoic vessel wall thickening in 1/21.
Stammler (48)	2000	22 PMR	STA halo in 7/22. 5/7 subsequently had positive TAB.
Schmidt (47)	2002	102 PMR	Abnormal VUS in 8. 4/8 had positive TAB.
González Porto (149)	2020	57 suspected GCA	22 had positive VUS (8 GCA, 4 diagnosed with PMR).
Schaefer	2020	50 PMR	54% had evidence of GCA on VUS.
De Miguel (68)	2022	346 PMR	22.8% had Subclinical GCA on VUS.
Burg (69)	2023	45 PMR	13 had Subclinical GCA on VUS (29%).

Table 1.11: Studies evaluating VUS in PMR.

1.4 Magnetic Resonance Imaging in GCA

1.4.1 Large Vessel Magnetic Resonance Imaging

CT angiography has traditionally been the imaging method of choice to depict LVV. However, advances in MRI technology mean that this imaging modality is assuming a more prominent role in recent years. Its high resolution gives detailed anatomical information such as vessel lumen configuration and vessel wall thickness while the use of contrast helps to delineate vessel wall oedema (150, 151). Additionally, it is non-invasive, free of radiation and allows for imaging in a number of different planes. While more expensive and less readily available than ultrasound, it is independent of variations in operator technique. Newer MRA protocols have incorporated combinations of previously independent protocols, allowing for the simultaneous imaging of thoracic, cervical and superficial cranial vessels (152, 153). Examining all of the vascular territories most commonly affected by GCA in such a manner, allows for a more comprehensive and efficient assessment of suspected cases of this disease. MRA has been shown to demonstrate similar sensitivity to PET for detecting LVV while it has a demonstrable role in follow-up too, displaying lesser degrees of vessel-wall inflammation in those in clinical remission (70, 154, 155). MRI has been incorporated into quantitative grading systems for LVV arterial involvement and longitudinal changes in these scoring systems have been shown to correlate with disease activity measures. This raises the possibility of MRI being used as a reliable outcome measure in future clinical trials. Furthermore, it has the added value of being able to identify GCA-related inflammation of intracerebral, ocular and

deep temporal arteries, which are thought to be involved in 35-50% of cases of GCA (156-158).

1.4.2 MRI of STA in diagnosis of GCA

A small number of studies have formally evaluated STA MRI in diagnosing GCA. In 2014, *Klink et al* published results from a large prospective multicentre trial of patients with suspected GCA. 102/185 had a final clinical diagnosis of GCA, 98 of whom had TAB performed of which 62 were positive and all patients had STA MRA. A 1.5T system was used on 55 patients and a 3T system in the other 130. Dedicated 12- and 32- channel (for 3T MR) or 16-channel (for 1.5T MR) phased-array coils were used. Post-contrast, fat-saturated T1-weighted (fsT1WI) spin-echo sequences with sub-millimetre spatial resolution (195 x 260 μ m) were acquired. Two independent, blinded radiologists scored images of the frontal and parietal branches of STA bilaterally and the occipital arteries bilaterally, from 0-3 depending on the degree of mural thickening and mural contrast enhancement. For the total study cohort, the sensitivities and specificities were 78.4%/83.3% and 90.4%/85.5% for both observers with a good inter-observer agreement (kappa coefficient 0.68). However, sensitivity of MRI declined in those treated with steroids for greater than 5 days (159).

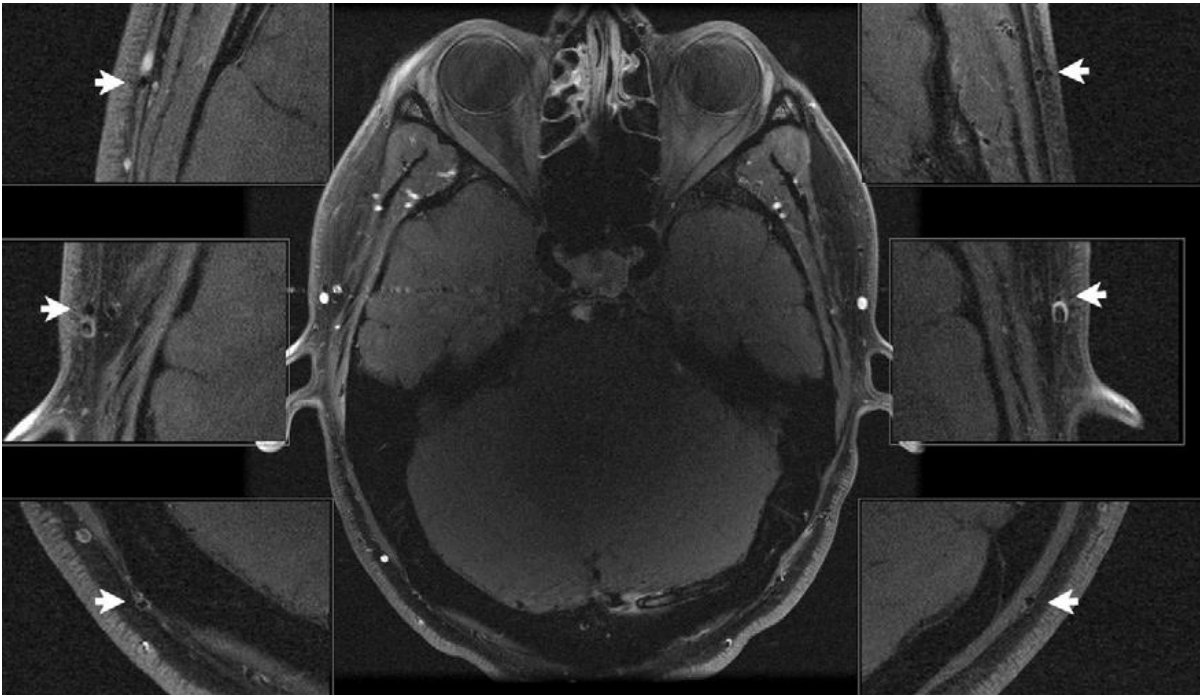


Figure 1.04: Normal STA MRA. Six normal arterial segments (arrows). Top- Frontal. Middle- Parietal. Bottom- Occipital. Artery differentiated from vein due to lack of luminal signal (signal void) (159).

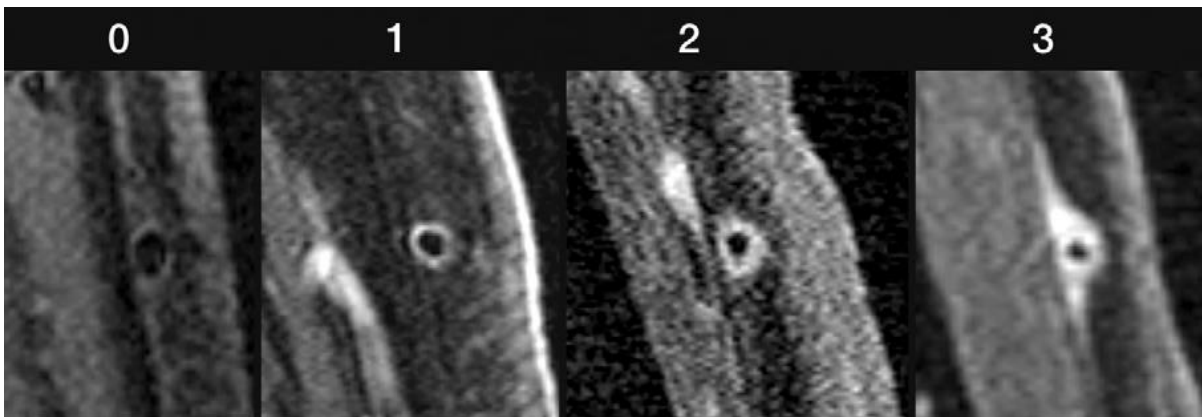


Figure 1.05: Abnormal STA MRA. Left frontal branch, evaluated over length of at least 3cm and assigned a score, 0-3, dependant on degree of mural thickening and contrast enhancement, with examples of scores outlined in above images (159).

Other prospective studies of cohorts ranging in size from 7-171 were undertaken using varying MR technologies, MR imaging protocols and study methodologies and yielded sensitivities ranging from 0-94% for STA MRI/MRA in diagnosing GCA (160-162). MRA was more sensitive than TAB for a diagnosis of GCA in 2 studies while the sensitivity of STA MRI appears to decline precipitously under corticosteroid treatment (156, 160). Importantly however, in a sizeable cohort of 171 suspected cases of GCA, normal MRI was highly predictive of negative TAB, suggesting that it may be useful as an initial screening tool to reduce the number of TABs performed (163). Lastly, a recent retrospective study of 268 patients suspected of having GCA, highlighted the importance of considering pre-test probability when interpreting STA MRA. The authors showed that STA MRA has a PPV of 93% in those with a pre-test probability of at least 50% and a NPV of 89.5% in those with a pre-test probability of less than 25% (164).

Comparison	N	TP	TN	FP	FN	Sens	Spec	PPV	NPV
MRI v ACR (all patients)	64	25	32	1	6	80.6%	97.0%	96.2%	84.2%
MRI v ACR (<10 days CS treatment)	50	24	21	1	4	85.7%	95.5%	96.0%	84.0%
MRI v ACR (> 10 days CS treatment)	14	1	11	0	2	33.3%	100%	100%	84.6%
Histology v ACR	32	21	5	0	6	77.8%	100%	100%	45.5%
MRI v ACR (patients with histology)	32	22	5	0	5	81.5%	100%	100%	50.0%
MRI v Histology	32	19	8	3	2	90.5%	72.7%	86.4%	80.0%
Wall thickness (on MRI) vs ACR (all patients)	64	22	26	7	9	71.0%	78.8%	75.9%	74.3%

Table 1.12: Validation of MRI versus TAB and ACR Classification Criteria in 64 consecutive patients with suspected GCA (156).

	TAB as reference standard	ACR criteria as reference standard
Sensitivity	94 %	39 %
Specificity	78 %	82 %
PPV	48 %	90 %
NPV	98 %	25 %

Table 1.13: Diagnostic performance of MRI in 171 patients with suspected GCA (163).

1.4.3 MRI of STA in monitoring GCA disease activity

In 2008, *Bley et al* looked at the role of STA MRI in following up a cohort of 17 confirmed cases of GCA. 2 blinded radiologists evaluated images, reaching a consensus score for the degree of vessel wall thickening and contrast enhancement. Baseline clinical, biochemical and radiological assessments were performed and again after 16 months of corticosteroid treatment. Clinical remission was achieved in 15/17 patients, biochemical remission in 9/17 and MRI signs of inflammation had normalised in all patients in clinical remission. 1 of 2 patients who had active disease clinically at follow-up also had a positive MRI. The authors concluded that the intensity of inflammatory hyper-enhancement decreased significantly during steroid treatment and this correlated positively with clinical and serological remission (165). Additionally, the same authors suggested a role for STA MRA in monitoring response to treatment in GCA in a number of case reports but there is otherwise a distinct lack of evidence addressing this question (166-169). A comprehensive summary of all studies relating to MRI in evaluating suspected GCA is tabulated in Appendix 1.4, with sensitivities ranging 69-94% and specificities ranging 78-100% for a diagnosis of GCA as defined by either TAB or ACR Classification Criteria.

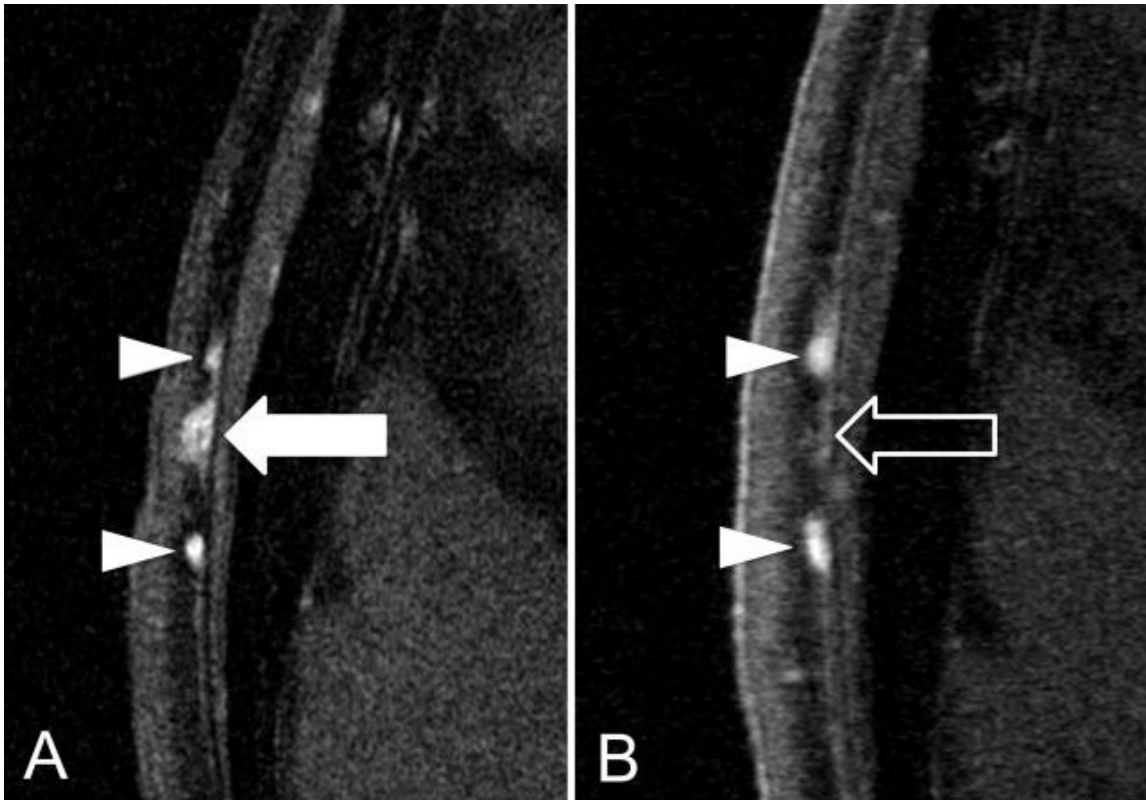


Figure 1.06: High-resolution MRI of the right STA of a patient with histologically-confirmed GCA. A) Mural thickening and contrast enhancement (large arrow). B) Inflammatory changes have disappeared after 2 months of treatment (large arrow). Small arrows in A and B depict veins (169).

1.4.4 Comparison of Ultrasound with MRI in evaluating suspected GCA

Few published studies to date have compared the performance of STA MRI with that of US. One of these studies interrogated both imaging modalities retrospectively in 36 GCA patients, 24 of whom had a positive TAB. The results showed that the sensitivity of baseline VUS and high-resolution STA MRI for diagnosing GCA are near equivocal, with a numerical tendency towards higher values for MRI, but sensitivities reduce rapidly under corticosteroid treatment (169). In a cross-sectional study of 35 patients with GCA, there was no statistical difference between VUS and MRI for detecting STA vasculitis, except for the right frontal STA branch, where MRI performed better. Interestingly in this study, VUS detected vasculitic change more frequently than MRI in large vessels and in those with both new-onset and chronic disease (170). Other studies comparing these two imaging modalities have found broadly similar results, with one report of 20 patients showing a sensitivity of STA MRI for biopsy-confirmed GCA of only 33.3%, versus 77.7% for that of VUS (171-173). A comprehensive summary of all studies comparing VUS with other imaging modalities for evaluating suspected GCA is tabulated in Appendix 1.5.

	n=	Sens	Spec	PPV	NPV
Clinical Diagnosis as Reference Standard	59				
MRI		69%	91%	93%	66%
VUS		67%	91%	92%	64%
TAB as Reference Standard	41				
MRI		83%	71%	80%	75%
VUS		79%	59%	73%	67%

Table 1.14: Diagnostic performance of MRI versus VUS in 59 patients with suspected GCA (169).

Duration of Corticosteroid Treatment prior to VUS/MRI	n=	Sensitivity	Specificity
Clinical Diagnosis as Reference Standard			
0-1 day before VUS	28	87.5%	91.7%
0-1 day before MRI	24	84.6%	100%
>4 days before VUS	15	50%	80%
>4 days before MRI	13	55.6%	100%
TAB as Reference Standard			
0-1 day before VUS	20	92.3%	57.1%
0-1 day before MRI	16	90%	66.7%
>4 days before VUS	10	50%	25%
>4 days before MRI	9	80%	75%

Table 1.15: Diagnostic performance of MRI and VUS under steroid treatment in 59 cases of suspected GCA (169).

1.5 Current applications of Vascular Ultrasound in GCA and evolving concepts

1.5.1 Reliability and routine use of VUS

While VUS is clearly a very useful clinical tool in rheumatology, as recently as 2014 only 1% of its use among rheumatologists was for the purpose of diagnosing vasculitis while 74-94% of rheumatologists preferred TAB over VUS as a confirmatory test for GCA (174-176). In a retrospective study of 241 GCA patients in France between 2007 and 2015, only 29.1% underwent VUS as part of their diagnostic workup for suspected GCA (95). Data from the ARTESER registry showed that of 1675 diagnosed cases of GCA between 2013 and 2019, TAB was the most commonly used confirmatory test for GCA, being used in 46.3% of cases (versus 30% for VUS). Significantly however, from 2013 to 2019, the use of VUS grew from 25.8% to 52.9%, along with other imaging methods, while use of TAB substantially decreased (177).

A number of European rheumatology centres have equipped themselves with the technology and expertise to operate fast-track GCA clinics, which consist of same-day VUS and initiation of treatment where indicated. In one report, the relative risk of permanent blindness in GCA patients diagnosed through a fast-track clinic was 88% lower compared with those diagnosed by the conventional route (relative risk 0.12) with a shorter mean duration of inpatient care by 3 days (178).

Therefore, available literature suggests that the rheumatology community has been slow in adopting VUS as a routine diagnostic tool for GCA. For those who have incorporated it into their practice, it has been used in some centres to guide TAB, although no significant benefit has been seen with this approach (179). More significantly, it has allowed for implementation of fast-track GCA clinics which have improved patient outcomes and crucially, there is now evidence highlighting excellent inter-reader agreement. The effectiveness of standardised training programmes for VUS has been demonstrated with excellent inter-reader reliability. In a study of 112 GCA patients who had VUS performed by 5 sonographers who underwent standardised training, an interobserver agreement of 95-96% with mean kappa values of 0.88-0.92 (95% CI 0.78 to 0.99) was achieved (180). Importantly, these findings have been replicated elsewhere (181).

1.5.2 Technological advances

Recently, very-high resolution ultrasound (VHRU, 55 MHz) has been shown to non-invasively and reliably, define the thickness of the arterial intima layer. In 37 patients who had negative TAB, intimal thickening (IT, >0.06 mm on histology) could be identified as a 'four-line pattern' in VHRU with a sensitivity and specificity of 96.3% and 100% respectively with excellent agreement between histologic and VHRU IT measurement (182). In a proof-of-concept study in 24 GCA patients, contrast-enhanced US (CEUS) of large vessels had a sensitivity and specificity of 91.7% and 100% for detecting active LVV (183). It provides detailed images of lumen-to-vessel wall border and abnormalities correlate well with those seen on FDG-PET (184, 185).

Roncato et al have described an automated image analysis tool for diagnosis of GCA using artificial intelligence algorithms. They reported on a retrospective cohort of 137 patients with suspected GCA, all of whom had VUS, which were labelled with VIA software. They obtained a sensitivity of 60% and specificity of 95% for their test set (186). Thus, while inter-rater agreements for VUS are high, it is an inherently subjective test with interpretation relying heavily upon sonographer expertise/ experience. Incorporation of AI algorithms will provide more objectivity and standardisation of VUS between individuals/centres and should help to eliminate some of the disparities in study results observed to date.

1.5.3 Quantifying vascular inflammation on US

Traditionally, VUS has had a binary outcome, deemed to be either positive or negative. In recent years however, investigators have sought to establish whether quantification of sonographic abnormalities can increase the diagnostic performance of VUS and perhaps provide some prognostic information. In a sub-study of 135 GCA patients from the TABUL cohort, combined VUS and clinical scores were used to predict likelihood of TAB positivity. Maximal IMT and bilaterality of STA/AA Halos were combined for an US score, with typical GCA symptoms and raised inflammatory markers used for clinical scoring. The investigators discovered that it was useful for predicting likelihood of positive TAB but not for predicting clinical outcome at 6 months (187).

Halo Counts (HC, number of STA/AA branches with Halo) and Halo Scores (HS, composite of number and size of halos) have been recently described. Both have shown a high degree of sensitivity for a clinical diagnosis of GCA (area under ROC

curve 0.89 and 0.92) and strong associations with degrees of systemic inflammation and likelihood of ocular complications. In addition, the scores correlate positively with likelihood of having a subsequent positive TAB and they appear to be unaffected by cumulative steroid dose over the first week of treatment (127).

Molina-Collada et al evaluated the impact of CV risk on the accuracy of HS in a retrospective observational study of patients referred to a fast-track GCA clinic. 47/157 patients had a clinical diagnosis of GCA and extra-cranial IMT and Halo Score were significantly higher in those with high CV risk scores, but only in patients without GCA. The AUC of Halo Score was slightly better in those with a low risk CV profile versus those with a high risk CV profile (0.97 versus 0.80) (188). In a study of 44 patients with LV-GCA and 42 patients with high risk atherosclerosis, US of carotid, SA and AA were performed. Mean IMT in all arteries was greater in the vasculitis group, however using a cut-off of 1.0mm, 38.6% of atherosclerosis patients met the sonographic definition of vasculitis, mostly in the carotid artery. Using a cut-off of >1 pathological vessel segment (out of 4 in total if AA and SA only used, or cut-off of 3/6 if carotids included) had an accuracy of 95% for vasculitis (189)

These scores have so far been validated in one inception cohort for diagnosis of GCA but research is ongoing to assess their utility in assessing disease activity long-term (190). Therefore, currently available data suggests that Halo quantification is useful for predicting the likelihood of positive TAB and ocular complications but has no added diagnostic value over and above that of the traditional binary positive/negative interpretation of VUS. Most recently, the OGUS has been proposed. This is a composite of halo size and thickness and while it has

been suggested that it may be used to monitor GCA disease activity over time, it requires external validation (145, 191-193).

Halo Grading	Common superficial TA halo thickness (mm)	Parietal TA halo thickness (mm)	Frontal TA halo thickness (mm)	Axillary artery halo thickness (mm)
Grade 0	0.3 or less	0.2 or less	0.1 or less	0.5 or less
Grade 1	0.4	0.3	0.2	0.6
Grade 2	0.5	0.4	0.3	0.7-0.8
Grade 3	0.6-0.7	0.5*	0.4	0.9-1.5
Grade 4	0.8 or more	0.6 or more	0.5 or more	1.6 or more

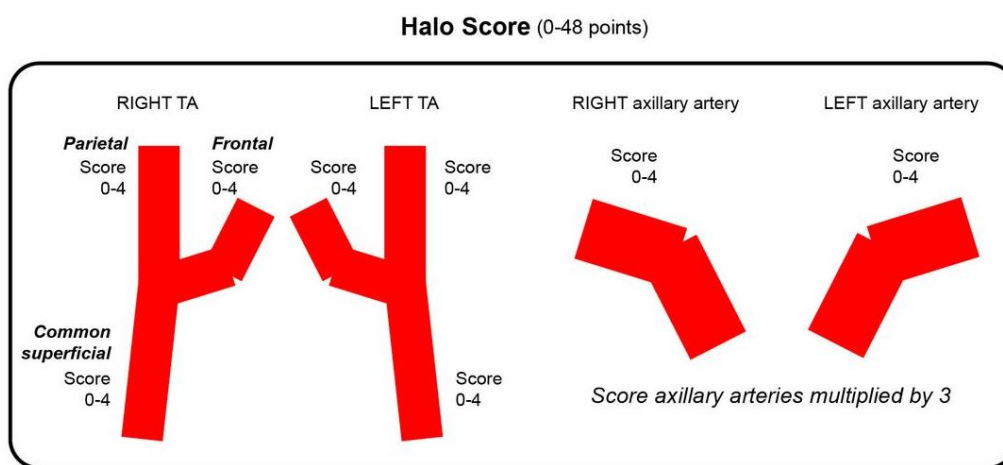


Figure 1.06: Halo Count (range 0-8) refers to the number of STA and AA branches affected and Halo Score (range 0-48), above, is a composite of the number of branches affected and the maximal IMT within each branch (127).

1.5.4 Pre-Test Probability Score

In 2020, *Sebastian et al* devised a probability-based algorithm to guide diagnostic tests in cases of suspected GCA. In a retrospective cohort of 354 referrals to a rapid-access GCA clinic they stratified patients into 3 distinct categories, namely low-risk (LR), intermediate-risk (IR) and high-risk (HR) for ultimately having a diagnosis of GCA. The Pre-Test Probability Score (PTPS) is a composite score combining patient demographics, symptoms, examination findings and laboratory

results on a scale of 0-30 with LR<9, IR 9-12 and HR >12 based on an overall median score of 9 and a 75th percentile score of 12. The reference standard was a clinical diagnosis of GCA using ultrasound but not biopsy. 354 patients were categorised as follows- LR 151, IR 137 and HR 66 with 89 ultimately being diagnosed with GCA. The prevalence of GCA in the 3 groups was as follows- LR 0%, IR 26% and HR 80%. For the HR group VUS had sensitivity 94% and specificity 85% while in the LR group VUS had specificity of 98%, with a reasonably high degree of accuracy seen in the IR group also. These results suggest that incorporation of the PTPS can significantly enhance the performance of VUS in investigating suspected GCA by substantially improving sensitivity (194). Only one prospective study to date has interrogated the performance of the PTPS, in a cohort of 104 patients with suspected GCA. In this study, the PTPS had a sensitivity of 100%, a specificity of 56.9%, a PPV of 42.3% and a NPV of 100% for a diagnosis of GCA (195). In a retrospective study of 297 patients referred to a rapid-access GCA clinic in Spain, the PTPS had a ROC 0.79 but 9.5% of those categorised as LR had a diagnosis of GCA while 70% of the HR category had a diagnosis of GCA (diagnosis based on combined clinical, biochemical, histological and imaging data) (196). Thus, in the setting of a high PTPS, sensitivity of VUS appears to increase to >94%, but conflicting results have been seen in relation to its specificity.

Weighting	-3	0	+1	+2	+3
Age (years)		<50	50-60	61-65	≥66
Sex			Male	Female	
Symptom duration		> 24 weeks	12-24 weeks	6-12 weeks	< 6 weeks
CRP		0-5 mg/L	6-10 mg/L	11-25 mg/L	≥ 25 mg/L
Headaches		No	Yes		
PMR		No		Yes	
Constitutional		No	Single		> 1
Ischaemia		No			Yes
AION/ CRAO/ Field Loss/ RAPD		No			Yes
TA abnormality		No	Tender	Thick	Pulseless
Extra-cranial artery abnormality		No	Thick	Bruit	Pulseless
Cranial nerve palsy		No			Yes
Infection	Yes				
Cancer	Yes				
Systemic Rheumatic Disease	Yes				
Head/ neck pathology	Yes				
Other	Yes				

Table 1.16: Southend Pre-Test Probability Score for GCA (194). Low-risk was classified as PTPS <9, intermediate-risk as PTPS 9–12 and high risk as PTPS >12.

1.5.5 Current recommendations for the use of VUS in GCA

In 2018, EULAR issued its first guidance document on the use of imaging in LVV, including ultrasound (197). In addition to some technical specifications, they state the following:

1. In patients with suspected GCA, an early imaging test is recommended to complement the clinical criteria for diagnosing GCA, assuming high expertise and prompt availability of the imaging technique.
2. In patients in whom there is a high clinical suspicion of GCA and a positive imaging test, the diagnosis of GCA may be made without an additional test (biopsy or further imaging). In patients with a low clinical probability and a negative imaging result, the diagnosis of GCA can be considered unlikely.
3. Ultrasound of temporal $\pm$ axillary arteries is recommended as the first imaging modality in patients with suspected predominantly cranial GCA. A non-compressible 'Halo' sign is the ultrasound finding most suggestive of GCA.

The BSR have also issued recommendations for evaluating and managing GCA (198). They strongly recommended using a confirmatory diagnostic test, either VUS, TAB, or both. They stress the importance of considering the pre-test probability prior to initiating investigations and they also state the following:

1. Ultrasound is operator dependent and requires adequate training but has the advantage of access to both STA in their entirety.
2. For a medium (20–50%) estimated probability of GCA, it may be useful to perform an ultrasound prior to biopsy, in case the biopsy is negative.

3. For a high clinical probability of GCA, a positive ultrasound alone may be sufficient.
4. In the absence of clinical features of cranial GCA, TAB can still be positive, but imaging of the extracranial large vessels may be considered instead of, or in addition to, TAB.

1.6 Discussion

GCA is not an uncommon disease with a lifetime risk estimated to be between 0.5-1.0%. Much evolution has occurred in GCA diagnosis over past few decades as a growing body of evidence highlights how the traditional gold standard TAB is expensive, has a low positive yield, has little impact on clinical decision-making and compares unfavourably to other diagnostic tools for detection of disease. While TAB is still the commonest confirmatory test used to diagnose GCA by rheumatologists despite its apparently poor sensitivity, use of VUS is increasing following EULAR guidelines in 2018. Halo and Compression signs are the characteristic hallmarks of vasculitis on VUS with a thickened IMT. While these signs show good inter-rater and intra-rater reliability, the accepted cut-offs values for normal versus abnormal IMT have only been validated in one study to date while there is evidence to suggest that age, sex and CV risk profile, in particular, should be taken into account when interpreting IMT measurements.

Much has been learnt from imaging studies about the true extent of GCA pathology, with widespread involvement of large and medium sized vessels occurring. While the aorta and lower limb arteries may be sub-clinically involved, among others, STA and AA appear to be the most reliable arteries to scan, with the addition of facial and occipital arteries only marginally increasing the diagnostic yield from VUS. Thus, the optimal imaging protocol for investigating suspected GCA with VUS is slowly being revealed. The accepted norm is to scan STA and AA together- these vessels appear to be consistently involved and so have the highest yield, with this being the most time-efficient strategy also. However, in cases of

negative STA and AA assessment, evaluation of other large vessels is recommended. Updated GCA classification were published in 2022 and appear to perform well for LVV but only 3 studies have evaluated these criteria, retrospectively, and have shown good sensitivity but varying degrees of specificity ranging from 57.5% to 85%.

Numerous studies to date have compared VUS to TAB for diagnosing GCA and variances in methodologies have resulted in widely disparate results. Six published systematic reviews and meta-analyses have shown sensitivity and specificity ranges of 55-77% and 81-100% respectively for VUS in diagnosing GCA. Between individual studies, ranges for sensitivity (9-100%), specificity (66-100%), PPV (36-100%) and NPV (33-100%) likely reflect heterogenous methodologies, evolutions in technology and variances in operator technique. There is some evidence that Halo presence and distribution can predict disease trajectory in GCA. STA involvement, particularly if bilateral, appears to be associated with cranial ischaemia while AA involvement appears to be associated with limb ischaemia, more relapsing disease, greater cumulative steroid exposure and ultimately a greater requirement for SSA. Most of this data comes from small studies however, and more evidence is needed to define the role of VUS in disease prognostication.

Halo regression has been shown to occur from as little as 2 days to as much as 7 months after commencing immunosuppressive therapy for GCA. It appears to occur more rapidly in STA than AA with no observable association with relapse rate or cumulative steroid dose. Relapse has been shown to be predicted by a rising IMT but this data comes from a cohort of only 17 patients, while little is known about the impact of glucocorticoids on longitudinal IMT changes. No reliable conclusions can be drawn from available data regarding the use of VUS in

monitoring GCA. More research in this field using conventional technology will allow for more precise measurement of longitudinal IMT changes in individual patients.

The inextricable link between GCA and PMR was highlighted by the recent description of 'GCA-PMR Spectrum Disease'. Many of those presenting with PMR have underlying GCA at diagnosis, so-called 'Subclinical GCA'. Identification of Subclinical GCA is of paramount importance given the relatively higher rate of vascular complications compared to those with 'Isolated PMR', which tends to run a more benign course. Certain clinical and biochemical parameters can hint at those with Subclinical GCA but more sensitive and robust methods are required. Studies using VUS to identify Subclinical GCA have suggested prevalence rates from 5-54% with one recent large study showing a prevalence of 22.8% but these results have only been replicated in one other cohort to date. Only 7 published studies in total have interrogated this concept however, with many being performed before the advent of modern US technology.

Halo Counts, Halo Scores and OGUS have recently been described and have provided a framework for quantifying the extent of inflammation on VUS. Early evidence suggests that they correlate positively with systemic inflammation, ocular complications and likelihood of a positive TAB. HC and HS have only been validated in one inception cohort and nothing is known about their utility in monitoring disease long-term. OGUS is yet to be externally validated. The recently described Southend PTPS appears to enhance the performance of VUS by increasing sensitivity to 94% in those with a score >12, but has only been validated in one prospective cohort to date where it demonstrated poor specificity for GCA diagnosis.

While the rheumatology community has been slow to adopt VUS as a first-line test, the excellent inter-observer agreement shown in studies is likely to result in more widespread training in this area. At the very least, VUS would appear useful in limiting the number of unnecessary TABs that are being performed. However, it is likelier that VUS will replace TAB as the gold standard diagnostic test moving forward, not in isolation, but rather as part of a diagnostic algorithm including other imaging modalities. TAB will continue to command importance however, for the small percentage of patients who remain undiagnosed after initial imaging.

Large vessel MRA has a well-established role in GCA but far less is known about STA MRA. Both small and large studies have shown varying results in terms of sensitivity, specificity, PPV and NPV with results in the ranges of 0-94%, 78-100%, 48-100% and 43-98% respectively. MRA has been shown to be more sensitive than TAB but with a value that declines to as low as 33.3% after 5-10 days of steroid treatment. Non-contrast-enhanced T2 weighted imaging has shown to be useful too, particularly in those with higher degrees of inflammation on contrast-enhanced scanning and may play a diagnostic role in those with contraindications to gadolinium. MRI has been shown to correlate strongly with clinical and serological remission in one study while in another study, normal STA MRA was highly predictive of a negative TAB. Only a few studies have directly compared VUS and STA MRA for initial diagnosis of GCA and mostly showed equivocal results. While the benefits of STA MRA have been cited by many case reports also, false positives have been reported (199-203). A consensus study group in the Mayo Clinic concluded that “the specificity and positive LR of high resolution MRI are sufficiently high that a positive MRI combined with other clinical and laboratory data consistent with GCA may be useful in diagnosing GCA. Given the relatively

low sensitivity of the test, a negative MRI would not be sufficient to rule out the diagnosis of GCA” (204). So as the role of MRI evolves, there remains much that we don’t know about its most useful applications in GCA. Its main role at present is in identifying vascular involvement in territories inaccessible by VUS or biopsy. We have seen conflicting results from studies comparing VUS with MRI and PET/CT but interestingly, it has been demonstrated that diagnostic algorithms incorporating combinations of these imaging modalities achieve sensitivities and specificities of 100% (205, 206). Future research should focus on the role of STA MRA as a more timely and non-invasive alternative to TAB for diagnosis, while investigating whether or not it can more accurately monitor disease activity than currently-available biomarkers.

This thesis aims to explore gaps in our current understanding of how best to utilise VUS in the diagnosis and monitoring of GCA-PMR Spectrum Disease. VUS is compared with TAB and MRA in an inception GCA cohort to identify which tool is the most accurate in confirming clinically-diagnosed GCA. The impact of demographic and clinical variables on the performance of VUS is evaluated and an assessment of whether or not VUS can help identify distinct phenotypic subsets of patients is undertaken. Recently updated 2022 ACR/EULAR GCA Classification Criteria are validated in a prospective cohort and consideration is given to how the addition of the Southend PTPS may improve the diagnostic performance of VUS.

This work examines what role, if any, quantifying the degree of sonographic inflammatory change has in diagnosing GCA. Halo Counts, Halo Scores and OGUS are assessed to see if they improve the performance of VUS compared to

the traditional binary interpretation of results. The accepted limits for what is considered normal IMT in STA and AA are re-evaluated and the impact of individual patient factors on IMT, irrespective of the presence or otherwise of GCA, is investigated. Time-to-regression of Halo is assessed as is its relationship with disease activity. HC, HS and OGUS are monitored over time and in doing so each score is validated to identify which is the most useful to incorporate into routine practice. Factors impacting on baseline scores are assessed as is the role of baseline scores in predicting future disease trajectory.

Lastly this thesis examines the prevalence of Subclinical GCA in an inception PMR cohort by performing baseline VUS. A longitudinal follow-up is performed to assess whether or not there are phenotypically distinct subsets of PMR patients which may be detected by routine baseline VUS.

Chapter 2: A Cross-Sectional Study Comparing Vascular Ultrasound, Temporal Artery Biopsy and Magnetic Resonance Angiography in Diagnosis of Giant Cell Arteritis

Abstract

TAB is costly, invasive and has a false negative rate as high as 60% (5). Both VUS and Superficial Temporal Artery (STA) MR-Angiography (MRA) have shown widely disparate results in studies to date (5, 63, 207). GCA Classification Criteria are often misused in clinical practice as diagnostic criteria. In this study VUS, TAB, MRI and classification criteria are compared to physician diagnosis after 6 months of treatment and follow-up.

A prospective study of all new referrals (n=124) to a Rapid Access GCA clinic over 18 months was performed. VUS of all 6 branches of the STA and both AA was undertaken on all patients using a GE P9 device. Sonographic abnormalities considered indicative of vasculitis in the STA included the Halo sign and non-compressible arteries with a thickened Intima-Media Complex (86). In the AA, a Halo sign and an IMT of >1.0mm was considered positive. A subset of patients were referred for TAB and/or MRA. MRAs were scored 0-4 based on mural wall thickness and signal intensity of mural peri-adventitial contrast enhancement (159). Results were compared to a clinical diagnosis of GCA at 6 months, verified by 2 rheumatologists, which incorporated treatment-response. Chi-Square tests with ROC analyses were performed to determine the performance of each diagnostic modality.

66 patients had a clinical diagnosis of GCA of which 58% were males (n=38) with a mean age of 73.3 years. The respective sensitivities and specificities relative to a clinical diagnosis of GCA at 6 months were as follows: VUS; 82.76% and 84.68%, TAB; 40.4% and 100%, STA MRA; 47.1% and 20%, 1990 ACR Classification Criteria; 72.7% and 69.1%, 2022 EULAR/ACR GCA Classification Criteria; 92.4% and 63.8%. PTPS when combined with VUS improves sensitivity and specificity to 100%.

VUS is a reliable tool for diagnosing GCA with a high degree of sensitivity and specificity. VUS outperformed TAB, MRA and ACR GCA Classification Criteria when compared to a clinical diagnosis of GCA at 6 months. These findings support the proposal that VUS should replace TAB as the gold standard diagnostic test and that all rheumatologists should acquire the necessary skills to accurately perform this investigation as part of routine clinical care. PTPS has a role in evaluating suspected GCA when used in combination with VUS. 2022 ACR/EULAR Classification Criteria are more sensitive than 1990 criteria but lack adequate specificity to be used in clinical practice. MRA of STA lacks sensitivity and specificity for GCA.

2.1 Introduction

2.1.1 Conventional approach to GCA diagnosis and classification

GCA is the commonest idiopathic systemic vasculitis and predominantly affects those aged greater than 70 years (2). The incidence is higher in Northern Europeans with a 1% lifetime risk for women versus 0.5% for that of men (3). GCA is a medical emergency and requires prompt diagnosis and initiation of corticosteroids to prevent the major complications of stroke, irreversible blindness and catastrophic aortic events (7, 8, 11-13). 1990 ACR GCA Classification Criteria have historically been used to classify this disease but were limited by focusing solely on cranial symptoms and also by giving equal weighting to each individual criterion and have been shown to have poor sensitivity when applied to recent GCA cohorts (55). In 2022, ACR and EULAR published updated classification criteria for GCA (54). These criteria are not diagnostic criteria and assume that GCA mimics have been excluded before being applied. A clinical Pre-Test Probability Score (PTPS) has recently been devised to stratify patients into low-, intermediate- and high-risk likelihood groups for having a diagnosis of GCA based on clinical and laboratory parameters (194).

The traditional gold standard for confirmation of diagnosis has, until recently, involved performing a TAB. In recent years, the use of VUS in assessing suspected GCA has increased considerably. A non-compressible Halo sign in a vessel with an enlarged IMT implies Superficial Temporal Artery (STA) vasculitis while the Halo and 'Slope' signs signify the presence of Axillary Artery (AA) vasculitis (63-66).

Recent studies have assessed the validity of quantifying the degree of vascular inflammation on US in suspected GCA using the so-called 'Halo Count' (HC) and 'Halo Score' (HS) and OGUS (127, 190).

MRA of STA has shown promise as a diagnostic tool for GCA. Evidence to date suggests that MRA is more sensitive than TAB but with a value that declines to as low as 33.3% after 5-10 days of steroid treatment.

2.1.2 Current limitations in GCA diagnosis and classification

Early and accurate diagnosis of GCA still has many limitations as does correct disease classification for research purposes. The 1990 Classification criteria lacked sensitivity for LV GCA and while updated criteria have improved in this regard, they have only been validated in 3 studies to date (56-58). TAB has been the traditional gold standard for diagnosis and a positive TAB result still has high value as a diagnostic test considering its specificity of 100%. TAB has many shortcomings which make it an undesirable test to rely upon when assessing suspected cases of GCA. Not only is it costly and invasive, but it has been shown to have a false negative rate as high as 60% with inadequate tissue sampling, skip lesions and pre-operative steroid use all contributing factors (5, 60, 61). Additionally, its impact on clinical decision-making is questionable. In routine clinical practice, patients with suspected GCA are usually treated empirically whilst a confirmatory test is awaited, often a TAB. A growing body of evidence suggests that the TAB result ultimately has little bearing on whether or not treatment is continued. Large cohort studies have shown that 40%-90% of patients with a negative TAB have steroid treatment for a presumptive diagnosis of GCA continued anyway suggesting that TAB only

serves to expose the majority of patients to unnecessary risk (4-6, 12, 51, 59-61). Additionally, it has been shown elsewhere that incorporating TAUS into the workup for suspected GCA increases the positive yield from TAB from 8.5% to 24% with an associated 38% reduction in the number of TABs being performed overall (62). Many studies have interrogated VUS as a diagnostic tool in GCA over the past two decades but have varied considerably in size and methodology with results showing wide discrepancies in sensitivity (9-100%), specificity (66-100%), positive predictive value (36-100%) and negative predictive value (33-100%) of VUS for a clinical or histological diagnosis of GCA (113-118). A number of systematic reviews and meta-analyses have also shown varying results in terms of the sensitivity of VUS (2, 119, 120). Most of the conflicting results in the literature to date likely relate to heterogeneous methodologies, variances in sonographer technique and/or advances in ultrasound technology (5, 82, 121-124). Incorporation of the PTPS appears to improve the performance of VUS but lacks specificity for GCA.

Much less is known about the role of MRI with/without angiography (MRA) in visualising STA in those with suspected GCA, or indeed in the monitoring of patients with confirmed GCA. Much of our understanding of the use of STA MRA comes from case reports but a small number of studies in cohorts ranging in size from 7-171 patients have been undertaken using varying MR technologies, MR imaging protocols and study methodologies and yielded sensitivities ranging from 0-94% for STA MRI/MRA in diagnosing GCA (160-162). Few published studies to date have directly compared the performance of STA MRI with that of VUS and in those that have done, results have been broadly equivocal (169, 170).

2.1.3 Aims of present study

This research hypothesises that VUS is the best initial diagnostic test for evaluating suspected GCA. The aim of this study is to compare VUS of STA and AA in the diagnosis of GCA with TAB, MRA of STA and GCA Classification Criteria using confirmation of clinical diagnosis of GCA by two experienced rheumatologists after 6 months of treatment and follow-up as the reference standard. This study also aims to externally validate the updated 2022 ACR/EULAR GCA Classification Criteria and define whether or not the Southend Pre-Test Probability Score has a place in the initial assessment of suspected GCA.

2.2 Methods

2.2.1 Rapid Access GCA clinic

A rapid-access GCA clinic was created across two university hospital sites in Ireland (Tallaght University Hospital and Cork University Hospital) . Patients with suspected GCA were referred from primary care physicians, emergency departments or inpatient wards via telephone, email or electronic patient record. All investigators were clinical rheumatologists experienced in the diagnosis and management of GCA and experienced in performing VUS. The target was to assess all patients within 24 hours from referral. In addition to routine clinical assessment and biochemical investigations, VUS was performed in all patients. If indicated, treatment was initiated on the day of assessment and patients meeting the pre-defined inclusion criteria were enrolled in the study. Participants then received a patient information leaflet outlining the study details and written informed consent was obtained. Patients were recruited over an 18-month period from July 2020 to January 2022.

2.2.2 Vascular Ultrasound Protocol

Sonographic assessment of the full length of both STA and all its' branches and both AA was performed in all patients. All arteries were interrogated using an 18MHz Linear probe and General Electronic P9 Ultrasound system. Each artery was examined in both transverse and longitudinal planes. Abnormalities deemed indicative of STA vasculitis included a Halo Sign (Fig. 2.01), Compression Sign

(Fig. 2.02) and abnormal IMT above pre-determined thresholds (Table 1.05).

Abnormalities deemed indicative of AA vasculitis included the Halo (Fig. 2.03) and Slope signs with an abnormal IMT above the pre-determined threshold (Table 1.05). Images and measurements were scored by the lead investigator. All images were reviewed by a second expert ultrasonographer blinded to the details of the clinical case and in the event of a discrepancy in diagnostic scoring a joint score was made by agreement.

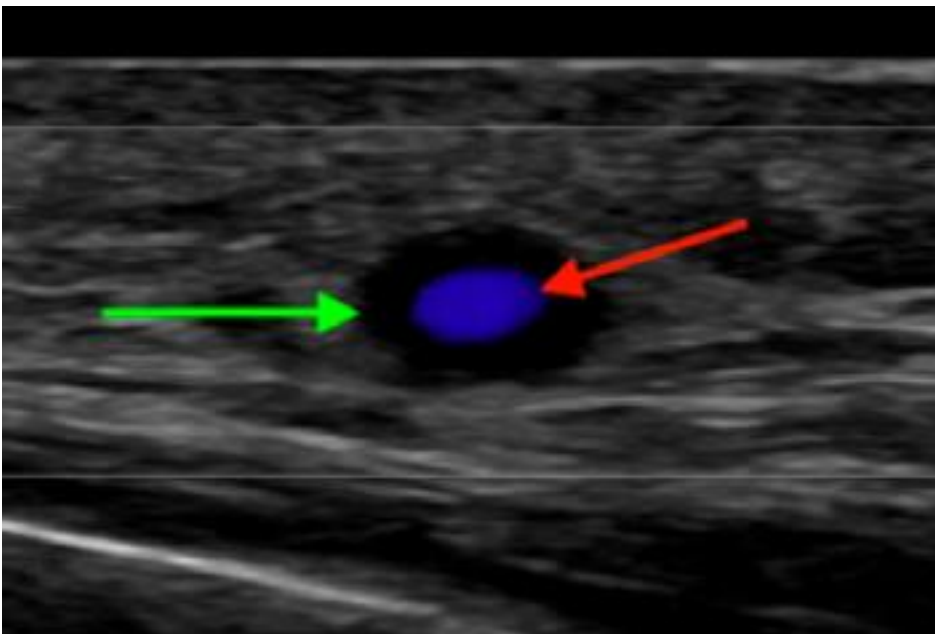


Figure 2.01: Representative image, transverse view of STA demonstrating a 'Halo' sign. Inner doppler signal (blue) indicated by red arrow, surrounded by anechoic (black) 'Halo', indicated by yellow arrow.

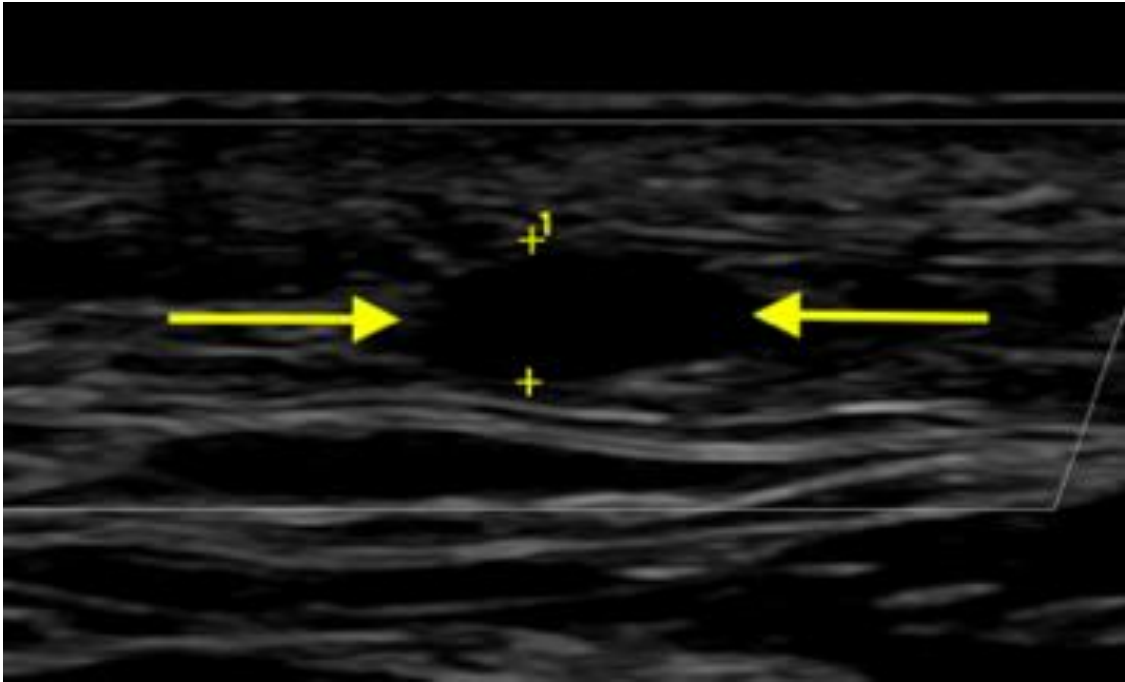


Figure 2.02: Representative image, transverse view of STA demonstrating the 'Compression' sign-anechoic (black) region that persists with transducer-imposed pressure, indicated by the area between yellow arrows.

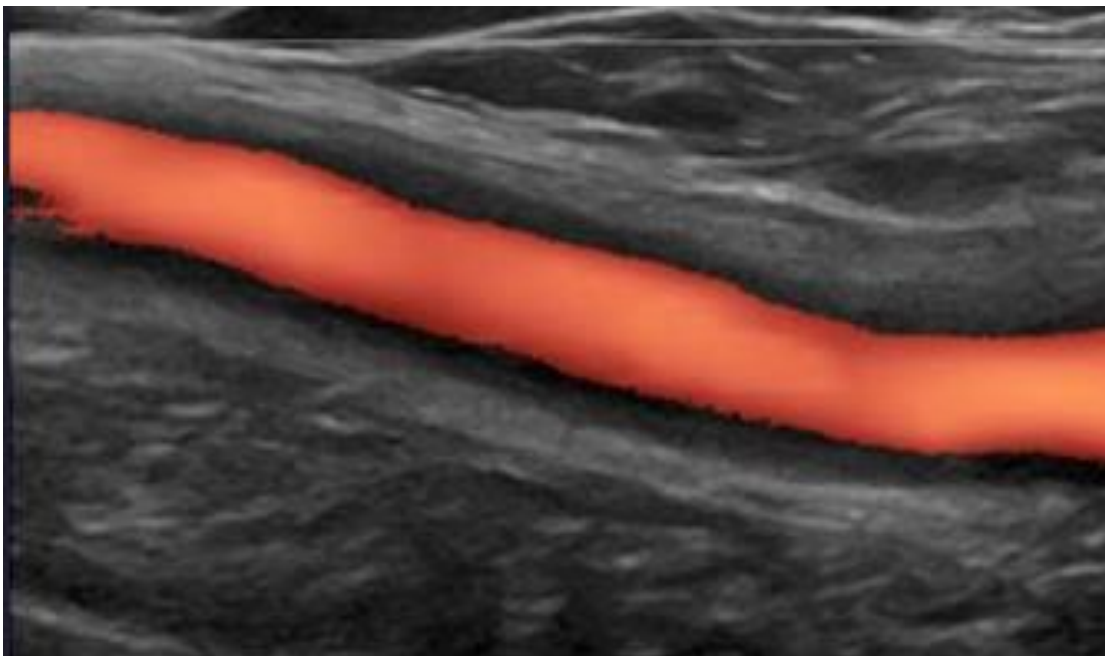


Figure 2.03: Representative image, Axillary Artery Halo sign, longitudinal view.

2.2.3 Magnetic Resonance Angiography

All scans were done using either 3T or 1.5T GE scanners in the same MRI department. The sequences performed were (i) Coronal CUBE T1 fat-sat pre contrast TR: 602, TE 18.41; (ii) Sagittal CUBE FLAIR fat-sat post contrast TR 6902, TE 113.13; (iii) Coronal CUBE T1 fat-sat post contrast (10 mins) TR 602, TE 18.41. Standard dose of IV gadolinium was administered. Scans were reconstructed and reviewed on a dedicated PACS workstation (IMPAX AGFA) and reconstructed in axial, sagittal and coronal planes. The scans were read according to the criteria specified by *Klink et al* (159). Vessel wall evaluation was performed according to a set anatomical format and scoring system: right frontal branch, left frontal branch, right parietal branch, left parietal branch, right occipital branch, left occipital branch. The scoring system used for each vessel was as outlined in Table 2.01.

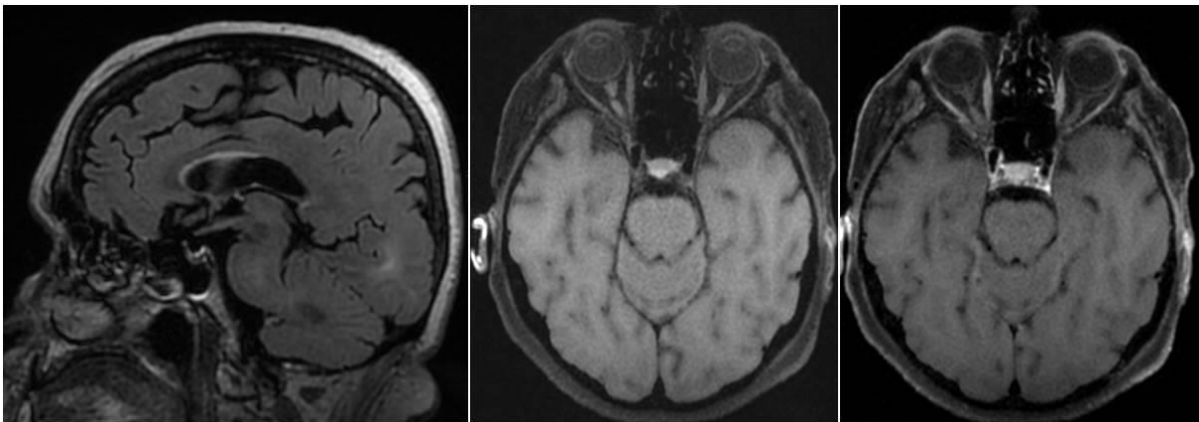


Figure 2.04: Representative MR images showing the 2-sequence scan protocol for STA MRA.

Score	Definition
0	No mural thickening or enhancement, vessel < 0.6 mm
1	No thickening but slight mural enhancement
2	Mural thickening > 0.6 mm and significant mural enhancement
3	Mural thickening >0.7 mm and strong mural and perivascular enhancement
MRI Negative (physiological)	Score 0 and 1
MRI Positive (active mural inflammation)	Score 2 and 3

Table 2.01: Scoring of STA Magnetic Resonance Angiography.

2.2.4 Clinical Diagnosis

All patients all had a clinical diagnosis of GCA established based on clinical presentation, compatible laboratory results and an appropriate response to corticosteroid therapy. All diagnoses were verified by 2 rheumatologists again after 6 months, at which point 4 study subjects were ultimately excluded due to a change in diagnosis. A clinical diagnosis of GCA at 6 months was the reference standard used in this study.

2.2.5 Inclusion and Exclusion Criteria

All newly referred patients to the rapid access clinic, aged over 50 years, with a clinic diagnosis compatible with GCA were included in this study. Those in whom an alternative diagnosis was deemed to be more likely, patients on long-term steroids or a SSA, and any patients aged under 50 years were excluded.

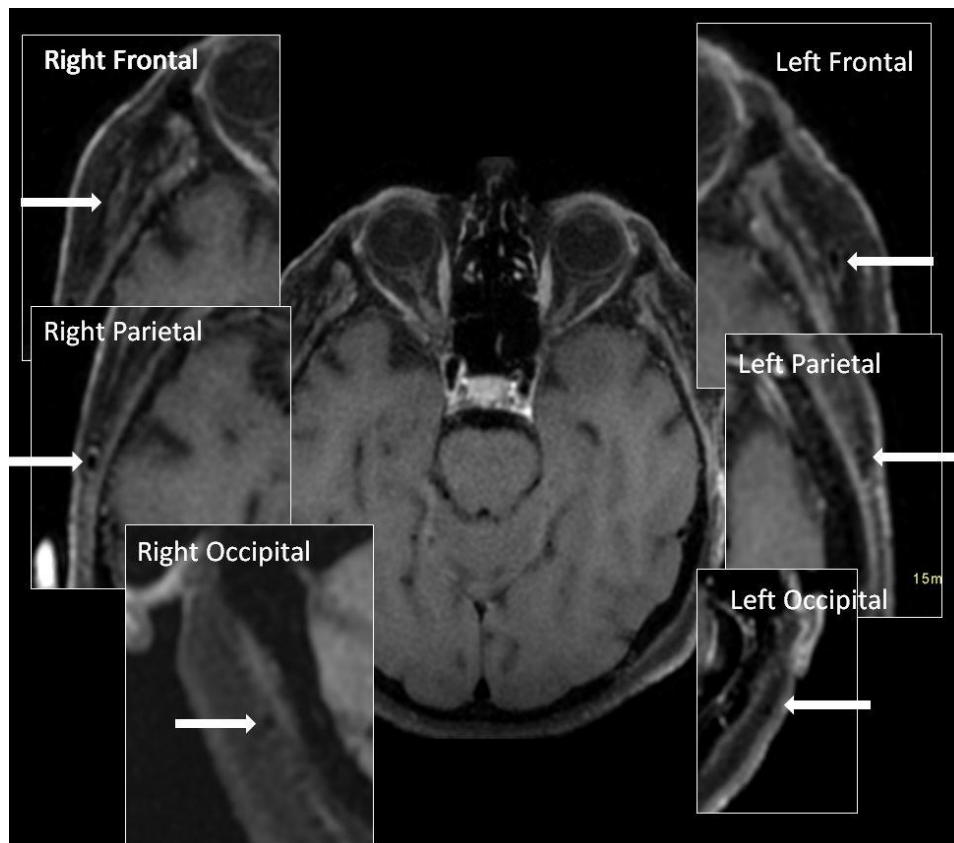


Figure 2.05: Diagram showing the anatomical labelling of the 3 main extracranial branches that were evaluated.

2.2.6 Temporal Artery Biopsy

Informed consent was obtained. Biopsies were carried out in the main operating theatre, or in a minor theatre with good overhead lighting. The patient's head was positioned facing away from the selected temporal artery site to anteriorly position the temporal artery. In most cases, the frontal branch was biopsied. It's position is

more consistent just at the level of the bifurcation anterior to the ear, but it is usually biopsied more distally in the temporal area to reduce the risk of nerve damage. When difficult to palpate it was mapped with a handheld Doppler. The artery was palpated and marked. When the appropriate site was located, the course of the artery was marked with an indelible marker. Then the skin was cleaned and local anaesthetic was infiltrated (3-4 mls of 2% plain lignocaine). The patient's skin was then prepared and drapes placed. The skin was incised with a blade. The subcutaneous tissue was dissected with a Metzenbaum dissecting scissors. Bipolar cautery was used for haemostasis where necessary and the skin edges were retracted with skin hooks or an Alms retractor. Underneath this tissue is a well-defined fascia layer and the artery is visible just under this. To expose the artery, the fascia was lifted with forceps, after which a small incision was made. The artery was then separated from the adjacent tissues and the artery pulsation was seen at this stage. A sterile Doppler was used to confirm if the pulsation was not obvious. There was minimal handling of the artery during dissection. Small arterial branches were ligated with 4/0 silk ties. When more than 1 cm of the artery was exposed, the artery was suture-ligated at either end, incised between the sutures with an 11 blade, and removed. The artery sample was placed in formalin. When haemostasis was confirmed the fascia was closed with an absorbable 3/0 suture. Skin closure was performed with an absorbable monocryl 4/0 suture.

2.2.7 Ethical Approval

This study was approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals and also by the St. James' Hospital / Tallaght University Hospital Joint Research Ethics Committee.

2.2.8 Statistics

For the descriptive statistics, binary and categorical variables are presented using counts and percentages. The distributions of continuous variables have been assessed using coefficients of skewness and then summarized by means and standard deviations (SD) for normally distributed variables or medians and interquartile ranges (IQR) for non-normally distributed variables. To assess for associations between variables; if the outcome of interest was binary or categorical the chi-square test was used. For continuous data, Mann-Whitney U tests or t-test were used, depending on whether the data had a skewed or normal distribution, respectively. All analyses were performed in Stata 15.0.

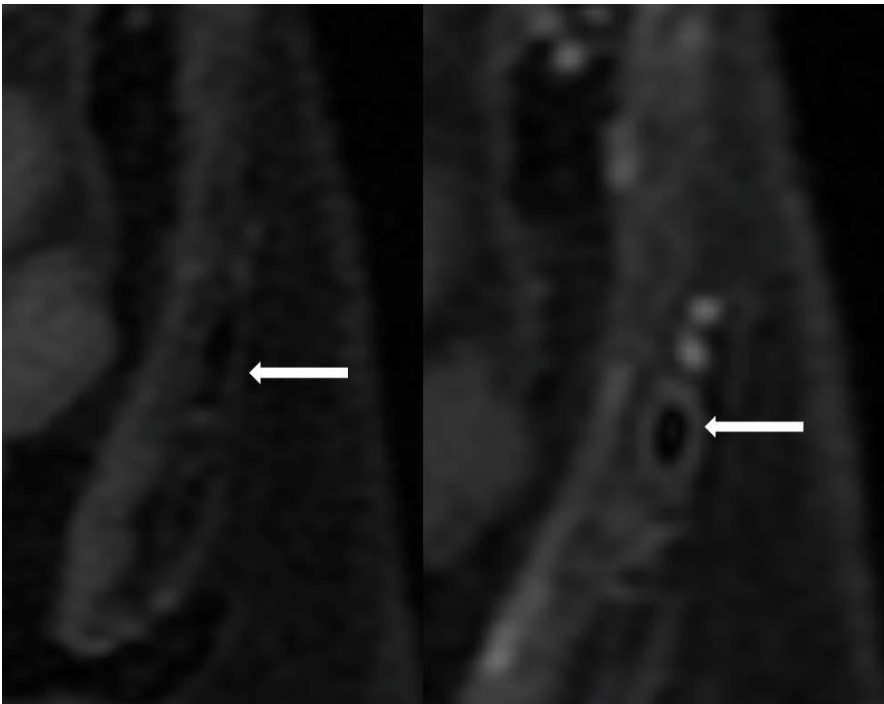


Figure 2.06: Representative Image. Coronal Fat-Sat T1 pre and post contrast images showing an example of a normal extracranial branch (score 0).

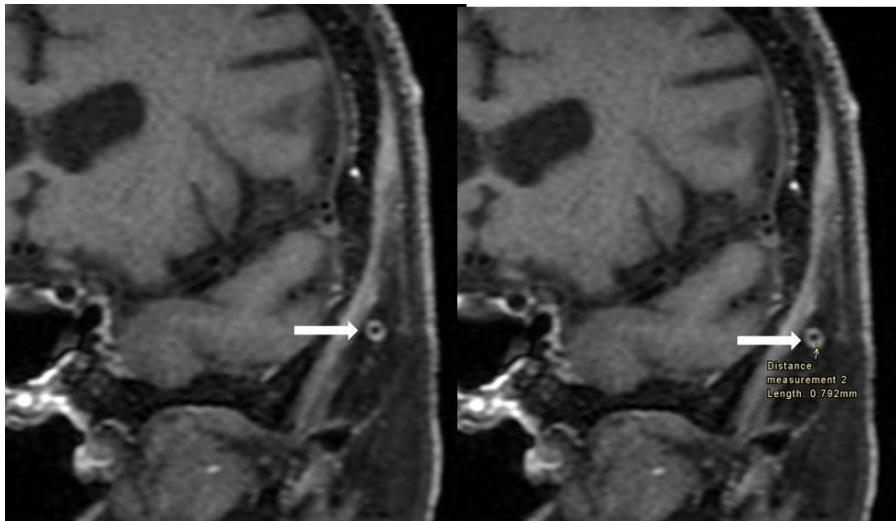


Figure 2.07: Representative Image. Coronal Fat-Sat T1 post contrast images showing an example of a positive study in a left frontal branch (score 2).

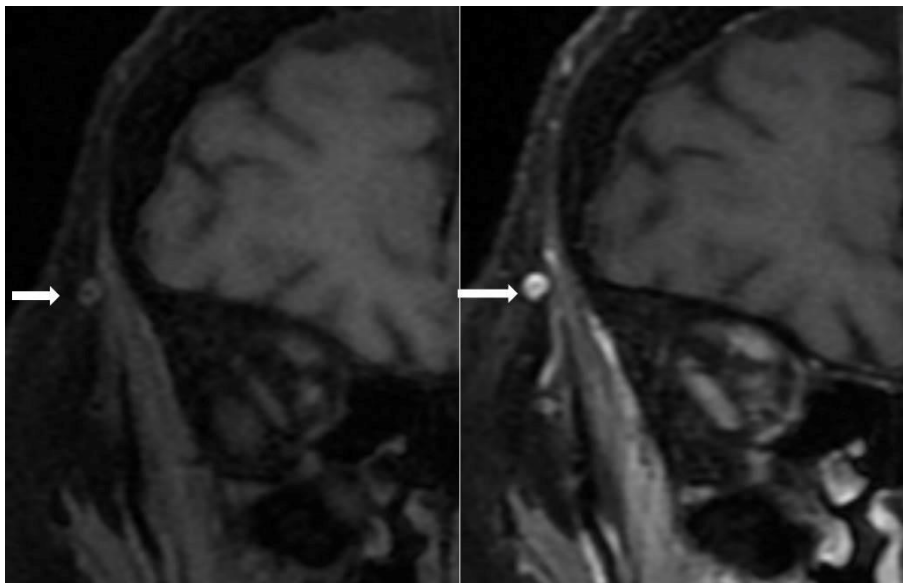


Figure 2.08: Representative Image. Coronal Fat-Sat T1 pre and post contrast images showing an example of a positive study in a right frontal branch (score 3).

2.3 Results

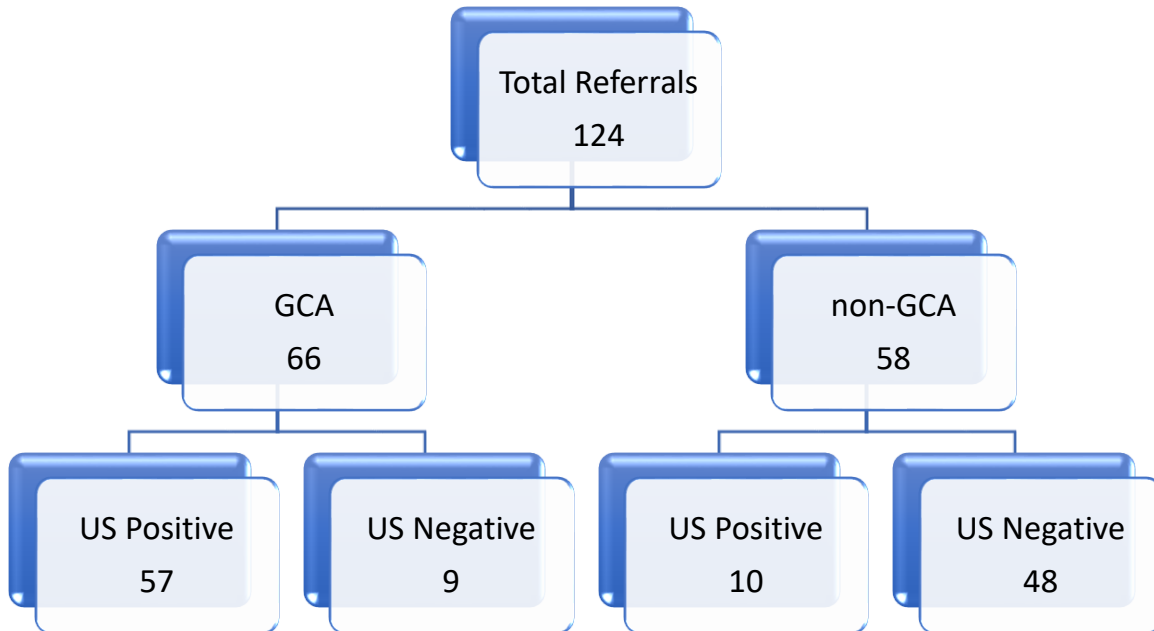


Figure 2.09: Schematic of referrals, diagnoses and VUS results from rapid-access GCA clinic.

2.3.1 Baseline characteristics of all patients referred to rapid-access GCA clinic

For 124 patients referred with suspected GCA, the average age was 68.9 years, average BMI was 28.1 kg/m² and 54% were female. 53.7% of patients fulfilled 1990 ACR GCA Classification Criteria and 66.1% fulfilled 2022 ACR/EULAR Classification Criteria. The mean PTPS was 10.7 and the mean 2022 ACR/EULAR GCA Classification Criteria score was 9.3. 93.5% had symptoms at study entry which, in order of prevalence, included headaches (60%), scalp tenderness (34%), blurred vision (26%), shoulder PMR (25%), anorexia (18%), weight loss (17%), jaw claudication (16%), hip PMR (16%), night sweats (12%), loss of vision (7.5%) and fever (8%). STA pulse was palpable in 97% and was thickened or tender in 9%. 62.6% had elevated inflammatory markers. 53% had a final diagnosis of GCA,

verified by two rheumatologists at six months, and 54% had a positive VUS. The median interval from initiation of corticosteroid therapy to performing VUS was 1 day (IQR 0-3).

Characteristics of All Patients with Suspected GCA (n=124)	Mean (SD)/ Median (IQR)/ N(%)
Age (years)	68.9 (10.97)
Body Mass Index (kg/m ²)	28.1 (24.8-31.4)
Sex (female)	67/124 (54.0%)
Pre-Test Probability Score	10.7 (3.61)
1990 ACR GCA Classification Criteria Fulfilled	65/121 (53.7%)
2022 ACR/EULAR Classification Criteria Fulfilled	82/124 (66.1%)
2022 ACR/EULAR Classification Criteria Score	9.3 (4.82)
Final Diagnosis is GCA	66/124 (53.2%)
VUS Positive	67/124 (54.0%)
TAB Positive	21/64 (32.8%)
MRA of STA Positive	12/22 (54.5%)
Time (days) from Initiation of GC to VUS	1 (0-3)
Time (days) from Initiation of GC to TAB	8 (4-14.5)
Time (days) from Initiation of GC to MRA	8 (5-18)
Symptoms (any GCA symptom) at Study Entry	116/124 (93.5%)
ESR or CRP Elevated	77/123 (62.6%)

Table 2.02: Characteristics of total study cohort.

2.3.2 Comparison of patients with and without GCA

Patients with GCA were older (73.3 v 63.4 years), had lower median BMI (27.1 v 29.0 kg/m², not statistically significant) and were mostly male. They had a higher mean number of CV risk factors, although not statistically significant. A greater proportion of this group fulfilled 1990 and 2022 GCA classification criteria and this group had higher PTPS and 2022 ACR/EULAR GCA Classification Criteria scores. These patients were more likely to have any symptom related to GCA but in particular, ischaemic symptoms such as loss of vision and jaw claudication, shoulder PMR and weight loss were more prevalent in this group. There were no significant between-group differences detected for STA examination abnormalities. GCA patients had higher baseline inflammatory markers and were likelier to have an abnormal VUS (86.4%) and TAB (40.4%). Notably, those with GCA were less likely to have an abnormal MRA (47.1% versus 80%) despite having a lower median interval between initiation of corticosteroids and MRA being performed (8 versus 14.5 days), although neither was statistically significant. This observation is likely due to a combination of the test having poor specificity and sample size being too small.

ESR, CRP and IL-6, neutrophils, monocytes and platelets were higher in the GCA group but there was no between-group difference in Hb. The GCA cohort had higher baseline Halo Counts and Halo Scores for STA and AA separately as well as combined total scores. Halo sign and Compression sign were commoner in all branches of STA and AA, and IMTmax was greater in all branches, in those patients with GCA. GCA patients were followed up for a median of six months, 39.2% of whom flared, with 5.9% developing ischaemic complications. 56.4% ultimately required Tocilizumab.

Patient Characteristics	GCA (n=66) Mean (SD)/ Median (IQR)/ N(%)	Non-GCA (n=58) Mean (SD)/ Median (IQR)/ N(%)
Age (years)	73.30 (8.73)	63.38 (11.16) ^{***}
Body Mass Index (kg/m ²)	27.1 (24.4-31.2)	29.0 (25.2-32.9)
Sex (female)	30/66 (45.5%)	37/58 (63.8%)*
Length of Follow-up (months)	6 (3-12)	-
Pre-Test Probability Score	12.6 (3.19)	8.6 (2.78) ^{***}
Any CV Risk Factor	57/66 (86.4%)	43/58 (74.1%)
Number of CV Risk Factors	1.64 (1.08)	1.17 (0.99)
Smoker	7/64 (10.9%)	9/58 (15.5%)
Established Vascular Disease	18/66 (27.3%)	15/58 (25.9%)
Flare of GCA at any point during Follow-up	20/51 (39.2%)	-
Ischaemia at Baseline (loss of vision, CVA etc)	15/68 (22.7%)	4/58 (6.9%) ^{**}
Ischaemia During Follow-up	3/51 (5.9%)	-
Baseline Treatment with Tocilizumab	9/57 (15.8%)	-
Ever Treated with Tocilizumab	31/55 (56.4%)	-
1990 ACR GCA Classification Criteria Fulfilled	48/66 (72.7%)	17/55 (30.9%) ^{***}
2022 ACR/EULAR Classification Criteria Fulfilled	61/66 (92.4%)	21/58 (36.2%) ^{***}
2022 ACR/EULAR Classification Criteria Score	12.38 (3.89)	5.74 (2.98) ^{***}
Ultrasound Positive	57/66 (86.4%)	10/58 (17.2%) ^{***}
TAB Positive	21/52 (40.4%)	0/12 (0.0%) ^{**}
MRA of STA Positive	8/17 (47.1%)	4/5 (80.0%)
Time (days) from Initiation of GC to VUS	1 (0-2)	1.5 (1-4) [*]
Time (days) from Initiation of GC to TAB	8 (4-15)	7.5 (4.5-11.5)
Time (days) from Initiation of GC to MRA	8 (5-15)	14.5 (8-21)
Symptoms (any GCA symptom) at Study Entry	65/66 (98.5%)	51/58 (87.9%)*

Table 2.03: Characteristics of those with and without GCA. *p< 0.05, **p<0.005, ***p<0.0005.

Clinical Features	GCA (n=66) Mean (SD)/ Median (IQR)/ N(%)	Non-GCA (n=58) Mean (SD)/ Median (IQR)/ N(%)
Headache	54/66 (81.8%)	45/58 (77.6%)
Scalp Tenderness	37/66 (56.1%)	24/58 (41.4%)
Blurring of Vision	26/66 (39.4%)	17/58 (29.3%)
Loss of Vision	14/66 (21.2%)	4/58 (6.9%)*
Jaw Claudication	18/66 (27.3%)	5/58 (8.6%)**
Shoulder PMR	23/66 (34.8%)	9/58 (15.5%)*
Hip PMR	14/66 (21.2%)	6/58 (10.3%)
Fever	7/66 (10.6%)	3/58 (5.2%)
Night Sweats	9/66 (13.6%)	6/58 (10.3%)
Anorexia	16/66 (24.2%)	7/58 (12.1%)
Weight Loss	16/66 (24.2%)	5/58 (8.6%)*
STA Pulse Impalpable on Either Side	2/66 (3.0%)	2/58 (3.4%)
STA Thickened on Palpation	9/66 (13.6%)	3/58 (5.2%)
STA Tender on Palpation	9/66 (13.6%)	11/58 (19.0%)
Any STA Abnormality on Examination	17/66 (25.8%)	13/58 (22.4%)

Table 2.04: Clinical features of those with and without GCA. *p< 0.05, **p<0.005, ***p<0.0005.

Laboratory Results	GCA (n=66) Mean (SD)/ Median (IQR)/ N(%)	Non-GCA (n=58) Mean (SD)/ Median (IQR)/ N(%)
ESR or CRP elevated	54/65 (83.1%)	23/58 (39.7%)***
ESR (mm/hr)	55 (35-82)	24.5 (13.5-54)***
CRP (mg/L)	43.5 (11-99.5)	6.5 (2-36)***
IL-6 (pg/ml)	4.91 (2.0-11.3)	2.4 (1.5-7.7)***
Haemoglobin (g/dl)	12.86 (1.60)	12.95 (1.75)
White Blood Cells (x10 ⁹ /L)	10.13 (3.48)	8.10 (2.77)***
Neutrophils (x10 ⁹ /L)	7.51 (3.29)	5.55 (2.58)***
Lymphocytes (x10 ⁹ /L)	1.62 (0.76)	1.74 (0.80)
Monocytes (x10 ⁹ /L)	0.78 (0.33)	0.62 (0.26)**
Eosinophils (x10 ⁹ /L)	0.17 (0.17)	0.16 (0.17)
Basophils (x10 ⁹ /L)	0.05 (0.04)	0.05 (0.04)
Platelets (x10 ⁹ /L)	354.68 (121.59)	302.29 (95.04)*

Table 2.05: Laboratory results for those with and without GCA. *p< 0.05, **p<0.005, ***p<0.0005

VUS Results	GCA (n=66) Mean (SD)/ Median (IQR)/ N(%)	Non-GCA (n=58) Mean (SD)/ Median (IQR)/ N(%)
Ultrasound Positive	57/66 (86.4%)	10/58 (17.2%) ***
Superficial Temporal Artery Halo Count	3 [0-6]	0 [0-6] ***
Axillary Artery Halo Count	0 [0-2]	0 [0-2] ***
Total Halo Count	4 [0-8]	0 [0-6] ***
Superficial Temporal Artery Halo Score	12[2-23]	5 [1-18]***
Axillary Artery Halo Score	12 [0-24]	6 [0-24] ***
Total Halo Score	24 [8-43]	13 [3-32] ***

Table 2.06: VUS scores for those with and without GCA. *p< 0.05, **p<0.005, ***p<0.0005.

VUS Results for Individual Vessel Branches	GCA (n=66) Mean (SD)/ Median (IQR)/ N(%)	Non-GCA (n=58) Mean (SD)/ Median (IQR)/ N(%)
Rt cSTA Halo	35/66 (53.0%)	5/58 (8.6%)***
Rt cSTA CS	35/66 (53.0%)	5/58 (8.6%)***
Rt cSTA IMTmax (mm)	0.52 (0.23)	0.32 (0.11) ***
Rt fSTA Halo	35/66 (53.0%)	3/58 (5.2%)***
Rt fSTA CS	36/66 (54.5%)	3/58 (5.2%)***
Rt fFTA IMTmax (mm)	0.40 (0.18)	0.24 (0.07) ***
Rt pSTA Halo	29/66 (43.9%)	2/58 (3.4%)***
Rt pSTA CS	29/66 (43.9%)	2/58 (3.4%)***
Rt pSTA IMTmax (mm)	0.31 (0.14)	0.21 (0.06) ***
Lt cSTA Halo	38/66 (57.6%)	3/58 (5.2%)***
Lt cSTA CS	38/66 (57.6%)	3/58 (5.2%)***
Lt cSTA IMTmax (mm)	0.48 (0.15)	0.33 (0.10) ***
Lt fSTA Halo	39/66 (59.1%)	6/58 (10.3%)***
Lt fSTA CS	39/66 (59.1%)	6/58 (10.3%)***
Lt fFTA IMTmax (mm)	0.41 (0.17)	0.26 (0.08) ***
Lt pSTA Halo	31/66 (47.0%)	3/58 (5.2%)***
Lt pSTA CS	31/66 (47.0%)	3/58 (5.2%)***
Lt pSTA IMTmax (mm)	0.34 (0.16)	0.23 (0.07) ***
Rt Axillary Artery Halo	21/66 (31.8%)	2/58 (3.4%)***
Rt Axillary Artery IMTmax (mm)	0.93 (0.43)	0.66 (0.25) ***
Lt Axillary Artery Halo	21/66 (31.8%)	4/58 (6.9%)***
Lt Axillary Artery IMTmax (mm)	0.91 (0.40)	0.66 (0.25) ***

Table 2.07: VUS results in individual vessel branches for those with and without GCA. *p< 0.05, **p<0.005, ***p<0.0005.

2.3.3 Comparison of those with and without positive ultrasound

Those with a positive VUS were older [73.8 (8.28) vs 63.1 years (11.00)], were mostly male and had lower median BMI, although this was not statistically significant. More patients in this group met 1990 and 2022 GCA classification criteria and had higher PTPS and 2022 ACR/EULAR GCA Classification Criteria scores. They had a higher mean number of CV risk factors, although this was not statistically significant. These patients had more prevalent typical GCA symptoms, in particular, loss of vision, jaw claudication and weight loss. STA palpation was abnormal in a greater proportion of those with a positive VUS, in particular STA thickening, while ESR, CRP, neutrophils, monocytes and platelets were higher. There was a trend towards higher IL-6 and neutrophil counts and lower lymphocyte counts, although these were not statistically significant. There was a difference in all measured sonographic parameters of STA and AA between the two groups although the median duration from initiation of glucocorticoids to performing VUS was lower in those with a positive VUS (1 versus 2 days). Halo Scores were higher in this group and although Halo Counts were higher, this did not reach statistical significance. A greater proportion of VUS positive patients had a positive TAB and a lower proportion had a positive MRA, but no statistical significance was observed. A greater proportion of patients in this group had a clinical diagnosis of GCA at 6 months, suffered ischaemic complications and were treated with biologic therapy.

Patient Characteristics	US Positive (n=67)	US Negative (n=57)
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	Mean (SD)/ Median (IQR)/ N(%)	Mean (SD)/ Median (IQR)/N(%)
Age (years)	73.79 (8.28)	63.11 (11.00)***
Body Mass Index (kg/m ²)	26.8 (24.4-31.2)	29.3 (26.0-32.9)
Sex (female)	30/67 (44.7%)	37/57 (64.9%)*
Length of Follow-up	6 (1-12)	-
Pre-test Probability Score	12.6 (3.19)	8.6 (2.82) ***
Any CV Risk Factor	57/66 (86.4%)	43/58 (74.1%)
Number of CV Risk Factors	1.51 (1.06)	1.32 (1.05)
Smoker	10/65 (15.4%)	6/57 (10.5%)
Established Vascular Disease	21/67 (31.3%)	12/57 (21.1%)
Flare of GCA During Follow-up	20/61 (32.7%)	-
Ischaemia at Baseline (vision loss, CVA etc)	16/67 (23.8%)	3/57 (5.0%)**
Ischaemia During Follow-up	3/51 (5.9%)	-
Baseline Treatment with Tocilizumab	9/67 (13.4%)	0/48 (0.0%)**
Ever Treated with Tocilizumab	31/67 (46.2%)	0/48 (0.0%)***
1990 ACR GCA Classification Criteria Fulfilled	51/67 (76.1%)	14/54 (25.9%)***
2022 ACR/EULAR Classification Criteria Fulfilled	66/67 (98.5%)	16/57 (28.0%)***
2022 ACR/EULAR Classification Criteria Score	12.9 (3.19)	5.0 (2.13) ***
Final Diagnosis is GCA	57/67 (85.1%)	9/57 (15.8%)***
VUS Positive	67/67 (100.0%)	0/57 (0.0%)***
TAB Positive	19/50 (38.0%)	2/14 (14.3%)
MRA of STA Positive	8/17 (47.1%)	4/5 (80.0%)
Time (days) from Initiation of GC to VUS	1 (0-2)	2 (1-5) **
Time (days) from Initiation of GC to TAB	8 (4-13)	13 (4-19)
Time (days) from Initiation of GC to MRA	8 (5-15)	12 (5-19)
Symptoms (any GCA symptom) at Study Entry	66/67 (98.5%)	50/57 (87.7%)*

Table 2.08: Characteristics of those with and without a positive VUS. *p< 0.05, **p<0.005, ***p<0.0005.

Clinical Features	US Positive (n=67) Mean (SD)/ Median (IQR)/ N(%)	US Negative (n=57) Mean (SD)/ Median (IQR)/N(%)
Headache	55/67 (82.1%)	44/57 (77.2%)
Scalp Tenderness	35/67 (52.2%)	26/57 (45.6%)
Blurring of Vision	25/67 (37.3%)	18/57 (31.6%)
Loss of Vision	15/67 (22.4%)	3/57 (5.3%)**
Jaw Claudication	19/67 (28.4%)	4/57 (7.0%)**
Shoulder PMR	20/67 (29.9%)	12/57 (21.1%)
Hip PMR	13/67 (19.4%)	7/57 (12.3%)
Fever	6/67 (9.0%)	4/57 (7.0%)
Night Sweats	11/67 (16.4%)	4/57 (7.0%)
Anorexia	16/67 (23.9%)	7/57 (12.3%)
Weight Loss	17/67 (25.4%)	4/57 (7.0%)**
STA Pulse Impalpable on Either Side	3/67 (4.5%)	1/57 (1.8%)
STA Thickened on Palpation	10/67 (14.9%)	2/57 (3.5%) *
STA Tender on Palpation	10/67 (14.9%)	10/57 (17.5%)
Any STA Abnormality on Exam	17/66 (25.8%)	13/58 (22.4%)

Table 2.09: Clinical features of those with and without a positive VUS. *p< 0.05, **p<0.005, ***p<0.0005.

Laboratory Results	US Positive (n=67) Mean (SD)/ Median (IQR)/ N(%)	US Negative (n=57) Mean (SD)/ Median (IQR)/N(%)
ESR or CRP elevated	56/67 (83.6%)	21/56 (37.5%)***
ESR (mm/hr)	55 (34-88)	27 (14.5-49.5)***
CRP (mg/L)	41 (9-90)	6.5 (2-37)***
IL-6 (pg/ml)	5.2 (2.0-11.3)	2.4 (1.5-6.9)
Haemoglobin (g/dl)	12.87 (1.63)	12.94 (1.72)
White Blood Cells (x10 ⁹ /L)	9.71 (3.46)	8.53 (3.02)
Neutrophils (x10 ⁹ /L)	7.13 (3.25)	5.94 (2.87) *
Lymphocytes (x10 ⁹ /L)	1.61 (0.76)	1.76 (0.80)
Monocytes (x10 ⁹ /L)	0.77 (0.34)	0.64 (0.25)*
Eosinophils (x10 ⁹ /L)	0.17 (0.18)	0.16 (0.15)
Basophils (x10 ⁹ /L)	0.05 (0.04)	0.05 (0.04)
Platelets (x10 ⁹ /L)	349.30 (121.85)	306.81 (96.26)*

Table 2.10: Laboratory results for those with and without a positive US. *p< 0.05, **p<0.005, ***p<0.0005.

VUS Results	US Positive (n=67) Mean (SD)/ Median (IQR)/ N(%)	US Negative (n=57) Mean (SD)/ Median (IQR)/N(%)
VUS Positive	67/67 (100.0%)	0/57 (0.0%)***
Superficial Temporal Artery Halo Count	4 [0-6]	0 [0-0]
Axillary Artery Halo Count	0 [0-2]	0 [0-0]
Total Halo Count	4 [1-8]	0 [0-0]
Superficial Temporal Artery Halo Score	12 [5-23]	5 [1-11]***
Axillary Artery Halo Score	12 [0-24]	6 [0-15]***
Total Halo Score	26 [8-43]	12 [3-23]***

Table 2.11: VUS scores for those with and without a positive VUS. *p< 0.05, **p<0.005, ***p<0.0005.

VUS Results in Individual Vessel Branches	US Positive (n=67) Mean (SD)/ Median (IQR)/ N(%)	US Negative (n=57) Mean (SD)/ Median (IQR)/N(%)
Rt cSTA Halo	40/67 (59.7%)	0/57 (0.0%)***
Rt cSTA CS	40/67 (59.7%)	0/57 (0.0%)***
Rt cSTA IMTmax (mm)	0.54 (0.22)	0.29 (0.07)***
Rt fSTA Halo	38/67 (56.7%)	0/57 (0.0%)***
Rt fSTA CS	39/67 (58.2%)	0/57 (0.0%)***
Rt fFTA IMTmax (mm)	0.41 (0.17)	0.23 (0.06)***
Rt pSTA Halo	31/67 (46.3%)	0/57 (0.0%)***
Rt pSTA CS	31/67 (46.3%)	0/57 (0.0%)***
Rt pSTA IMTmax (mm)	0.31 (0.13)	0.20 (0.06)***
Lt cSTA Halo	41/67 (61.2%)	0/57 (0.0%)***
Lt cSTA CS	41/67 (61.2%)	0/57 (0.0%)***
Lt cSTA IMTmax (mm)	0.49 (0.15)	0.32 (0.07)***
Lt fSTA Halo	45/67 (67.2%)	0/57 (0.0%)***
Lt fSTA CS	45/67 (67.2%)	0/57 (0.0%)***
Lt fFTA IMTmax (mm)	0.42 (0.16)	0.24 (0.05)***
Lt pSTA Halo	34/67 (50.7%)	0/57 (0.0%)***
Lt pSTA CS	34/67 (50.7%)	0/57 (0.0%)***
Lt pSTA IMTmax (mm)	0.35 (0.16)	0.22 (0.05)***
Rt Axillary Artery Halo	23/67 (34.3%)	0/57 (0.0%)***
Rt Axillary Artery IMTmax (mm)	0.96 (0.44)	0.62 (0.14)***
Lt Axillary Artery Halo	25/67 (37.3%)	0/57 (0.0%)***
Lt Axillary Artery IMTmax (mm)	0.94 (0.41)	0.62 (0.17)***

Table 2.12: VUS results in individual vessel branches for those with and without a positive VUS. *p< 0.05, **p<0.005, ***p<0.0005.

2.3.4 Diagnostic performance of VUS for a clinical diagnosis of GCA

	Ultrasound Positive	Ultrasound Negative	Total
GCA Positive	57	9	66
GCA Negative	10	48	58
Total	67	57	124
Sensitivity	Specificity	Area under the curve	
82.76%	84.68%	0.85 (0.78-0.91)	

Table 2.13: Sensitivity and Specificity of VUS for a clinical diagnosis of GCA.

2.3.5 Diagnostic performance of TAB for a clinical diagnosis of GCA

	TAB Positive	TAB Negative	Total
GCA Positive	21	31	52
GCA Negative	0	12	12
Total	21	43	64
Sensitivity	Specificity	Area under the curve	
40.4%	100.0%	0.70 (0.63-0.77)	

Table 2.14: Sensitivity and Specificity of TAB for a clinical diagnosis of GCA.

2.3.6 Diagnostic performance of GCA Classification criteria for a clinical diagnosis of GCA

	1990 criteria fulfilled	1990 criteria not fulfilled	Total
GCA Positive	48	18	66
GCA Negative	17	38	55
Total	65	56	121
Sensitivity	Specificity	Area under the curve	
72.7%	69.1%	0.70 (0.62-0.79)	

Table 2.15: Sensitivity and Specificity of 1990 ACR Classification Criteria for a clinical diagnosis of GCA.

	2022 criteria fulfilled	2022 criteria not fulfilled	Total
GCA Positive	61	5	66
GCA Negative	21	37	58
Total	82	42	124
Sensitivity	Specificity	Area under the curve	
92.4%	63.8%	0.78 (0.71-0.85)	

Table 2.16: Sensitivity and Specificity of 2022 EULAR/ACR Classification Criteria for a clinical diagnosis of GCA.

2.3.7 Diagnostic performance of MRA for a clinical diagnosis of GCA

	MRA Positive	MRA Negative	Total
GCA Positive	8	9	17
GCA Negative	4	1	5
Total	12	10	22
Sensitivity	Specificity	Area under the curve	
47.1%	20.0%	0.34 (0.10-0.57)	

Table 2.17: Sensitivity and Specificity of MRA for a clinical diagnosis of GCA.

	Sensitivity	Specificity	AUC
Vascular Ultrasound	82.76%	84.68%	0.85 (0.78-0.91)
Temporal Artery Biopsy	40.4%	100.0%	0.70 (0.63-0.77)
1990 ACR GCA Classification Criteria	72.7%	69.1%	0.70 (0.62-0.79)
2022 EULAR/ACR GCA Classification Criteria	92.4%	63.8%	0.78 (0.71-0.85)
Superficial Temporal Artery MRA	47.1%	20.0%	0.34 (0.10-0.57)

Table 2.18: Diagnostic performance of VUS, TAB, classification criteria and MRA in a cohort of 124 patients with suspected GCA.

2.3.8 Diagnostic performance of PTPS for a clinical diagnosis of GCA

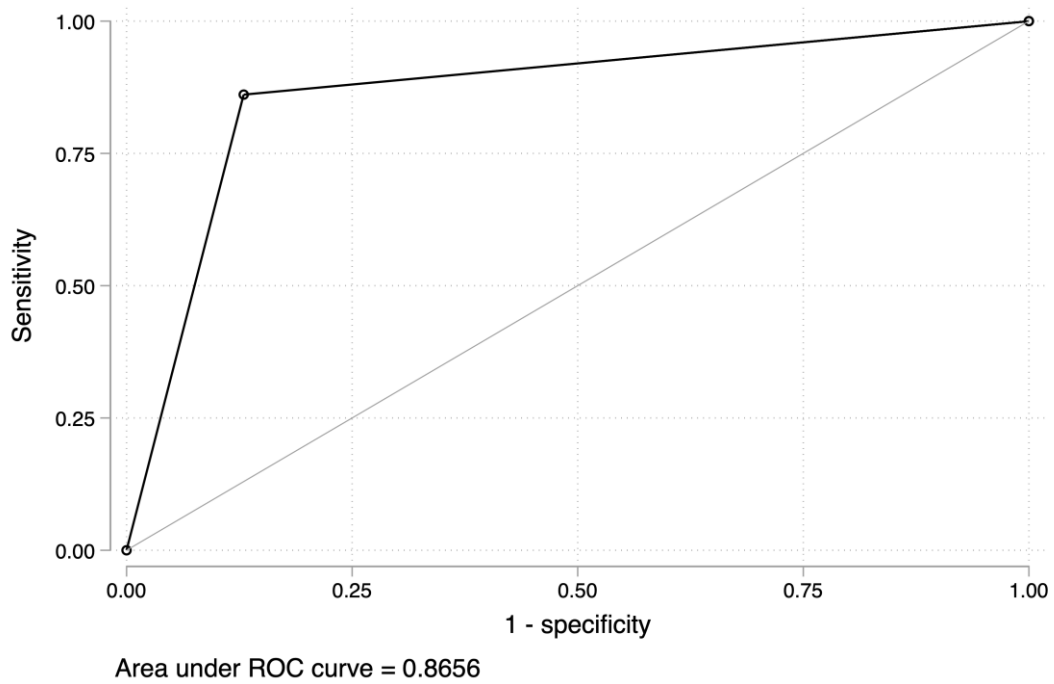


Figure 2.10: AUC for PTPS in GCA is 0.87.

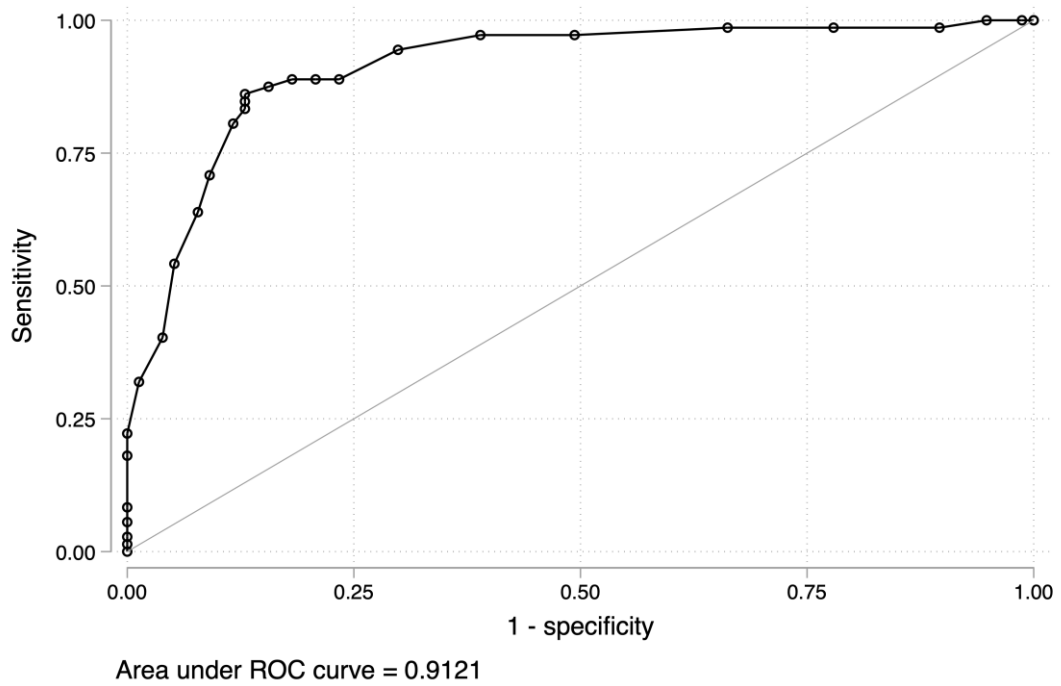


Figure 2.11: AUC for combined PTPS and VUS in GCA is 0.912.

PTPS Cut-off	Sensitivity (VUS negative)	Specificity (VUS Positive)	Correctly Classified
>=3	100%	0.00%	48.32%
>=4	100%	1.30%	48.99%
>=5	100%	5.19%	51.01%
>=6	97.22%	10.39%	52.35%
>=7	95.83%	22.08%	57.72%
>=8	95.83%	33.77%	63.76%
>=9	91.67%	51.95%	71.14%
>=10	81.94%	64.94%	73.15%
>=11	72.22%	75.32%	73.83%
>=12	56.94%	84.42%	71.14%
>=13	43.06%	88.31%	66.44%
>=14	34.72%	93.51%	65.10%
>=15	23.61%	97.40%	61.74%
>=16	18.06%	100%	60.40%
>=17	8.33%	100%	55.70%
>=18	5.56%	100%	54.36%
>=19	2.78%	100%	53.02%
>=20	1.39%	100%	52.35%
>=21	0.00%	100%	51.68%

Table 2.19: Sensitivities and specificities of VUS and PTPS combined, for GCA diagnosis.

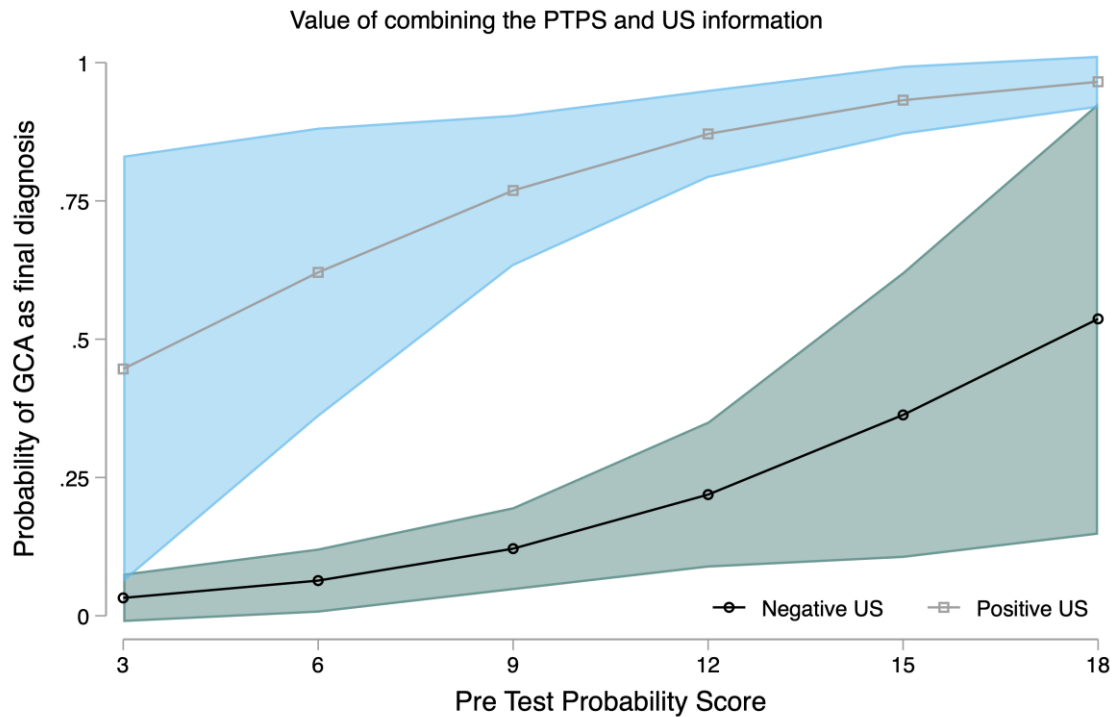


Figure 2.12: Value of combining PTPS and VUS results.

The value of combining PTPS and VUS results is highlighted in Figures 2.10 and 2.11. AUC improves from 0.87 to 0.91, which is better than the AUC for either VUS or PTPS in isolation. Table 2.19 and Fig 2.12 highlight how these can be used in practical terms. In the case of a negative VUS (represented in grey region in Fig 2.13) a PTPS of <6 has 100% sensitivity for GCA. In the case of a positive VUS (represented in blue region in Fig 2.13), a PTPS >16 has 100% specificity for GCA.

2.4 Discussion

The potentially catastrophic consequences of untreated GCA, in the context of a lifetime risk of 0.5-1.0% for developing this condition, makes clarifying the optimal diagnostic test a high priority for rheumatologists. TAB has a high false-negative rate and impacts little on clinical decision-making while studies looking at VUS have shown inconsistent results for a variety of reasons including variances in technology, sonographer training and study methodologies. MRA has been studied little, particularly in direct head-to-head studies with VUS, and while classification criteria for GCA have been updated, they require real-world validation as does the PTPS.

In this study, a large cohort of patients with suspected GCA were enrolled (n=124). A firm clinical diagnosis of GCA was established in 66 patients by two experienced rheumatologists. STA and AA US was performed in all patients, TAB was performed in 64 while MRA was performed in 22 patients. GCA classification criteria and PTPS were applied to the entire cohort and a combined VUS/PTPS model was evaluated for diagnostic accuracy.

This cohort was mostly female with a mean age of 68.9 years, 53% of whom were ultimately diagnosed with GCA and 54% of whom had a positive VUS, with a mean interval of 1 day from initiation of glucocorticoids to having VUS performed. In comparing VUS with TAB, classification criteria and MRA a number of important findings were made. 2022 EULAR/ACR GCA Classification Criteria was the best screening tool with a sensitivity of 92.4% followed by VUS at 82.76%. MRA performed poorly with a sensitivity of just 47.1% along with TAB at 40.4%. After

TAB, VUS had the second highest specificity at 84.68% and overall the highest AUC at 0.85, implying that this is the most accurate test of those evaluated here, for investigating suspected cases of GCA. Incorporating PTPS and VUS results appeared to improve diagnostic performance over and above that of either tool being used in isolation. 2022 EULAR/ACR GCA Classification Criteria had a higher AUC than 1990 criteria and MRA performed poorly with an AUC of just 0.34.

This study confirms the superiority of VUS over TAB and MRA for GCA diagnosis and highlights that incorporation of PTPS can improve its performance further. Additionally, it provides external validation for 2022 EULAR/ACR GCA Classification Criteria and shows their superiority over 1990 criteria.

This study has a number of strengths. Firstly, VUS was performed at a median interval of 1 day after commencing glucocorticoids. The sensitivity for VUS in this study is slightly higher than that seen in other cohorts and may be explained by this short interval between treatment and test. Secondly, all sonographers in this study were specifically trained in VUS and performed all scans in line with OMERACT guidelines. The heterogeneity seen in study results heretofore is almost certainly impacted by variances in methodologies including sonographer experience, technique and image-interpretation. Standardising studies using OMERACT guidelines and definitions eliminates this as a potential confounding factor. Thirdly, this cohort is large with 124 study participants and is only the 7th cohort of more than 100 patients evaluating the sensitivity and specificity of VUS in GCA. Lastly, the results described for VUS are broadly in-line with published meta-analyses which show sensitivities ranging 68-77% and specificities ranging 82-96%. While sensitivity for TAB in this cohort is low at 40%, the findings match those seen in the TABUL study.

This study has some weaknesses. While the investigators endeavoured to scan all patients within 24 hours of referral, this was not possible in all cases and may have impacted on results. The aim was to scan a steroid-naïve cohort but due to the practicalities of operating a rapid-access clinic across two sites, there was a median of 1 day between commencing steroids and performing scans. Secondly, TAB could not be performed in all cases. TAB was performed in 64 patients and access was limited due to operating theatre scheduling. TAB was predominantly reserved for those deemed to be at a high likelihood of having a diagnosis of GCA, so it is unlikely that the relatively low number of TABs performed significantly impacted on results. Lastly, the sample size for those who underwent MRA is small at 22. While the AUC for MRA is poor at 0.34, this is not statistically significant. It should be noted that there was a median of 8 days from initiation of glucocorticoids to having MRA performed and as we know from studies such as that performed by Klink et al, MRA abnormalities regress rapidly under corticosteroid therapy. This may explain why 9 false-negative scans were observed. Nonetheless, 4 study participants had false-positive MRAs which raises concerns about the specificity of this test.

2.5 Conclusions

VUS is the best diagnostic test for evaluating suspected GCA with an AUC 0.85 in a cohort of 124 patients with suspected GCA. TAB does not have adequate sensitivity to be used for this purpose and should be reserved for those with a high likelihood of having GCA who have a negative baseline VUS. The Southend PTPS has a role in evaluating suspected GCA when used in combination with VUS.

When PTPS ≥ 16 and VUS is positive, specificity for GCA diagnosis is 100%. When PTPS < 6 and VUS is negative, sensitivity for GCA diagnosis is 100%. 2022

ACR/EULAR GCA Classification Criteria have shown better sensitivity than 1990 criteria, but they have no role in routine clinical practice due to their poor specificity for GCA diagnosis. MRA of STA lacks specificity for GCA but these findings should be confirmed in a larger cohort.

Chapter 3: A Prospective Cohort Study Evaluating the Role of Quantifying Sonographic Inflammatory Changes in Giant Cell Arteritis

Abstract

VUS is a well-validated tool for diagnosing GCA (5). Early use of VUS in GCA relied upon identifying gross changes such as the 'Halo' sign but more recently there is a focus on objective quantification of sonographic inflammatory change with scoring, which appears to have improved the accuracy of VUS. Little is known about the role of VUS in prognostication or disease-monitoring. Different quantification scores have been proposed for VUS in GCA which incorporate IMT measurements. Halo Count (HC), Halo Score (HS) and OGUS have all been described, although their precise role in routine clinical practice is yet to be determined.

This study compares IMT measurements, HC, HS and OGUS in a prospective cohort of GCA patients in order to assess the role of sonographic vasculitis quantification in the diagnosis and management of GCA. US of STA and AA was repeated at 1, 3, 6 and 12 months in a cohort of patients who had an abnormal baseline VUS. AUC analysis was performed to determine the optimal cut-off IMT in each branch of STA and AA for GCA diagnosis. Mean HC, HS and OGUS were calculated at each study timepoint. Wald tests were used to determine the significance of longitudinal trends in each score. Time-to-normalization of HC, HS and OGUS were evaluated with abnormal thresholds considered ≥ 1 , ≥ 21 and ≥ 1.0 respectively. Correlation coefficients were compared between all clinical and

biochemical parameters and baseline VUS quantification scores (HC, HS and OGUS) to determine which patient factors may predict VUS outcomes. Correlation coefficients were calculated and AUC analysis was performed for all clinical, biochemical and VUS parameters to determine reliability for predicting future adverse events (GCA diagnosis, GCA flare, ischaemic complications and future biologic requirement). DeLong test was used to validate the OGUS score.

48/50 patients were followed up at 6 months and 27 at 12 months. The optimal IMT cut-offs for diagnosing GCA in this cohort were: Common STA 0.42mm, Frontal STA, 0.35, Parietal STA 0.29, Axillary Artery 0.75 with no significant difference observed between groups with and without CV risk factors. Mean HC, HS and OGUS all declined over 12 months with statistically significant differences observed between each study timepoint. Of 48 patients, HC, HS and OGUS normalized in 21, 32 and 39 patients respectively by 6 months and no association was seen between time-to-normalisation and adverse events. Fulfilling 2022 ACR/EULAR Classification Criteria showed moderate correlation with baseline HC, HS and OGUS with higher classification criteria scores showing strong correlation with higher VUS outcome scores. HC, HS and OGUS were superior to all clinical and laboratory parameters for predicting future adverse events with OGUS outperforming HC and HS.

This data allows clinicians to confirm or refute a diagnosis of GCA using VUS with 100% sensitivity and specificity if certain parameters are met, and challenges the currently-accepted definitions of normal IMT values in STA and AA. VUS quantification scores performed better than other clinical variables in predicting future adverse events in GCA and OGUS is validated in a prospective cohort. This data suggests that VUS quantification scores are candidate biomarkers for GCA

and may be important outcome variables in clinical trials. Measuring IMT has a role in diagnosing and monitoring GCA and should be considered a standard aspect of VUS in GCA diagnosis.

3.1 Introduction

3.1.1 Background

GCA is the most prevalent idiopathic systemic vasculitis, primarily causes inflammation of large and medium-sized vessels, mostly affects those over the age of 70 years and carries a lifetime risk of 0.5-1.0% (1-3). It is a medical emergency due to the associated risks of potentially catastrophic vascular complications such as permanent blindness (7, 8, 11-13). The traditional gold-standard for diagnosis, TAB, has many limitations as a diagnostic test and its place is slowly being overtaken by VUS (4-6). However, our understanding of the precise definitions of what constitutes vasculitis on US as well as its true place in GCA diagnosis and monitoring continues to evolve.

The presence of a Halo and Compression sign in a vessel with an enlarged IMT denotes sonographic vasculitis. Our current definitions of normal IMT cut-points for individual branches of STA and AA, published in 2017 in a cohort of 40 GCA patients and outlined in Table 1.05, have only been validated in one other cohort to date, while evidence exists that prevalent CV risk factors may affect IMT interpretation (86-88).

Time-to-normalisation of Halo has varied in studies to date with evidence showing regression from as little as 2 days to as late as 7 months after commencing immunosuppressive therapy (82, 89, 108, 114, 118, 137-140). Regression may occur earlier in STA than AA and in those with a lower baseline burden of sonographic inflammation but no associations have been seen in terms of relapse

rate or cumulative steroid consumption (136, 142-144). It has been suggested that rising longitudinal IMT values may be predictive of future flare but based on available data, no reliable conclusions can be made regarding VUS as a tool for monitoring GCA (133).

Conventionally, VUS has a binary outcome with the presence of any one single abnormality considered diagnostic of vasculitis but recent evidence suggests that quantifying sonographic abnormalities in STA and AA, incorporating the size and frequency of halos, has added value. Halo Counts (HC, number of STA/AA branches with Halo), Halo Scores (HS, composite of number and size of halos) and OGUS have all been described. Early evidence suggests that they are sensitive for refractory disease, may be useful for predicting likelihood of positive TAB and correlate positively with likelihood of having ocular complications, but like IMT, are affected by CV risk profile (127, 132, 133, 187, 188). To date however, HC and HS have only been validated in one inception cohort while OGUS has yet to be externally validated (190). Little is known about what specific patient factors are associated with higher baseline scores, while there is conflicting data regarding their role in predicting future disease trajectory.

3.1.2 Aims of Current Study

This research hypothesises that quantification of changes on VUS adds value in GCA diagnosis and may be a useful biomarker. This study aims to define the optimal IMT cut-off values in each branch of STA and AA that can reliably identify the presence of vasculitis in that vessel. It aims to monitor sonographic signs of vasculitis over time to determine how early/late normalisation of IMT occurs. It evaluates what value, if any, exists in quantifying the degree of vasculitis observed sonographically and investigates whether or not this can help with disease prognostication. Lastly, it looks for predictors of higher baseline VUS quantification scores and aims to validate these scoring systems in an inception GCA cohort.

3.2 Methods

3.2.1 Rapid Access GCA clinic

A rapid-access GCA clinic was established in Tallaght University Hospital and Cork University Hospital which accepted referrals from both primary and secondary care clinicians and endeavoured to assess all referred patients within 24 hours.

Assessments included a standard consultation plus comprehensive VUS and same-day treatment where indicated. All investigators involved in this study were rheumatologists with vast experience in managing suspected GCA. Those meeting pre-defined inclusion criteria were enrolled in the study having received a patient information leaflet and having provided written informed consent. Patients were recruited over an 18-month period from July 2020 to January 2022.

3.2.2 Vascular Ultrasound Protocol

VUS of the full length of both STA including Common, Frontal and Parietal branches and both AA, in both transverse and longitudinal planes, was performed in all patients using an 18MHz Linear probe and General Electronic P9 Ultrasound system. In line with OMERACT guidelines, STA vasculitis was defined as a vessel containing a Halo sign (Fig. 2.01) with non-compressibility (Fig. 2.02) and IMT enlargement (Table 1.05) while AA vasculitis was identified by the presence of a Halo sign (Fig. 2.03) with IMT enlargement (Table 1.05). All investigators had prior comprehensive training and vast experience in VUS. Images were reviewed by two

trained ultrasonographers, one blinded to the clinical details, and in the event of a discrepancy in diagnostic scoring a joint score was made by agreement.

3.2.3 Inclusion and Exclusion Criteria, Clinical Diagnosis and Follow-up

All newly diagnosed GCA patients, aged over 50 years were included and anyone on long-term steroids or SSA and anyone aged under 50 years were excluded from this study. Patients all had a clinical diagnosis of GCA established by two rheumatologists based on clinical presentation, laboratory results and response to corticosteroids which was verified again six months after initial diagnosis. Clinical and VUS assessments were repeated at 1, 3, 6 and 12 months. The GiACTA steroid tapering protocol was used in all patients (208). Tocilizumab was initiated in the event of a second flare.

3.2.4. Halo Count, Halo Score, OGUS

Halo Counts, Halo Score, IMTmax and OGUS were calculated at each study timepoint. Halo Counts (HC) refers to the number of STA/AA branches with a Halo while Halo Score (HS) is a composite of both the frequency and size of Halos (Fig. 1.07). OGUS is calculated as follows: sum of IMT measured in every segment divided by the rounded cut-off values of IMTs in each segment; the resulting value is then divided by the number of segments available (191).

3.2.5 Ethical Approval

This study was approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals and also by the St. James' Hospital / Tallaght University Hospital Joint Research Ethics Committee.

3.2.6 Statistics

AUC analysis was performed to determine the optimal cut-off IMT in each branch of STA and AA to diagnose GCA. In evaluating the optimal IMT cut-off for each vessel branch, Chi-square test with ROC analysis was performed to determine the sensitivity and specificity of each measured IMT value in each vessel branch. Youden index was used to identify the best IMT cut-offs to use. Time-to-normalization of HC, HS and OGUS were evaluated with abnormal thresholds considered ≥ 1 , ≥ 21 and ≥ 1.0 respectively. Mean values for HC, HS, IMTmax and OGUS were calculated at each study timepoint and Wald tests were used to determine the significance of longitudinal trends. Correlation coefficients between all clinical and biochemical parameters and baseline VUS outcome scores (HC, HS and OGUS) were compared to determine which patient factors may predict VUS outcomes. Correlation coefficients were calculated and AUC analyses were performed for all clinical, biochemical and VUS parameters to determine reliability for predicting future adverse events (GCA diagnosis, flare during follow-up, ischaemic complications and future biologic requirement) and DeLong test was utilised to validate the OGUS score. Chi square and fisher tests were used for comparisons involving HC. For the descriptive statistics, binary and categorical variables are presented using counts and percentages. The distributions of

continuous variables have been assessed using coefficients of skewness and then summarized by means and standard deviations (SD) for normally distributed variables or medians and interquartile ranges (IQR) for non-normally distributed variables. To assess for associations between variables; if the outcome of interest was binary or categorical the chi-square test was used. For continuous data, Mann-Whitney U tests or t-test were used, depending on whether the data had a skewed or normal distribution, respectively. All analyses were performed in Stata 15.0.

3.3 Results

Of 124 patients reviewed with suspected GCA, 66 had a clinical diagnosis of GCA verified by two rheumatologists after 6 months. 57/66 had a positive baseline VUS. 50 were followed up at 1 month, 47 at 3 months, 48 at 6 months and 27 had 12 months of follow-up. 4 study subjects were ultimately excluded due to a change in diagnosis at 6 months.

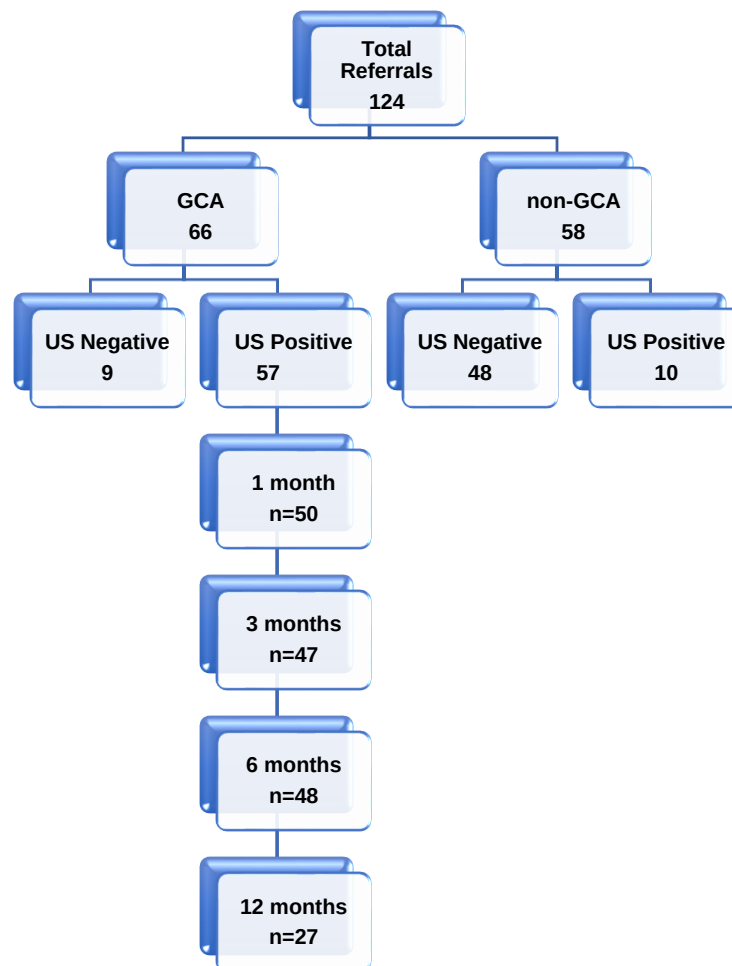


Figure 3.01: Study numbers, diagnoses, VUS results and follow-up duration.

3.3.1 Determining Optimal IMT Cut-offs for diagnosing GCA on VUS

The sensitivities and specificities for each measured IMT value in each vessel branch are outlined in Tables 3.01-3.08. In Table 3.09, cut-off values that give sensitivities and specificities of 90%, 95% and 100% for a diagnosis of GCA are outlined. Table 3.10 outlines the optimal IMT cut-off values for a diagnosis of GCA in each vessel branch. This test was repeated comparing those with and without CV risk factors (Table 3.11). Some differences were observed between the groups with the optimal IMT cut-off value being greater in 5/8 vessel branches for those without CV risk factors and greater in 3/8 vessel branches for those with prevalent CV risk factors.

IMT Cut-point (mm)	Sensitivity	Specificity	Correctly Classified	LR+	LR-
≥ 0.15	100.00%	0.00%	53.23%	1.0000	
≥ 0.2	100.00%	5.17%	55.65%	1.0545	0.0000
≥ 0.21	98.48%	10.34%	57.26%	1.0985	0.1465
≥ 0.25	96.97%	10.34%	56.45%	1.0816	0.2929
≥ 0.28	86.36%	37.93%	63.71%	1.3914	0.3595
≥ 0.30	86.36%	39.66%	64.52%	1.4312	0.3439
≥ 0.35	78.79%	63.79%	71.77%	2.1760	0.3325
≥ 0.40	74.24%	75.86%	75.00%	3.0758	0.3395
≥ 0.41	54.55%	91.38%	71.77%	6.3273	0.4974
≥ 0.45	53.03%	93.10%	71.77%	7.6894	0.5045
≥ 0.50	46.97%	93.10%	68.55%	6.8106	0.5696
≥ 0.55	42.42%	94.83%	66.94%	8.2020	0.6072
≥ 0.60	37.88%	96.55%	65.32%	10.9848	0.6434
≥ 0.65	30.30%	96.55%	61.29%	8.7879	0.7219
≥ 0.70	27.27%	98.28%	60.48%	15.8182	0.7400
≥ 0.75	22.73%	98.28%	58.06%	13.1818	0.7863
≥ 0.80	18.18%	98.28%	55.65%	10.5455	0.8325
≥ 0.85	12.12%	100.00%	53.23%		0.8788
≥ 0.90	10.61%	100.00%	52.42%		0.8939
≥ 0.95	4.55%	100.00%	49.19%		0.9545
≥ 1.05	3.03%	100.00%	48.39%		0.9697
> 1.05	0.00%	100.00%	46.77%		1.0000

Table 3.01: Sensitivities and specificities of Right Common STA IMT values for a diagnosis of GCA. ROC area 0.79, standard error 0.04, 95% CI 0.71-0.87.

IMT Cut-point (mm)	Sensitivity	Specificity	Correctly Classified	LR+	LR-
≥ 0.1	100.00%	0.00%	53.23%	1.0000	
≥ 0.15	100.00%	5.17%	55.65%	1.0545	0.0000
≥ 0.2	95.45%	18.97%	59.68%	1.1779	0.2397
≥ 0.23	87.88%	37.93%	64.52%	1.4158	0.3196
≥ 0.24	87.88%	39.66%	65.32%	1.4563	0.3057
≥ 0.25	86.36%	39.66%	64.52%	1.4312	0.3439
≥ 0.28	75.76%	65.52%	70.97%	2.1970	0.3700
≥ 0.30	75.76%	67.24%	71.77%	2.3126	0.3605
≥ 0.33	54.55%	93.10%	72.58%	7.9091	0.4882
≥ 0.35	54.55%	94.83%	73.39%	10.5454	0.4793
≥ 0.40	53.03%	94.83%	72.58%	10.2525	0.4953
≥ 0.44	36.36%	98.28%	65.32%	21.0909	0.6475
≥ 0.45	34.85%	98.28%	64.52%	20.2121	0.6629
≥ 0.46	28.79%	100.00%	62.10%		0.7121
≥ 0.50	27.27%	100.00%	61.29%		0.7273
≥ 0.55	19.70%	100.00%	57.26%		0.8030
≥ 0.60	13.64%	100.00%	54.03%		0.8636
≥ 0.65	9.09%	100.00%	51.61%		0.9091
≥ 0.70	7.58%	100.00%	50.81%		0.9242
≥ 0.85	6.06%	100.00%	50.00%		0.9394
≥ 0.90	3.03%	100.00%	48.39%		0.9697
≥ 0.95	1.52%	100.00%	47.58%		0.9848
> 0.95	0.00%	100.00%	46.77%		1.0000

Table 3.02: Sensitivities and specificities of Right Frontal STA IMT values for a diagnosis of GCA. ROC area 0.80, standard error 0.04, 95% CI 0.72-0.87.

IMT Cut-point (mm)	Sensitivity	Specificity	Correctly Classified	LR+	LR-
≥ 0.01	100.00%	0.00%	53.23%	1.0000	
≥ 0.05	98.48%	0.00%	52.42%	0.9848	
≥ 0.10	96.97%	1.72%	52.42%	0.9867	1.7576
≥ 0.15	95.45%	6.90%	54.03%	1.0253	0.6591
≥ 0.20	86.36%	27.59%	58.87%	1.1926	0.4943
≥ 0.25	71.21%	58.62%	65.32%	1.7210	0.4911
≥ 0.29	46.97%	93.10%	68.55%	6.8106	0.5696
≥ 0.30	45.45%	93.10%	67.74%	6.5909	0.5859
≥ 0.35	42.42%	96.55%	67.74%	12.3030	0.5963
≥ 0.36	30.30%	98.28%	62.10%	17.5758	0.7092
≥ 0.38	27.27%	98.28%	60.48%	15.8182	0.7400
≥ 0.40	25.76%	98.28%	59.68%	14.9394	0.7554
≥ 0.45	21.21%	100.00%	58.06%		0.7879
≥ 0.48	13.64%	100.00%	54.03%		0.8636
≥ 0.50	12.12%	100.00%	53.23%		0.8788
≥ 0.55	7.58%	100.00%	50.81%		0.9242
≥ 0.60	3.03%	100.00%	48.39%		0.9697
≥ 0.75	1.52%	100.00%	47.58%		0.9848
> 0.75	0.00%	100.00%	46.77%		1.0000

Table 3.03: Sensitivities and specificities of Right Parietal STA IMT values for a diagnosis of GCA. ROC area 0.73, standard error 0.04, 95% CI 0.64-0.82.

IMT Cut-point (mm)	Sensitivity	Specificity	Correctly Classified	LR+	LR-
≥ 0.13	100.00%	0.00%	53.23%	1.0000	
≥ 0.15	100.00%	1.72%	54.03%	1.0175	0.0000
≥ 0.20	100.00%	3.45%	54.84%	1.0357	0.0000
≥ 0.25	98.48%	12.07%	58.06%	1.1200	0.1255
≥ 0.30	96.97%	31.03%	66.13%	1.4061	0.0976
≥ 0.35	84.85%	43.10%	65.32%	1.4913	0.3515
≥ 0.37	78.79%	68.97%	74.19%	2.5387	0.3076
≥ 0.40	77.27%	70.69%	74.19%	2.6364	0.3215
≥ 0.44	57.58%	94.83%	75.00%	11.1313	0.4474
≥ 0.45	56.06%	94.83%	74.19%	10.8384	0.4634
≥ 0.47	51.52%	94.83%	71.77%	9.9596	0.5113
≥ 0.50	50.00%	94.83%	70.97%	9.6667	0.5273
≥ 0.55	34.85%	94.83%	62.90%	6.7374	0.6871
≥ 0.60	21.21%	94.83%	55.65%	4.1010	0.8309
≥ 0.65	12.12%	96.55%	51.61%	3.5151	0.9102
≥ 0.70	12.12%	98.28%	52.42%	7.0303	0.8942
≥ 0.75	6.06%	100.00%	50.00%		0.9394
≥ 0.80	4.55%	100.00%	49.19%		0.9545
≥ 0.90	3.03%	100.00%	48.39%		0.9697
> 0.90	0.00%	100.00%	46.77%		1.0000

Table 3.04: Sensitivities and specificities of Left Common STA IMT values for a diagnosis of GCA. ROC area 0.81, standard error 0.04, 95% CI 0.73-0.89.

IMT Cut-point (mm)	Sensitivity	Specificity	Correctly Classified	LR+	LR-
≥ 0.10	100.00%	0.00%	53.23%	1.0000	
≥ 0.15	100.00%	3.45%	54.84%	1.0357	0.0000
≥ 0.20	95.45%	12.07%	56.45%	1.0856	0.3766
≥ 0.23	89.39%	31.03%	62.10%	1.2962	0.3418
≥ 0.25	87.88%	31.03%	61.29%	1.2742	0.3906
≥ 0.29	78.79%	63.79%	71.77%	2.1760	0.3325
≥ 0.30	78.79%	65.52%	72.58%	2.2848	0.3238
≥ 0.33	60.61%	86.21%	72.58%	4.3939	0.4570
≥ 0.35	60.61%	89.66%	74.19%	5.8586	0.4394
≥ 0.37	59.09%	89.66%	73.39%	5.7121	0.4563
≥ 0.40	57.58%	89.66%	72.58%	5.5657	0.4732
≥ 0.43	46.97%	98.28%	70.97%	27.2424	0.5396
≥ 0.44	45.45%	98.28%	70.16%	26.3637	0.5550
≥ 0.45	43.94%	98.28%	69.35%	25.4849	0.5704
≥ 0.46	30.30%	98.28%	62.10%	17.5758	0.7092
≥ 0.50	28.79%	98.28%	61.29%	16.6970	0.7246
≥ 0.55	19.70%	100.00%	57.26%		0.8030
≥ 0.65	12.12%	100.00%	53.23%		0.8788
≥ 0.70	7.58%	100.00%	50.81%		0.9242
≥ 0.75	6.06%	100.00%	50.00%		0.9394
≥ 0.85	3.03%	100.00%	48.39%		0.9697
≥ 0.90	1.52%	100.00%	47.58%		0.9848
> 0.90	0.00%	100.00%	46.77%		1.0000

Table 3.05: Sensitivities and specificities of Left Frontal STA IMT values for a diagnosis of GCA. ROC area 0.79, standard error 0.04, 95% CI 0.72-0.87.

IMT Cut-point (mm)	Sensitivity	Specificity	Correctly Classified	LR+	LR-
≥ 0.08	100.00%	0.00%	53.23%	1.0000	
≥ 0.10	100.00%	1.72%	54.03%	1.0175	0.0000
≥ 0.15	100.00%	5.17%	55.65%	1.0545	0.0000
≥ 0.17	96.97%	18.97%	60.48%	1.1966	0.1598
≥ 0.18	95.45%	18.97%	59.68%	1.1779	0.2397
≥ 0.20	93.94%	18.97%	58.87%	1.1593	0.3196
≥ 0.25	77.27%	44.83%	62.10%	1.4006	0.5070
≥ 0.26	53.03%	91.38%	70.97%	6.1515	0.5140
≥ 0.29	51.52%	93.10%	70.97%	7.4697	0.5208
≥ 0.30	48.48%	94.83%	70.16%	9.3737	0.5433
≥ 0.35	42.42%	94.83%	66.94%	8.2020	0.6072
≥ 0.36	34.85%	94.83%	62.90%	6.7374	0.6871
≥ 0.40	33.33%	94.83%	62.10%	6.4444	0.7030
≥ 0.45	24.24%	96.55%	58.06%	7.0303	0.7846
≥ 0.50	16.67%	98.28%	54.84%	9.6667	0.8480
≥ 0.55	13.64%	100.00%	54.03%		0.8636
≥ 0.60	10.61%	100.00%	52.42%		0.8939
≥ 0.80	4.55%	100.00%	49.19%		0.9545
≥ 0.85	3.03%	100.00%	48.39%		0.9697
> 0.85	0.00%	100.00%	46.77%		1.0000

Table 3.06: Sensitivities and specificities of Left Parietal STA IMT values for a diagnosis of GCA. ROC area 0.74, standard error 0.04, 95% CI 0.66-0.82.

IMT Cut-point (mm)	Sensitivity	Specificity	Correctly Classified	LR+	LR-
≥ 0.40	100.00%	0.00%	53.23%	1.0000	
≥ 0.49	95.45%	6.90%	54.03%	1.0253	0.6591
≥ 0.50	93.94%	6.90%	53.23%	1.0090	0.8788
≥ 0.55	87.88%	34.48%	62.90%	1.3413	0.3515
≥ 0.60	86.36%	36.21%	62.90%	1.3538	0.3766
≥ 0.63	69.70%	55.17%	62.90%	1.5548	0.5492
≥ 0.70	69.70%	56.90%	63.71%	1.6170	0.5326
≥ 0.80	59.09%	79.31%	68.55%	2.8561	0.5158
≥ 0.90	46.97%	89.66%	66.94%	4.5404	0.5915
≥ 0.91	33.33%	93.10%	61.29%	4.8333	0.7160
≥ 0.92	31.82%	93.10%	60.48%	4.6136	0.7323
≥ 1.0	31.82%	94.83%	61.29%	6.1515	0.7190
≥ 1.1	30.30%	96.55%	61.29%	8.7879	0.7219
≥ 1.2	27.27%	98.28%	60.48%	15.8182	0.7400
≥ 1.3	16.67%	98.28%	54.84%	9.6667	0.8480
≥ 1.5	13.64%	98.28%	53.23%	7.9091	0.8788
≥ 1.6	9.09%	98.28%	50.81%	5.2727	0.9250
≥ 1.7	7.58%	98.28%	50.00%	4.3939	0.9405
≥ 1.8	4.55%	98.28%	48.39%	2.6364	0.9713
≥ 1.9	3.03%	98.28%	47.58%	1.7576	0.9867
≥ 2.1	1.52%	98.28%	46.77%	0.8788	1.0021
≥ 2.7	1.52%	100.00%	47.58%		0.9848
> 2.7	0.00%	100.00%	46.77%		1.0000

Table 3.07: Sensitivities and specificities of Right Axillary Artery IMT values for a diagnosis of GCA. ROC area 0.72, standard error 0.05, 95% CI 0.63-0.81.

IMT Cut-point (mm)	Sensitivity	Specificity	Correctly Classified	LR+	LR-
≥ 0.34	100.00%	0.00%	53.23%	1.0000	
≥ 0.40	98.48%	0.00%	52.42%	0.9848	
≥ 0.50	96.97%	12.07%	57.26%	1.1028	0.2511
≥ 0.58	89.39%	36.21%	64.52%	1.4013	0.2929
≥ 0.60	89.39%	37.93%	65.32%	1.4402	0.2796
≥ 0.67	71.21%	58.62%	65.32%	1.7210	0.4911
≥ 0.70	71.21%	60.34%	66.13%	1.7958	0.4771
≥ 0.76	53.03%	74.14%	62.90%	2.0505	0.6335
≥ 0.77	53.03%	75.86%	63.71%	2.1970	0.6191
≥ 0.80	51.52%	75.86%	62.90%	2.1342	0.6391
≥ 0.90	39.39%	89.66%	62.90%	3.8081	0.6760
≥ 1.0	33.33%	93.10%	61.29%	4.8333	0.7160
≥ 1.1	33.33%	94.83%	62.10%	6.4444	0.7030
≥ 1.2	25.76%	96.55%	58.87%	7.4697	0.7689
≥ 1.3	18.18%	98.28%	55.65%	10.5455	0.8325
≥ 1.4	13.64%	98.28%	53.23%	7.9091	0.8788
≥ 1.5	12.12%	98.28%	52.42%	7.0303	0.8942
≥ 1.7	9.09%	98.28%	50.81%	5.2727	0.9250
≥ 1.9	4.55%	98.28%	48.39%	2.6364	0.9713
≥ 2.0	1.52%	98.28%	46.77%	0.8788	1.0021
> 2.0	0.00%	100.00%	46.77%		1.0000

Table 3.08: Sensitivities and specificities of Left Axillary Artery IMT values for a diagnosis of GCA. ROC area 0.72, standard error 0.04, 95% CI 0.63-0.81.

Vessel Branch	100% Sensitivity	>95%	>90%	100% Specificity	>95%	>90%
Rt Common STA	0.20	0.25	0.25	0.85	0.60	0.41
Rt Frontal STA	0.15	0.20	0.20	0.46	0.44	0.33
Rt Parietal STA	0.01	0.15	0.15	0.45	0.35	0.29
Rt Axillary Artery	0.40	0.49	0.50	2.70	1.10	0.91
Lt Common STA	0.20	0.30	0.30	0.75	0.65	0.44
Lt Frontal STA	0.15	0.20	0.20	0.55	0.43	0.35
Lt Parietal STA	0.15	0.18	0.20	0.55	0.35	0.26
Lt Axillary Artery	0.34	0.50	0.50	2.00	1.10	0.90

Table 3.09: Baseline Intima-Media Thickness (IMT) values in each Superficial Temporal (STA) and Axillary Artery (AA) branch that give 100%, >95% and >90% sensitivity and specificity for a clinical diagnosis of GCA.

Vessel Branch	AUC	IMT Cut-off in mm	TPR	FPR
Rt CSTA	0.79	0.40	0.74	0.24
Rt FTA	0.80	0.35	0.55	0.05
Rt PTA	0.73	0.29	0.47	0.07
Lt CSTA	0.81	0.44	0.58	0.05
Lt FTA	0.79	0.35	0.61	0.10
Lt PTA	0.74	0.29	0.52	0.07
Rt AA	0.72	0.80	0.59	0.21
Lt AA	0.72	0.70	0.71	0.40

Table 3.10: Optimal IMT cut-offs for a diagnosis of GCA.

Vessel Branch	CV Risk- AUC (n=100)	CV Risk- Best Cut-off IMT (mm)	No CV Risk- AUC (n=24)	No CV Risk- Best Cut-off IMT (mm)
Rt CSTA	0.79	0.40	0.81	0.60
Rt FTA	0.80	0.35	0.81	0.30
Rt PTA	0.70	0.29	0.89	0.45
Lt CSTA	0.78	0.44	0.88	0.40
Lt FTA	0.79	0.30	0.82	0.45
Lt PTA	0.69	0.26	0.95	0.30
Rt AA	0.68	0.90	0.85	0.70
Lt AA	0.73	0.70	0.68	0.90

Table 3.11: Optimal IMT cut-offs for a diagnosis of GCA in those with and without CV risk factors.

3.3.2 Longitudinal trends in VUS Quantification Scores

In a longitudinal analysis of the mean scores for OGUS, Halo Score and Halo Count, all values decreased over time (Tables 3.12-3.18, Figures 3.02-3.03). A similar pattern is seen for IMTmax values in each vessel branch with the exception of the left common STA branch which increases between months 6 and 12 (Table 3.22, Figure 3.04). Statistically significant differences were observed at each study timepoint as determined by Wald testing (Table 3.27).

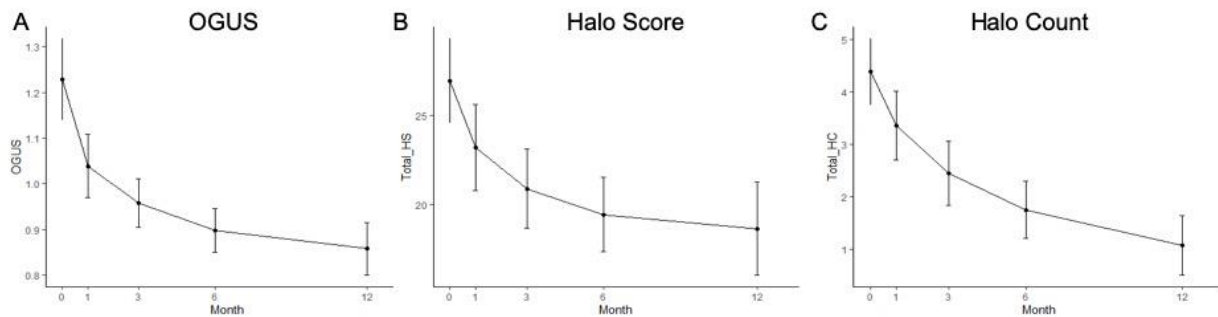


Figure 3.02: Mean OGUS, Halo Counts and Halo Scores with confidence intervals over 12 months.

Month	N=	Min	Max	Median	q1	q3	IQR	mad	Mean	SD
0	50	0.79	2.13	1.14	0.99	1.38	0.39	0.25	1.23	0.32
1	50	0.68	1.84	0.98	0.85	1.17	0.32	0.25	1.04	0.25
3	47	0.65	1.44	0.92	0.82	1.03	0.21	0.17	0.96	0.19
6	48	0.60	1.29	0.89	0.78	1.02	0.25	0.18	0.90	0.17
12	27	0.53	1.22	0.83	0.75	0.98	0.23	0.14	0.86	0.15

Table 3.12: OGUS over 12 months (normal range 0-1).

Month	N=	Min	Max	Median	q1	q3	IQR	mad	Mean	SD
0	50	1	8	4	2	6.00	4.00	2.96	4.38	2.28
1	50	0	8	3	2	5.75	3.75	2.22	3.36	2.38
3	47	0	8	2	1	4.00	3.00	2.96	2.45	2.12
6	48	0	7	1	0	3.00	3.00	1.48	1.75	1.93
12	27	0	6	0	0	2.00	2.00	0.00	1.07	1.49

Table 3.13: Total Halo Count over 12 months (range 0-8).

Month	N=	Min	Max	Median	q1	q3	IQR	mad	Mean	SD
0	50	8	43	26.5	22.0	34.0	12.0	7.41	26.90	8.53
1	50	6	46	22.0	17.2	29.5	12.2	8.90	23.20	8.66
3	47	6	38	20.0	15.0	27.0	12.0	7.41	20.90	7.77
6	48	2	32	19.0	13.8	26.0	12.2	8.90	19.40	7.34
12	27	8	29	19.0	13.5	23.5	10.0	7.41	18.70	6.86

Table 3.14: Total Halo Score over 12 months (range 0-48).

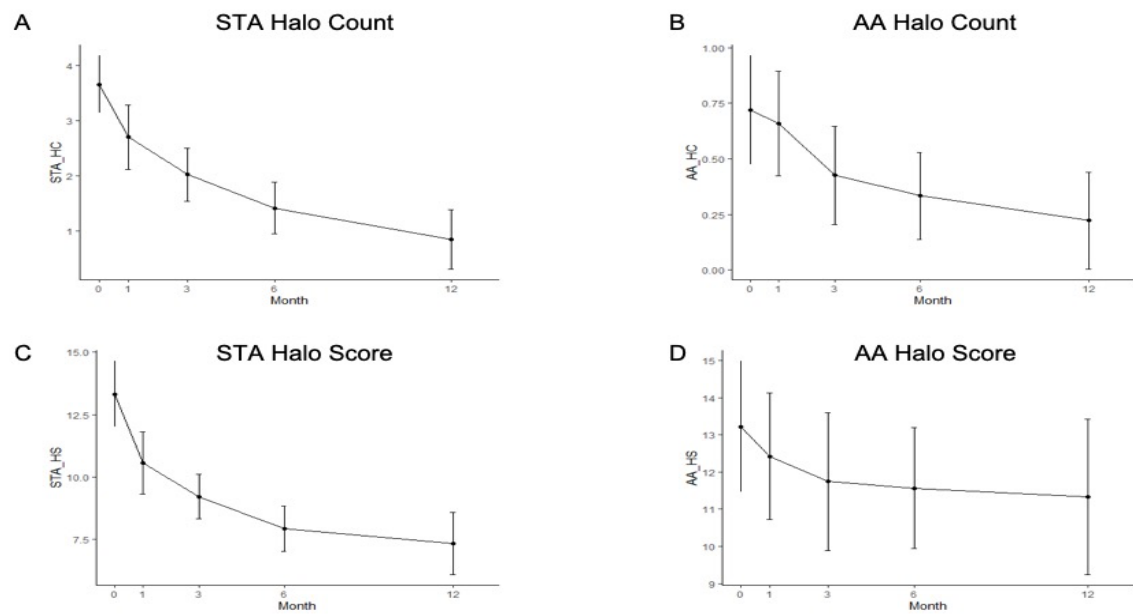


Figure 3.03: Mean STA and AA Halo Counts and Halo Scores with confidence intervals over 12 months.

Month	N=	Min	Max	Median	q1	q3	IQR	mad	Mean	SD
0	50	0	6	4	2	6.0	4.0	2.96	3.66	1.88
1	50	0	6	2	1	4.0	3.0	2.96	2.70	2.09
3	47	0	6	2	1	3.5	2.5	1.48	2.02	1.70
6	48	0	5	1	0	3.0	3.0	1.48	1.42	1.66
12	27	0	6	0	0	1.5	1.5	0.00	0.85	1.43

Table 3.15: STA Halo Count over 12 months (range 0-6).

Month	N=	Min	Max	Median	q1	q3	IQR	mad	Mean	SD
0	50	0	2	0	0	2.0	2.0	0	0.72	0.88
1	50	0	2	0	0	1.0	1.0	0	0.66	0.85
3	47	0	2	0	0	0.5	0.5	0	0.43	0.77
6	48	0	2	0	0	0.0	0.0	0	0.33	0.69
12	27	0	2	0	0	0.0	0.0	0	0.22	0.58

Table 3.16: Axillary Artery Halo Count over 12 months (range 0-2).

Month	N=	Min	Max	Median	q1	q3	IQR	mad	Mean	SD
0	50	5	23	13	10	16.0	6.00	4.45	13.3	4.77
1	50	1	22	10	7	13.8	6.75	4.45	10.6	4.54
3	47	3	16	9	7	11.5	4.50	2.96	9.21	3.13
6	48	2	14	8	6	10.2	4.25	2.96	7.94	3.22
12	27	2	17	7	5	8.5	3.50	2.96	7.33	3.29

Table 3.17: STA Halo Score over 12 months (range 0-24).

Month	N=	Min	Max	Median	q1	q3	IQR	mad	Mean	SD
0	50	0	24	15	9.00	18	9.0	4.45	13.2	6.35
1	50	0	24	12	6.75	18	11.2	8.90	12.4	6.15
3	47	0	24	12	7.50	18	10.5	8.90	11.7	6.47
6	48	0	21	12	9.00	18	9.0	8.90	11.6	5.74
12	27	0	21	12	6.00	15	9.0	4.45	11.3	5.54

Table 3.18: Axillary Artery Halo Score over 12 months (range 0-24).

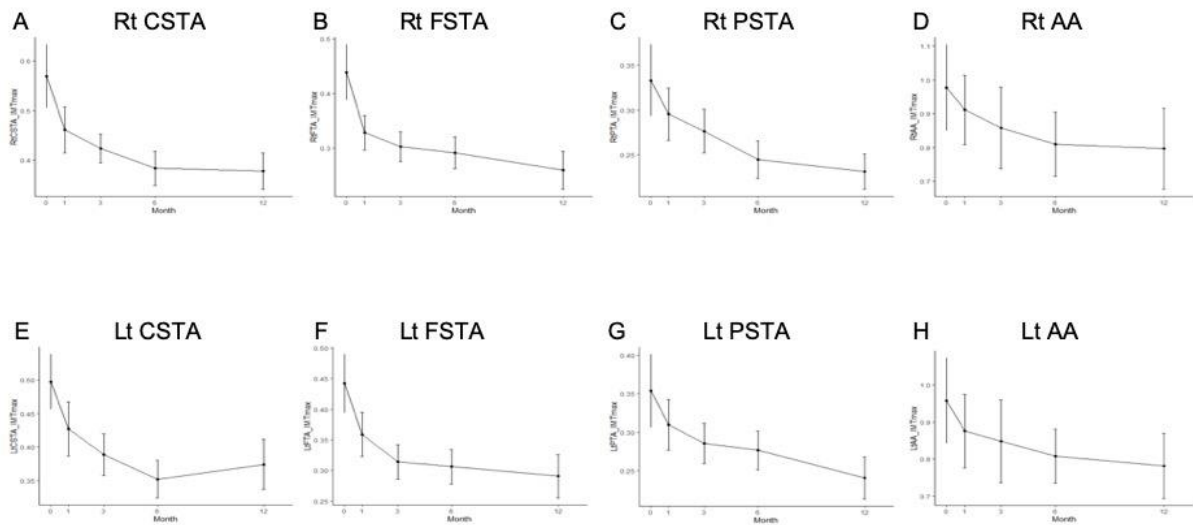


Figure 3.04: Mean maximum measured IMT (mm) in each branch of STA and AA over 12 months.

Month	N=	Min	Max	Median	q1	q3	IQR	mad	Mean	SD
0	50	0.21	1.05	0.55	0.40	0.75	0.35	0.22	0.57	0.23
1	50	0.10	0.90	0.45	0.35	0.59	0.24	0.15	0.46	0.17
3	47	0.15	0.65	0.40	0.35	0.50	0.15	0.07	0.42	0.10
6	48	0.10	0.60	0.40	0.30	0.50	0.20	0.15	0.38	0.12
12	27	0.20	0.55	0.40	0.35	0.40	0.05	0.07	0.38	0.10

Table 3.19: Right Common STA IMTmax (mm) over 12 months.

Month	N=	Min	Max	Median	q1	q3	IQR	mad	Mean	SD
0	50	0.15	0.95	0.40	0.30	0.54	0.24	0.15	0.44	0.18
1	50	0.10	0.60	0.30	0.25	0.40	0.15	0.07	0.33	0.11
3	47	0.15	0.65	0.30	0.25	0.34	0.09	0.07	0.30	0.10
6	48	0.10	0.50	0.30	0.24	0.31	0.08	0.07	0.29	0.10
12	27	0.10	0.50	0.25	0.20	0.30	0.10	0.07	0.26	0.09

Table 3.20: Right Frontal STA IMTmax (mm) over 12 months.

Month	N=	Min	Max	Median	q1	q3	IQR	mad	Mean	SD
0	50	0.01	0.75	0.35	0.25	0.45	0.20	0.15	0.33	0.14
1	50	0.10	0.55	0.25	0.25	0.35	0.10	0.12	0.30	0.11
3	47	0.10	0.45	0.25	0.20	0.35	0.15	0.07	0.28	0.09
6	48	0.10	0.40	0.25	0.20	0.25	0.05	0.07	0.25	0.07
12	27	0.10	0.35	0.25	0.20	0.25	0.05	0.00	0.23	0.05

Table 3.21: Right Parietal STA IMTmax (mm) over 12 months.

Month	N=	Min	Max	Median	q1	q3	IQR	mad	Mean	SD
0	50	0.20	0.9	0.50	0.40	0.55	0.15	0.15	0.50	0.15
1	50	0.20	0.9	0.45	0.30	0.55	0.25	0.19	0.43	0.15
3	47	0.15	0.6	0.40	0.30	0.48	0.18	0.15	0.39	0.11
6	48	0.20	0.6	0.35	0.25	0.40	0.15	0.07	0.35	0.10
12	27	0.20	0.6	0.35	0.30	0.40	0.10	0.07	0.37	0.10

Table 3.22: Left Common STA IMTmax (mm) over 12 months.

Month	N=	Min	Max	Median	q1	q3	IQR	mad	Mean	SD
0	50	0.15	0.90	0.45	0.30	0.54	0.24	0.15	0.44	0.17
1	50	0.15	0.80	0.33	0.26	0.45	0.19	0.11	0.36	0.13
3	47	0.10	0.55	0.30	0.25	0.40	0.15	0.07	0.31	0.10
6	48	0.10	0.50	0.30	0.25	0.40	0.15	0.11	0.31	0.10
12	27	0.10	0.50	0.30	0.25	0.35	0.10	0.07	0.29	0.09

Table 3.23: Left Frontal STA IMTmax (mm) over 12 months.

Month	N=	Min		Max	Median	q1	q3	IQR	mad	Mean	SD
0	50	0.15		0.85	0.30	0.25	0.40	0.15	0.14	0.35	0.17
1	50	0.15		0.65	0.25	0.25	0.40	0.15	0.07	0.31	0.12
3	47	0.15		0.55	0.25	0.25	0.35	0.10	0.07	0.29	0.09
6	48	0.10		0.50	0.25	0.25	0.31	0.06	0.04	0.28	0.09
12	27	0.15		0.50	0.25	0.20	0.25	0.05	0.00	0.24	0.07

Table 3.24: Left Parietal STA IMTmax (mm) over 12 months.

Month	N=	Min	Max	Median	q1	q3	IQR	mad	Mean	SD
0	50	0.4	2.7	0.9	0.7	1.20	0.50	0.45	0.98	0.46
1	50	0.3	1.8	0.8	0.7	1.10	0.40	0.30	0.91	0.37
3	47	0.4	2.7	0.7	0.6	0.95	0.35	0.30	0.86	0.42
6	48	0.4	2.3	0.7	0.6	0.90	0.30	0.15	0.81	0.34
12	27	0.4	1.7	0.7	0.6	0.85	0.25	0.15	0.80	0.32

Table 3.25: Right Axillary Artery IMTmax (mm) over 12 months.

Month	N=	Min	Max	Median	q1	q3	IQR	mad	Mean	SD
0	50	0.40	2.0	0.8	0.70	1.20	0.50	0.30	0.96	0.42
1	50	0.28	1.7	0.7	0.60	1.18	0.58	0.30	0.88	0.36
3	47	0.30	2.1	0.7	0.60	0.90	0.30	0.30	0.85	0.39
6	48	0.40	1.5	0.7	0.70	0.90	0.20	0.22	0.81	0.26
12	27	0.50	1.5	0.7	0.65	0.90	0.25	0.15	0.78	0.23

Table 3.26: Left Axillary Artery IMTmax (mm) over 12 months.

Score	p-value
OGUS	>0.005
Total Halo Count	>0.005
Total Halo Score	>0.005
STA Halo Count	>0.005
AA Halo Count	>0.005
STA Halo Score	>0.005
AA Halo Score	>0.005
RtCSTA IMTmax	>0.005
RtFTA IMTmax	>0.005
RtPTA IMTmax	>0.005
LtCSTA IMTmax	>0.005
LtFTA IMTmax	>0.005
LtPTA IMTmax	>0.005
RtAA IMTmax	>0.005
LtAA IMTmax	>0.005

Table 3.27: Wald test p-values for longitudinal analysis of VUS scoring. The results imply statistically significant differences in mean values of all parameters between each study timepoint.

3.3.3 Time-to-halo regression

Time-to-normalisation for each VUS outcome score was evaluated in 48 patients. Most normalised by 6 months but a significant proportion of the cohort continued to have abnormal scores despite clinical remission. 39/48 patients had normalised their OGUS score by 6 months, more than those who normalised HC or HS. There was no significant association seen between the time-to-normalisation of scores and future adverse events, although the sample size was too small to say definitively.

Parameter	Abnormal Value
OGUS	≥ 1.0
STA HC	≥ 1
AA HC	≥ 1
Total HC	≥ 1
STA HS	≥ 9
AA HS	≥ 13
Total HS	≥ 21
RtCSTA IMTmax	$\geq 0.42\text{mm}$
RtFTA IMTmax	$\geq 0.34\text{mm}$
RtPTA IMTmax	$\geq 0.29\text{mm}$
LtCSTA IMTmax	$\geq 0.42\text{mm}$
LtFTA IMTmax	$\geq 0.34\text{mm}$
LtPTA IMTmax	$\geq 0.29\text{mm}$
RtAA IMTmax	$\geq 1.00\text{mm}$
LtAA IMTmax	$\geq 1.00\text{mm}$

Table 3.28: Cut-off values for halo regression analysis. Cut-off values determined by the maximum possible score achievable in a negative VUS scan.

	Total Normal at Baseline (n=50)	Total Normal by Month 1 (n=50)	Total Normal by Month 3 (n=47)	Total Normal by Month 6 (n=48)
OGUS	15	28	37	39
Total HS	10	24	30	32
Total HC	0	4	10	21
STA HC	2	9	14	25
AA HC	28	32	38	41
STA HS	8	21	30	36
AA HS	24	33	36	40
RtCSTA IMTmax	18	26	34	39
LtCSTA IMTmax	18	27	38	45
RtFTA IMTmax	17	34	43	47
LtFTA IMTmax	15	28	37	42
RtPTA IMTmax	23	32	37	43
LtPTA IMTmax	25	36	43	45
RtAA IMTmax	33	37	40	44
LtAA IMTmax	32	36	42	44

Table 3.29: Time-to-normalisation for VUS outcome scores (listed by the number that have fallen below normal threshold (Table 3.28) at each timepoint).

3.3.4 Patient variables associated with high baseline VUS outcome scores

Table 3.30 lists the patient variables associated with high baseline VUS outcome scores in order of decreasing correlation coefficient. 11 correlations with a coefficient >0.6 were found. Fulfilling 2022 ACR/EULAR Classification Criteria showed strong correlation (0.6-0.79) with VUS outcome scores including HC, HS and OGUS. All other correlations including symptoms and laboratory results were, at best, moderate. A comprehensive list of all correlations can be found in Appendix 3.1.

Variable	Outcome	Correlation Coefficient	95% CI	p-value
22 ACR/EULARcc Score	Total HC	0.79	0.71-0.84	<0.0005
22 ACR/EULARcc Score	OGUS	0.76	0.69-0.82	<0.0005
22 ACR/EULARcc Score	STA HC	0.76	0.69-0.82	<0.0005
22 ACR/EULARcc Score	STA HS	0.74	0.66-0.80	<0.0005
22 ACR/EULARcc Score	Total HS	0.69	0.60-0.77	<0.0005
22 ACR/EULARcc Score	LtFTA IMTmax	0.67	0.58-0.75	<0.0005
22 ACR/EULARcc Score	RtCSTA IMTmax	0.63	0.52-0.72	<0.0005
22 ACR/EULARcc Score	RtFTA IMTmax	0.63	0.52-0.72	<0.0005
22 ACR/EULARcc Fulfilled	STA HC	0.61	0.50-0.71	<0.0005
22 ACR/EULARcc Fulfilled	Total HC	0.61	0.50-0.70	<0.0005
22 ACR/EULARcc Score	LtCSTA IMTmax	0.61	0.50-0.70	<0.0005
22 ACR/EULARcc Fulfilled	STA HS	0.60	0.48-0.69	<0.0005
22 ACR/EULARcc Fulfilled	OGUS	0.58	0.47-0.68	<0.0005
22 ACR/EULARcc Fulfilled	Total HS	0.57	0.45-0.67	<0.0005
PTPS	Total HC	0.56	0.44-0.66	<0.0005
PTPS	STA HC	0.54	0.41-0.64	<0.0005
22 ACR/EULARcc Score	AA HC	0.54	0.41-0.64	<0.0005
22 ACR/EULARcc Score	LtPTA IMTmax	0.54	0.41-0.64	<0.0005
PTPS	OGUS	0.52	0.40-0.63	<0.0005
TAB Positive	OGUS	0.52	0.32-0.68	<0.0005
PTPS	STA HS	0.51	0.38-0.62	<0.0005
22 ACR/EULARcc Fulfilled	LtFTA IMTmax	0.50	0.37-0.61	<0.0005
22 ACR/EULARcc Fulfilled	RtCSTA IMTmax	0.50	0.36-0.61	<0.0005

Table 3.30: Correlation coefficients between baseline patient variables and VUS outcome scores.

3.3.5 VUS quantification scores as predictors of future adverse events

In comparing AUCs for clinical symptoms and signs, laboratory results and baseline VUS, VUS outcome scores were superior in predicting GCA diagnosis, future flare and future biologic requirement (Table 3.31). In comparing correlation coefficients, VUS outcome scores were superior to all clinical and laboratory variables in predicting GCA diagnosis and future biologic requirement and performed as well as serum IL-6 concentration in predicting future flare. Blurring of vision was predictive of future ischaemic complications (Table 3.33). A comprehensive list of all AUCs and correlation coefficients can be found in Appendices 3.2 and 3.3. DeLong test was performed to directly compare ROCs and while OGUS appears equivocal with Halo Count and superior to Halo Score for predicting adverse events, most values did not reach statistical significance (Table 3.32). A full list of DeLong test results is available in Appendix 3.4. This data suggests that VUS quantification scores are better than all other patient variables for predicting future adverse events with OGUS appearing to outperform Halo Score.

Variable	Outcome	AUC	95% CI	p-value
OGUS	GCA	0.91	0.86-0.91	<0.0005
Halo Count	GCA	0.89	0.84-0.89	<0.0005
Halo Count	Biologic	0.88	0.82-0.88	<0.0005
OGUS	Biologic	0.87	0.81-0.87	<0.0005
Halo Score	GCA	0.86	0.80-0.86	<0.0005
Halo Score	Biologic	0.83	0.75-0.83	<0.0005
Halo Count	Flare	0.80	0.71-0.80	<0.0005
OGUS	Flare	0.77	0.68-0.77	<0.0005
ESR	Biologic	0.76	0.66-0.76	<0.0005
Halo Score	Flare	0.75	0.63-0.75	<0.0005

Table 3.31: AUCs for baseline patient variables and future adverse events, only including those with AUC ≥ 0.75 which have significant p-value.

Predictor	Outcome	OGUS ROC	Predictor ROC	p- value
Halo Count	GCA	0.91	0.89	>0.05
Halo Count	Ischaemia	0.68	0.69	>0.05
Halo Count	Biologic	0.87	0.88	>0.05
Halo Count	Flare	0.77	0.80	>0.05
Halo Count	Biologic	0.87	0.88	>0.05
Halo Score	GCA	0.91	0.86	<0.05
Halo Score	Ischaemia	0.68	0.47	>0.05
Halo Score	Biologic	0.87	0.83	>0.05
Halo Score	Flare	0.77	0.75	>0.05
Halo Score	Biologic	0.87	0.83	>0.05

Table 3.32: DeLong Test comparing ROC of OGUS to that of Halo Count and Halo Score for predicting future adverse events.

Variable	Outcome	Correlation Coefficient	95% CI	p-value
Halo Count	GCA	0.65	0.55-0.73	<0.0005
OGUS	GCA	0.63	0.52-0.72	<0.0005
Halo Score	GCA	0.62	0.51-0.71	<0.0005
Halo Count	Biologic	0.58	0.45-0.68	<0.0005
OGUS	Biologic	0.55	0.41-0.66	<0.0005
Halo Score	Biologic	0.52	0.38-0.63	<0.0005
ESR	Biologic	0.39	0.23-0.53	<0.0005
Jaw Claudication	Biologic	0.38	0.22-0.51	<0.0005
Halo Count	Flare	0.37	0.21-0.51	<0.0005
ESR	GCA	0.35	0.20-0.49	<0.0005
CRP	GCA	0.35	0.20-0.49	<0.0005
Halo Score	Flare	0.34	0.17-0.48	<0.0005
Blurred Vision	Ischaemia	0.32	0.05-0.55	<0.05
Jaw Claudication	Flare	0.32	0.15-0.46	<0.0005
CRP	Biologic	0.31	0.15-0.46	<0.0005
IL6	Flare	0.31	0.09-0.51	<0.05
Scalp Tenderness	Biologic	0.31	0.15-0.46	<0.0005
OGUS	Flare	0.31	0.14-0.46	<0.0005
Platelets	Biologic	0.30	0.14-0.46	<0.005
Monocytes	Biologic	0.30	0.13-0.45	<0.005

Table 3.33: Correlation Coefficients for baseline patient variables and future adverse events, only including those ≥ 0.30 .

3.4 Discussion

The current understanding of normal IMT values in STA and AA are informed by only two studies (86, 87). Additionally, other data suggests that higher cut-points should be considered when dealing with those who have prevalent CV risk factors (88). In this study, 124 suspected cases of GCA were evaluated, of whom 66 ultimately had a clinical diagnosis of GCA verified by two rheumatologists after 6 months. Values for optimal cut-off points for normal IMT differ to those published by *Schaefer et al* in the frontal STA and AA. Table 3.09 provides a framework which allows clinicians to either confirm or refute a diagnosis of GCA using VUS, with 100% confidence, if certain thresholds are met. Using the Right Frontal STA as an example; IMTmax <0.15mm had 100% sensitivity for GCA, IMTmax >0.46mm had 100% specificity for GCA. This data also suggests that the presence or absence of CV risk factors has no significant effect on optimal IMT cut-off points giving further credence to VUS as the optimal tool for assessing suspected GCA.

VUS quantification scores have shown promise for disease monitoring and prognostication but they require external validation and longitudinal evaluation (127, 133, 145, 187-190). In this cohort, higher 2022 EULAR/ACR Classification Criteria scores correlated with higher baseline VUS outcome scores and these scores outperformed symptoms and laboratory results for predicting GCA diagnosis, disease recurrence and future biologic requirement, with OGUS outperforming Halo Score. Time-to-resolution of halo has varied widely in studies to date with some data suggesting IMTmax declines steadily over time and that higher baseline values may be associated with more persistent disease (82, 89, 108, 114, 118, 133, 137-142, 145). In this cohort, 48 patients had 6-month follow-up and 27 were followed up at 12 months. OGUS, HC, HS and IMTmax (except for left

common STA) mean values decreased significantly between study timepoints with more patients normalising OGUS at 6 months than other outcome scores.

However, almost 25% had not normalised their OGUS at 6 months and although the sample size was relatively small, no association was seen between failure to normalise OGUS and future adverse events. In a larger cohort, such an association may become apparent. OGUS appears to be superior to the other scoring systems proposed, has the most sensitivity to change and would appear to be the best candidate scoring system to apply to larger cohorts to further clarify the role of VUS in GCA disease monitoring. This study also confirms that IMT quantification is a key aspect of VUS in GCA diagnosis and has clear potential as a biomarker for longitudinal disease monitoring.

A strength of this study is that optimal IMT cut-off points were evaluated in a larger cohort than was used to define the internationally-accepted normal values outlined in Table 1.05, and other IMT cut-off points were interrogated which improve both the sensitivity and specificity of VUS for diagnosing GCA. This data clearly shows the superiority of VUS quantification scores over other clinical variables in predicting adverse events and highlights their potential as candidate biomarkers in GCA. Lastly, this data externally validates the various VUS quantification scores, in particular the recently-described OGUS score.

There are some weakness in this study. Sample size was too small to generate adequate numbers of ischaemic events that would allow for identification of any association with baseline VUS scores. Secondly, this data has not accounted for cumulative steroid dose during follow-up however a standard steroid taper was used in all patients which mitigates the significance of this as a potential confounding factor.

3.5 Conclusions

This study defines the optimal IMT cut-off values in each branch of STA and AA that can reliably identify the presence of vasculitis in that vessel. The cut-offs appear to be independent of the presence of CV risk factors but this finding should be confirmed in a larger cohort. Additionally, this study provides a framework that allows clinician sonographers to either confirm or refute a diagnosis of GCA with 100% accuracy if certain IMT thresholds are met. Using the Right Frontal STA as an example; IMTmax <0.15mm had 100% sensitivity for GCA, IMTmax >0.46mm had 100% specificity for GCA. It reaffirms the importance of IMT quantification when performing VUS in GCA and suggests that simply identifying the presence of a Halo is suboptimal.

This study also confirms that VUS has a role in GCA disease monitoring. Using VUS quantification scores, degrees of vascular inflammation within individuals can be followed longitudinally. HC, HS and OGUS were all validated in this study. In our cohort, OGUS performed best and is the best candidate scoring system to be trialled in larger cohorts. Higher 2022 ACR/EULAR GCA Classification Criteria score was associated with higher baseline VUS quantification scores. No association was seen between failure-to-normalise OGUS at 6 months and future adverse events but such an association may potentially be seen if a larger cohort was examined for a longer period. This study also confirms that VUS quantification scores perform better than all other clinical variables in predicting future adverse events.

Chapter 4: A Cross-Sectional Study Evaluating the Prevalence of Subclinical Giant Cell Arteritis in an Inception Polymyalgia Rheumatica Cohort.

Abstract

It has been reported that 20-50% of patients with PMR have Subclinical GCA (50). The natural history of US-defined Subclinical GCA in PMR is not known.

Twenty five newly-diagnosed PMR patients, with a clinical diagnosis of PMR as verified by 2 rheumatologists, were examined by VUS. US of all 8 branches of the STA and AA was performed using a GE P9 device. Sonographic abnormalities considered indicative of vasculitis in the STA included the Halo and Compression Signs with an enlarged Intima-Media Complex (86). In the AA, a Halo Sign and an IMT of >1.0mm was considered positive. Follow-up consultations after 1 year were undertaken to review the clinical diagnosis. In our Subclinical GCA group, a PMR-dose steroid taper was used in those with a prompt clinical response, a GCA-dose steroid taper was initiated for those who subsequently flared and Tocilizumab was initiated in the event of a second flare.

This cohort consisted of 60% females (n=15) with a mean age of 66.9 years. 2012 ACR/EULAR PMR classification criteria were met in 16/25 patients (primarily due to prior corticosteroid use in primary care resulting in normal ESR/CRP). Five patients (20%) were identified as having Subclinical GCA on US (5/5 met 2012 ACR/EULAR PMR classification criteria, 0/5 met ACR GCA classification criteria).

Superficial Temporal Artery involvement was identified in 5/5, with Axillary Artery involvement in 1/5. Mean Halo Count was 3 (range 1-5) and mean Halo Score was 21.2 (range 17-29) (127). Two patients were managed with a PMR-dose of prednisolone but relapsed. Three patients were treated with a GCA-dose of prednisolone (after failure to respond promptly to lower dose), all of whom relapsed. At a median of 12 months follow up, 1/20 (5%) of the PMR-only cohort had developed a clinical syndrome consistent with GCA. 5/5 (100%) of the Subclinical GCA cohort had developed a clinical diagnosis of GCA with 3/5 requiring an increase in steroid dose during the follow-up period and 2/5 ultimately requiring Tocilizumab. At 12 months follow up 0% of patients had developed ischaemic complications. Relative to those with isolated PMR, those with Subclinical GCA were older, likelier to meet 2022 ACR/EULAR GCA Classification Criteria, have less hip PMR, have elevated ESR/CRP and lower platelets.

This study shows that a single screening VUS of STA and AA accurately identified 83.3% of patients with Subclinical GCA in an inception PMR cohort, the prevalence of which was 24%. The patients represented a distinct phenotypic subset. The results indicate that these patients are likely to be resistant to PMR-dose steroids and ultimately may require biologic therapy.

4.1 Introduction

4.1.1 Isolated PMR and Subclinical GCA

GCA is the commonest idiopathic systemic vasculitis with a 0.5-1.0% lifetime risk and typically presents with cranial symptoms such as headaches, jaw claudication and visual disturbance (1-3). If untreated, catastrophic vascular complications can ensue in the form of blindness, strokes, aneurysms or MI (7, 8, 11-13). PMR affects a similar demographic and typically causes shoulder and hip girdle pain and stiffness due to varying combinations of synovitis, tenosynovitis and bursitis (14-18, 22-25). As much as 50% of GCA patients have PMR as feature of their disease which can occur before, during or after the onset of GCA (37-40). Likewise, those presenting with PMR may have true underlying GCA at diagnosis with early studies suggesting prevalence rates ranging 2-32% for underlying GCA in those presenting with PMR while more recent meta-analyses have made more precise estimates of 22-23% (40, 44-50). The close inter-relationship between these two disease states has resulted in revised nomenclature to encompass both under the one single umbrella term- so-called 'GCA-PMR Spectrum Disease' (41). Thus, 'pure' PMR (i.e. no cranial or ischaemic features) at diagnosis can now be subdivided based on phenotype into 'Isolated PMR' (no evidence of GCA at PMR diagnosis) and 'Subclinical GCA' (sonographic/imaging evidence of underlying GCA despite a pure PMR-like presentation). Accurate identification of Subclinical GCA has important implications for patients given the estimated prevalence rates of vascular complications being at approximately 50%, whereas Isolated PMR tends to run a more benign disease course (12, 35, 51).

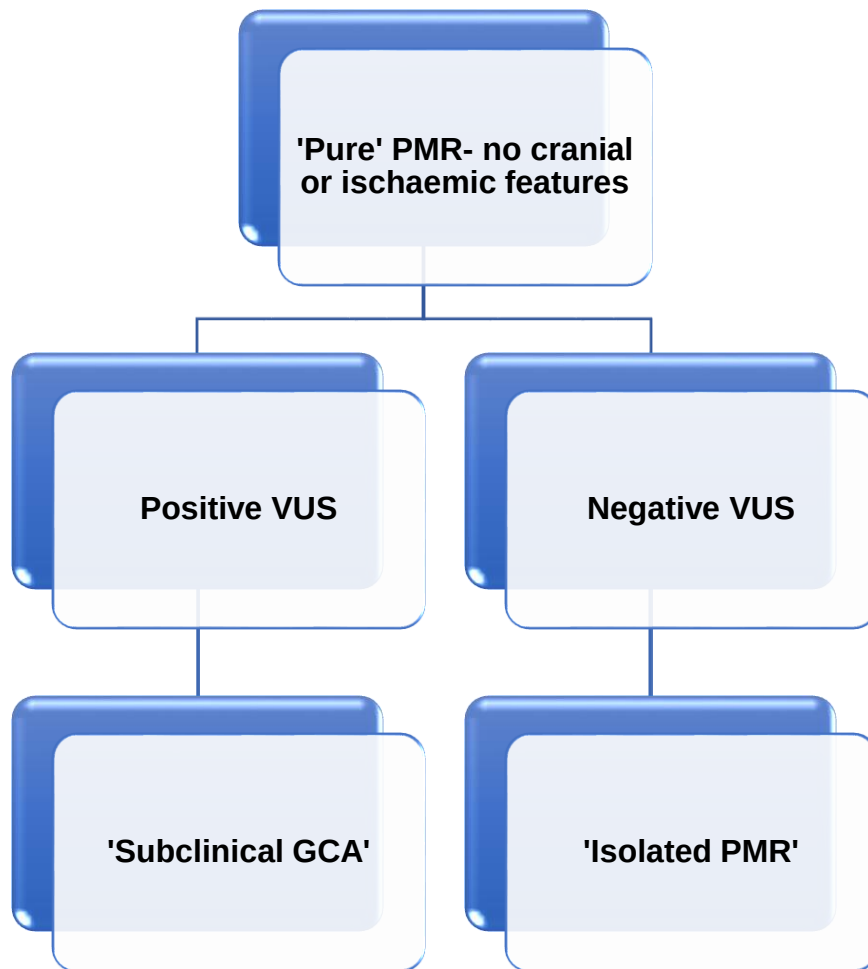


Figure 4.01: Isolated PMR and Subclinical GCA.

4.1.2 Vascular Ultrasound Identifying Subclinical GCA

Recent interest has focused on the utility of performing baseline VUS in those presenting with PMR to identify Subclinical GCA. Studies in the early 2000s showed little/no vascular inflammation in these cohorts, however as our understanding of VUS has changed and as available technology has improved, more recent studies have shown prevalence rates of over 20% (47, 67-69). The most significant of these studies was recently published. In an international multi-center cross-sectional study of 346 patients with 'pure' PMR, 22.8% had

sonographic evidence of underlying GCA and some phenotypic differences were observed between those with and without Subclinical GCA (68). Only one other study has shown similar results and further evidence is needed to confirm these findings (69).

4.1.3 Aims and Objectives

This research hypothesises that Subclinical GCA in those presenting with PMR is under-recognised and VUS may help identify a potentially unique disease phenotype. This study sought to determine the prevalence of sonographically-defined Subclinical GCA in an inception PMR cohort. It also investigated the natural history of Subclinical GCA to see how this clinical phenotype differs, if at all, from classical GCA.

4.2 Methods

4.2.1 Rapid Access PMR/GCA clinic

A rapid-access PMR clinic was established across two university hospital sites in Ireland. Patients with suspected PMR were referred from primary care physicians, emergency departments or inpatient wards via telephone, email or electronic patient record. All investigators were clinical rheumatologists experienced in the diagnosis and management of PMR and experienced in performing VUS. The investigators endeavoured to assess all patients within 24 hours of referral. For all patients, in addition to routine clinical assessment and biochemical investigations, VUS was performed. If indicated, treatment was initiated on the day of assessment and patients meeting the pre-defined inclusion criteria were enrolled in the study. Subjects then received a patient information leaflet outlining the study details and written informed consent was obtained from all. Patients were recruited over a 12-month period from January 2021 to January 2022.

4.2.2 Vascular Ultrasound Protocol

Sonographic assessment of the full length of both STA and all its' branches and both AA was performed. All arteries were interrogated using an 18MHz Linear probe and General Electronic P9 Ultrasound system. Each artery was examined in both transverse and longitudinal planes. Abnormalities deemed indicative of STA vasculitis included a Halo Sign (Fig. 2.01), Compression Sign (Fig. 2.02) and abnormal IMT above pre-determined thresholds (Table 1.05). Abnormalities

deemed indicative of AA vasculitis included the Halo and Slope signs (Fig. 2.03) with an abnormal IMT above the pre-determined threshold (Table 1.05). Images and measurements were scored by the lead investigator. All images and videos were reviewed by a second expert ultrasonographer blinded to the details of the clinical case and in the event of a discrepancy in diagnostic scoring a joint score was made by agreement.

4.2.3 Clinical Diagnosis and Management

PMR diagnosis was established based on clinical presentation, compatible laboratory results, steroid-response and exclusion of PMR mimics. In this cohort, 'PMR' refers to those patients with a 'pure' PMR-like syndrome i.e. no cranial or ischaemic symptoms. A diagnosis of 'Subclinical GCA' in this cohort was established if positive features were found on VUS.

In the Subclinical GCA group, a PMR-dose steroid taper (prednisolone 20mg daily for two weeks, tapering by 2.5mg fortnightly to 10mg, then tapering by 1mg per month) was used in those with a prompt clinical response, a GCA-dose steroid taper (as per GiACTA protocol, tapering from 60mg in those with visual or large vessel involvement, tapering from 40mg in those without) was initiated for those who subsequently flared and Tocilizumab was initiated in the event of a second flare. Regular follow-up was provided for those with Subclinical GCA. Follow-up consultations after 1 year were undertaken to review the clinical diagnosis and outcome in all study participants. All diagnoses were verified by 2 rheumatologists.

4.2.4 Inclusion and Exclusion Criteria

All newly referred patients to the rapid access clinic, aged over 50 years, with a clinic diagnosis compatible with PMR were included in this study. Anyone in whom an alternative diagnosis was deemed to be more likely, any patients on long-term steroids or SSA for another reason, patients with cranial symptoms and any patients aged under 50 years were excluded.

4.2.5 Ethical Approval

This study was approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals and also by the St. James' Hospital / Tallaght University Hospital Joint Research Ethics Committee.

4.2.6 Statistics

For the descriptive statistics, binary and categorical variables are presented using counts and percentages. The distributions of continuous variables have been assessed using coefficients of skewness and then summarized by means and standard deviations (SD) for normally distributed variables or medians and interquartile ranges (IQR) for non-normally distributed variables. To assess for associations between variables; if the outcome of interest was binary or categorical the chi-square test was used. For continuous data, Mann-Whitney U tests or t-test were used, depending on whether the data had a skewed or normal distribution, respectively. All analyses were performed in Stata 15.0.

4.3 Results

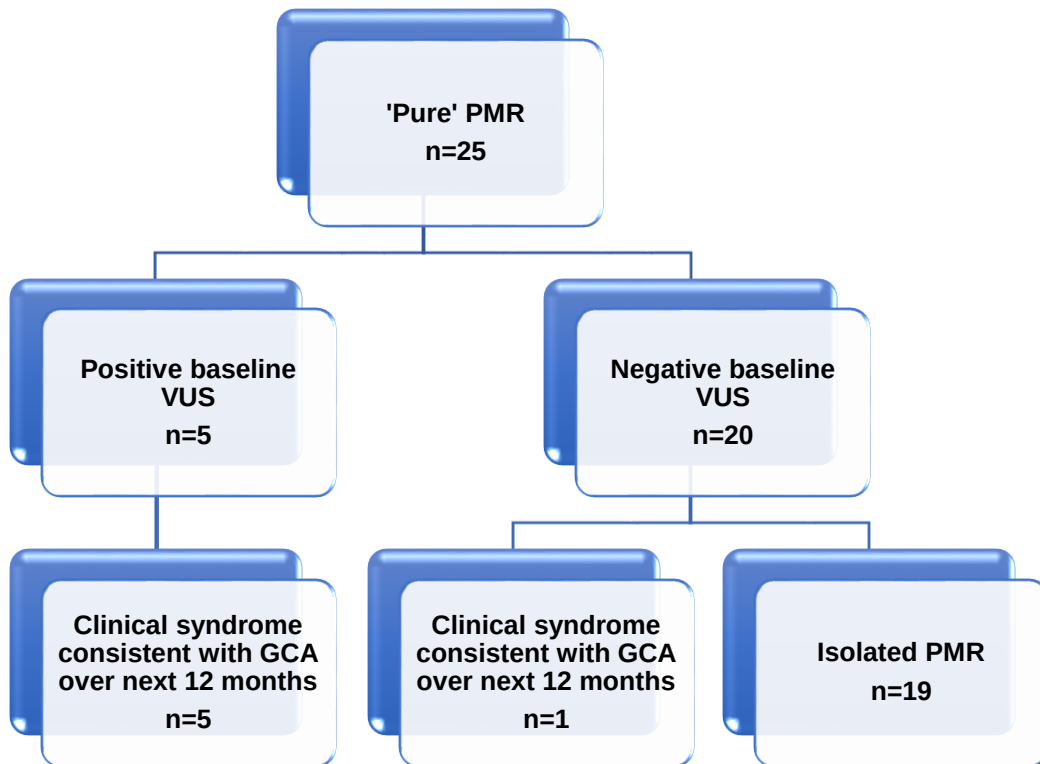


Figure 4.02: Schematic of VUS results and final diagnoses in 25 patients presenting with PMR.

4.3.1 Baseline characteristics of PMR cohort

For the PMR study participants (n=25) the mean age at recruitment was 66.9 (± 8.06) years and median body mass index (BMI) was 27.3kg/m² (24.8-32.7).

Participants had a mean of 1.4 CV risk factors. 60% of the cohort were female and the mean PTPS at study entry was 9.2 (± 2.72). 0% of patients fulfilled 1990 ACR GCA Classification Criteria while 36% fulfilled 2022 ACR/EULAR GCA Classification Criteria (due to varying combinations of morning stiffness, laboratory, and imaging criteria, and not cranial symptoms in the case of the Subclinical GCA

group) with a mean score 5.2. Low numbers of participants reported headaches (20%), scalp tenderness (12%), blurring of vision (4%) and loss of vision (4%). 88% and 72% reported polymyalgia of the shoulder and hip, respectively. All of the PMR participants had a palpable left and right temporal artery pulsation. The median (IQR) for ESR, CRP and Interleukin-6 were 23 mm/hr (9-57), 7 mg/L (4-23) and 11 pg/ml (4-38), respectively and mean platelet count was $323 \times 10^9/L$. ESR or CRP was elevated in 12/25 (48%) due in part to glucocorticoid use prior to study enrolment. Of those diagnosed with PMR at study entry, a total of 6 (24%) went on to develop GCA. 5/25 (20%) had a positive baseline VUS with a median Halo Count 0 and median Halo Score 11.

Patient Characteristics	Mean (SD)/ Median (IQR)/ N(%)
Age (years)	66.9 (8.06)
Body Mass Index (kg/m ²)	27.3 (24.8-32.7)
Sex (female)	15/25 (60.0%)
Pre-Test Probability Score	9.2 (2.72)
Any CV Risk Factor	18/25 (72.0%)
Number of CV Risk Factors	1.40 (1.22)
Smoker	1/24 (4.2%)
Established Vascular Disease	5/25 (20.0%)
1990 ACR GCA Classification Criteria Fulfilled	0/5 (0.0%)
2012 ACR/EULAR PMR Classification Criteria Fulfilled	16/25 (64%)
2022 ACR/EULAR Classification Criteria Fulfilled	9/25 (36.0%)
2022 ACR/EULAR Classification Criteria Score	5.2 (3.19)
Initial Diagnosis at Study Entry is PMR	25/25 (100.0%)
Final Diagnosis at 12 months is PMR	19/25 (76.0%)
Final Diagnosis is GCA	6/25 (24.0%)
Days From Initiation of GC to VUS Being Performed	0 (0-18)

Table 4.01: Characteristics of PMR cohort.

Clinical Features	Mean (SD)/ Median (IQR)/ N(%)
Headache	5/25 (20.0%)
Scalp Tenderness	3/25 (12.0%)
Blurring of Vision	1/25 (4.0%)
Loss of Vision	1/25 (4.0%)
Jaw Claudication	0/25 (0.0%)
Shoulder PMR	22/25 (88.0%)
Hip PMR	18/25 (72.0%)
Fever	0/25 (0.0%)
Night Sweats	0/25 (0.0%)
Anorexia	1/25 (4.0%)
Weight Loss	2/25 (8.0%)
STA Pulse Impalpable on Either Side	0/25 (0.0%)
STA Thickened on Palpation	2/25 (8.0%)
STA Tender on Palpation	1/25 (4.0%)
Any STA Abnormality on Exam	2/25 (8.0%)

Table 4.02: Clinical features of PMR cohort.

Laboratory Results	Mean (SD)/ Median (IQR)/ N(%)
ESR or CRP elevated	12/25 (48.0%)
ESR (mm/hr)	23 (9-57)
CRP (mg/L)	7 (4-23)
IL-6 (pg/ml)	11 (4-38)
Haemoglobin (g/dl)	13.2 (1.04)
White Blood Cells (x10 ⁹ /L)	10.6 (3.01)
Neutrophils (x10 ⁹ /L)	7.9 (2.86)
Lymphocytes (x10 ⁹ /L)	1.9 (0.91)
Monocytes (x10 ⁹ /L)	0.68 (0.23)
Eosinophils (x10 ⁹ /L)	0.1 (0.08)
Basophils (x10 ⁹ /L)	0.04 (0.05)
Platelets (x10 ⁹ /L)	323 (100.6)

Table 4.03: Laboratory results for PMR cohort.

VUS Results	Mean (SD)/Median (IQR)/N(%)
VUS Positive	5/25 (20.0%)
Superficial Temporal Artery Halo Count	0 [0-4]
Axillary Artery Halo Count	0 [0-1]
Total Halo Count	0 [0-5]
Superficial Temporal Artery Halo Score	4 [1-14]
Axillary Artery Halo Score	6 [0-18]
Total Halo Score	11 [0-29]

Table 4.04: VUS scores for PMR cohort.

VUS Results for Individual Vessels Branches	Mean (SD)/Median (IQR)/N(%)
Rt cSTA Halo	3/25 (12.0%)
Rt cSTA CS	3/25 (12.0%)
Rt cSTA IMTmax (mm)	0.32 (0.12)
Rt fSTA Halo	3/25 (12.0%)
Rt fSTA CS	3/25 (12.0%)
Rt fFTA IMTmax (mm)	0.26 (0.09)
Rt pSTA Halo	1/25 (4.0%)
Rt pSTA CS	1/25 (4.0%)
Rt pSTA IMTmax (mm)	0.02 (0.06)
Lt cSTA Halo	3/25 (12.0%)
Lt cSTA CS	3/25 (12.0%)
Lt cSTA IMTmax (mm)	0.31 (0.11)
Lt fSTA Halo	1/25 (4.0%)
Lt fSTA CS	1/25 (4.0%)
Lt fFTA IMTmax (mm)	0.22 (0.07)
Lt pSTA Halo	3/25 (12.0%)
Lt pSTA CS	3/25 (12.0%)
Lt pSTA IMTmax (mm)	0.22 (0.09)
Rt Axillary Artery Halo	1/25 (4.0%)
Rt Axillary Artery IMTmax (mm)	0.65 (0.20)
Lt Axillary Artery Halo	0/25 (0.0%)
Lt Axillary Artery IMTmax (mm)	0.61 (0.16)

Table 4.05: VUS results in individual vessel branches for PMR cohort.

4.3.2 Comparison between those with baseline PMR who were later diagnosed with GCA (Subclinical GCA) versus those who were not later diagnosed with GCA (Isolated PMR).

In this cohort, 6 participants had Subclinical GCA (24%), 19 had Isolated PMR (76%). Those with Subclinical GCA were older (73.0 years (± 7.82) vs 65.0 years (± 7.30)), more met the 2022 ACR/EULAR GCA Classification Criteria (83% vs 21%) and they had higher 2022 ACR/EULAR GCA Classification Criteria scores (8.3 (± 2.87) vs 4.3 (± 2.77)) than the Isolated PMR group. No patients fulfilled 1990 ACR GCA Classification Criteria. There were more males in the Subclinical GCA group with a higher median BMI, a higher mean PTPS and a higher mean number

of CV risk factors, but these results did not reach statistical significance. None of those with Subclinical GCA reported cranial symptoms at baseline, and hip PMR was significantly less prevalent in those with Subclinical GCA. ESR or CRP was elevated in more patients with Subclinical GCA (83% vs 37%) as were platelets. With respect to ESR and CRP individually, their medians were insignificantly higher while IL-6 was insignificantly lower along with WBCs. 5/6 (83.3%) of those with Subclinical GCA had a positive baseline VUS while no patient with Isolated PMR had a positive VUS. Median STA HC and HS as well as median Total HC and HS were higher in the Subclinical GCA group while median AA HS, but not HC, was insignificantly higher. Significant differences were demonstrated for the presence of Halo and IMTmax for the right and left cSTA, right fSTA, left pSTA and left AA between the two groups. 0/3 patients with Subclinical GCA had an abnormal TAB, although at a median of 8 days after commencing immunosuppressive therapy. Patients were followed up for 12 months and all 6 of the Subclinical GCA group had a GCA flare during this period. No patients developed ischaemic complications but 2 required biologic therapy.

Patient Characteristics	Subclinical GCA (n=6) Mean (SD)/ Median (IQR)/ N(%)	Isolated PMR (n=19) Mean (SD)/ Median (IQR)/ N(%)
Age (years)	73.0 (7.82)	65.0 (7.30)*
Body Mass Index (kg/m ²)	30.8 (27-36.1)	26.5 (23.2-28.3)
Sex (female)	2/6 (33.3%)	13/19 (68.4%)
Length of Follow-up (months)	12	12
Pre-Test Probability Score	9.33 (3.08)	9.11 (2.69)
Any CV Risk Factor	6/6 (100.0%)	12/19 (63.2%)
Number of CV Risk Factors	2.50 (1.38)	1.05 (0.97)
Smoker	1/5 (20.0%)	0/19 (0.0%)
Established Vascular Disease	3/6 (50.0%)	2/19 (10.5%)
Flare of GCA During Follow-up	6/6 (100%)	0/0 (0.0%)*
Ischaemia During Follow- up	-	-
Ever Treated with Tocilizumab	2/6 (33.3%)	0/19 (0.0%)
1990 ACR GCA Classification Criteria Fulfilled	0/6 (0.0%)	-
2022 ACR/EULAR Classification Criteria Fulfilled	5/6 (83.3%)	4/19 (21.0%)*
2022 ACR/EULAR Classification Criteria Score	8.3 (2.87)	4.3 (2.77) **
Initial Diagnosis at study Entry is PMR	6/6 (100.0%)	19/19 (100.0%)
Final Diagnosis at 12 Months is PMR	0/6 (0.0%)	19/19 (100.0%)
Final Diagnosis is GCA	6/6 (100.0%)	0/19 (0.0%)
TAB Positive	0/3 (0.0%)	-
Time (days) from Initiation of GC to VUS	0 (0-18)	4 (0-14.5)
Time (days) from Initiation of GC to TAB	8 (1-21)	-

Table 4.06: Characteristics of patients with Subclinical GCA vs Isolated PMR. *p< 0.05, **p<0.005, ***p<0.0005.

Clinical Features	Subclinical GCA (n=6) Mean (SD)/ Median (IQR)/ N(%)	Isolated PMR (n=19) Mean (SD)/ Median (IQR)/ N(%)
Headache	0/6 (0.0%)	5/19 (26.3%)
Scalp Tenderness	0/6 (0.0%)	3/19 (15.8%)
Blurring of Vision	0/6 (0.0%)	1/19 (5.3%)
Loss of Vision	0/6 (0.0%)	1/19 (5.3%)
Jaw Claudication	0/6 (0.0%)	0/19 (0.0%)
Shoulder PMR	5/6 (83.3%)	17/19 (89.5%)
Hip PMR	2/6 (33.3%)	16/19 (84.2%)*
Fever	0/6 (0.0%)	0/19 (0.0%)
Night Sweats	0/6 (0.0%)	0/19 (0.0%)
Anorexia	0/6 (0.0%)	1/19 (5.3%)
Weight Loss	1/6 (16.7%)	1/19 (5.3%)
STA Pulse Impalpable on Either Side	0/6 (0.0%)	0/19 (0.0%)
STA Thickened on Palpation	0/6 (0.0%)	2/19 (10.5%)
STA Tender on Palpation	0/6 (0.0%)	1/19 (5.3%)
Any STA Abnormality on Exam	0/6 (0.0%)	2/19 (10.5%)

Table 4.07: Clinical features of patients with Subclinical GCA vs Isolated PMR. *p< 0.05, **p<0.005, ***p<0.0005.

Laboratory Results	Subclinical GCA (n=6) Mean (SD)/ Median (IQR)/ N(%)	Isolated PMR (n=19) Mean (SD)/ Median (IQR)/ N(%)
ESR or CRP elevated	5/6 (83.3%)	7/19 (36.8%)*
ESR (mm/hr)	27.5 (17-56)	20 (8-57)
CRP (mg/L)	13.5 (11-86)	6 (2-23)
IL-6 (pg/ml)	5.9 (3.7-37.6)	17.1 (17.1-17.1)
Haemoglobin (g/dl)	13.55 (0.92)	13.10 (1.08)
White Blood Cells (x10 ⁹ /L)	9.98 (2.60)	10.76 (3.17)
Neutrophils (x10 ⁹ /L)	7.62 (2.35)	7.99 (3.06)
Lymphocytes (x10 ⁹ /L)	1.52 (0.63)	1.96 (0.97)
Monocytes (x10 ⁹ /L)	0.68 (0.28)	0.67 (0.23)
Eosinophils (x10 ⁹ /L)	0.10 (0.06)	0.10 (0.08)
Basophils (x10 ⁹ /L)	0.03 (0.05)	0.04 (0.05)
Platelets (x10 ⁹ /L)	248.50 (75.69)	347.16 (97.17)*

Table 4.08: Laboratory results for patients with Subclinical GCA vs Isolated PMR. *p< 0.05, **p<0.005, ***p<0.0005.

VUS Scores	Subclinical GCA (n=6) Mean (SD)/ Median (IQR)/ N(%)	Isolated PMR (n=19) Mean (SD)/ Median (IQR)/ N(%)
VUS Positive	5/6 (83.3%)	0/19 (0.0%) ^{***}
Superficial Temporal Artery Halo Count	2.5 [0-4]	0 [0-0] ^{***}
Axillary Artery Halo Count	0 [0-1]	0 [0-0]
Total Halo Count	2.5 [0-5]	0 [0-0] ^{***}
Superficial Temporal Artery Halo Score	11 [1-14]	4 [2-7] [*]
Axillary Artery Halo Score	10.5 [6-18]	6 [0-15]
Total Halo Score	19.5 [17-29]	10 [2-19] ^{**}

Table 4.09: VUS scores for patients with Subclinical GCA vs Isolated PMR. *p< 0.05, **p<0.005, ***p<0.0005.

VUS Results for Individual Vessels Branches	Subclinical GCA (n=6) Mean (SD)/ Median (IQR)/ N(%)	Isolated PMR (n=19) Mean (SD)/ Median (IQR)/ N(%)
Rt cSTA Halo	3/6 (50.0%)	0/19 (0.0%) ^{***}
Rt cSTA CS	3/6 (50.0%)	0/19 (0.0%) ^{***}
Rt cSTA IMTmax (mm)	0.42 (0.17)	0.28 (0.08) ^{**}
Rt fSTA Halo	3/6 (50.0%)	0/19 (0.0%) ^{***}
Rt fSTA CS	3/6 (50.0%)	0/19 (0.0%) ^{***}
Rt fFTA IMTmax (mm)	0.33 (0.18)	0.23 (0.05) [*]
Rt pSTA Halo	1/6 (16.7%)	0/19 (0.0%)
Rt pSTA CS	1/6 (16.7%)	0/19 (0.0%)
Rt pSTA IMTmax (mm)	0.22 (0.08)	0.19 (0.05)
Lt cSTA Halo	3/6 (50.0%)	0/19 (0.0%) ^{***}
Lt cSTA CS	3/6 (50.0%)	0/19 (0.0%) ^{***}
Lt cSTA IMTmax (mm)	0.43 (0.15)	0.28 (0.07) [*]
Lt fSTA Halo	1/6 (16.7%)	0/19 (0.0%)
Lt fSTA CS	1/6 (16.7%)	0/19 (0.0%)
Lt fFTA IMTmax (mm)	0.28 (0.10)	0.21 (0.06)
Lt pSTA Halo	3/6 (50.0%)	0/19 (0.0%) [*]
Lt pSTA CS	3/6 (50.0%)	0/19 (0.0%)
Lt pSTA IMTmax (mm)	0.32 (0.11)	0.19 (0.05) ^{***}
Rt Axillary Artery Halo	1/6 (16.7%)	0/19 (0.0%)
Rt Axillary Artery IMTmax (mm)	0.75 (0.30)	0.62 (0.15)
Lt Axillary Artery Halo	0/6 (0.0%)	0/19 (0.0%)
Lt Axillary Artery IMTmax (mm)	0.77 (0.12)	0.57 (0.14) [*]

Table 4.10: VUS results in individual vessel branches for patients with Subclinical GCA vs Isolated PMR. *p< 0.05, **p<0.005, ***p<0.0005.

4.3.3 Sensitivity and Specificity of VUS for Subclinical GCA in those presenting with PMR

The sensitivity of VUS for underlying GCA in those presenting with 'pure' PMR was 83% and the specificity was 100%. The AUC was 0.92 (0.75-1.00)]. However, these results should be interpreted with caution due to the small samples size and should be confirmed in a larger cohort.

Diagnostic Performance of VUS for Detecting Subclinical GCA	
True Positive	5
True Negative	19
False Positive	0
False Negative	1
Sensitivity	83.3%
Specificity	100%
AUC	0.92 (0.75-1.00)

Table 4.11: Diagnostic performance of VUS for identifying Subclinical GCA in an inception PMR cohort.

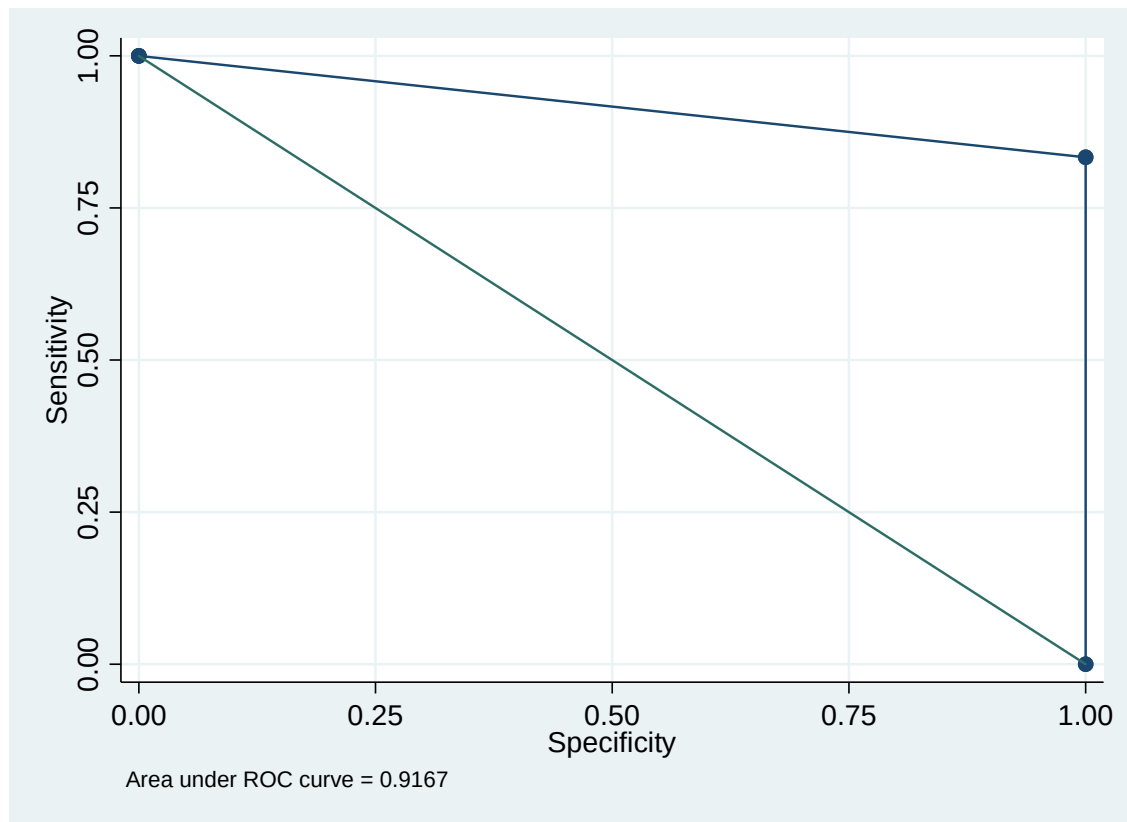


Figure 4.03: ROC curve of VUS for Subclinical GCA in 25 PMR patients.

4.3.4 Comparison of baseline VUS data between GCA and PMR cohorts

An analysis comparing the PMR cohort with another cohort of 124 patients referred to a Rapid-Access GCA Clinic with a suspected diagnosis of GCA was performed. The GCA cohort had significantly higher STA HC and HS as well as Total HC and HS compared with the PMR study cohort while mean IMTmax was greater in all branches.

VUS Results	Suspected GCA (n=124) Mean (SD)/ Median (IQR)/ N(%)	PMR (n=25) Mean (SD)/ Median (IQR)/ N(%)
Rt cSTA Halo	40/124 (32.3%)	3/25 (12.0%)*
Rt cSTA CS	40/124 (32.3%)	3/25 (12.0%)*
Rt cSTA IMTmax (mm)	0.43 (0.21)	0.32 (0.12)*
Rt fSTA Halo	38/124 (30.7%)	3/25 (12.0%)
Rt fSTA CS	39/124 (31.5%)	3/25 (12.0%)*
Rt fFTA IMTmax (mm)	0.33 (0.16)	0.26 (0.10)*
Rt pSTA Halo	31/124 (25%)	1/25 (4.0%)*
Rt pSTA CS	31/124 (25.0%)	1/25 (4.0%)*
Rt pSTA IMTmax (mm)	0.26 (0.12)	0.20 (0.06)**
Lt cSTA Halo	41/124 (33.01%)	3/25 (12.0%)*
Lt cSTA CS	41/124 (33.01%)	3/25 (12.0%)*
Lt cSTA IMTmax (mm)	0.41 (0.15)	0.31 (0.12)**
Lt fSTA Halo	45/124 (36.3%)	1/25 (4.0%)*
Lt fSTA CS	45/124 (36.3%)	1/25 (4.0%)*
Lt fFTA IMTmax (mm)	0.34 (0.15)	0.22 (0.08)*
Lt pSTA Halo	34/124 (27.4%)	3/25 (12.0%)
Lt pSTA CS	34/124 (27.4%)	3/25 (12.0%)
Lt pSTA IMTmax (mm)	0.29 (0.14)	0.22 (0.09)*
Rt Axillary Artery Halo	23/124 (18.6%)	1/25 (4.0%)*
Rt Axillary Artery IMTmax (mm)	0.80 (0.38)	0.65 (0.20)*
Lt Axillary Artery Halo	25/124 (20.2%)	0/25 (0.0%)*
Lt Axillary Artery IMTmax (mm)	0.79 (0.36)	0.61 (0.16)*

Table 4.12: VUS results in patients referred to a Rapid-Access PMR clinic vs those referred to a Rapid-Access GCA clinic. *p< 0.05, **p<0.005, ***p<0.0005.

4.3.5 Study entry characteristic of those with PMR and Subclinical GCA versus those with GCA and positive VUS

The Subclinical GCA cohort was compared to a cohort of patients referred to a Rapid-Access GCA Clinic who had positive VUS (n=57) and a number of significant differences were observed. Those presenting with classical GCA were older, had higher PTPS and were likelier to fulfil 1990 ACR and 2022 ACR/EULAR GCA Classification Criteria with higher 2022 ACR/EULAR GCA Classification Criteria scores. This group had more females and lower BMI but these results did not reach statistical significance. They reported more cranial symptoms and less shoulder PMR than the Subclinical GCA group while baseline and future ischaemic complications were more prevalent also. Baseline platelet counts were significantly higher in those presenting with GCA and they had insignificantly higher median ESR, CRP and lymphocyte counts and insignificantly lower median IL-6, and mean Hb and neutrophil counts. All Halo Counts and Halo Scores were greater in the GCA group, significantly so in the case of Total Halo Score. With regard to sonographic parameters measured in individual vascular branches, there were higher mean values for Halo, Compression Sign and IMTmax in all branches for those with GCA, significantly so in the case of left fSTA. Mean length of follow-up was longer in the PMR cohort (12 versus 8.18 months) and a great proportion of these patients had a flare of GCA during the follow-up period (100% versus 39%). A greater proportion of GCA patients had a positive TAB despite no difference in the mean interval between commencing immunosuppressive therapy and performing TAB and this group had a greater requirement for biologic therapy (56.4% v 33.3%) but this results did not reach statistical significance.

Patient Characteristics	Subclinical GCA and US+ (n=5) Mean (SD)/ Median (IQR)/ N(%)	Subclinical GCA (n=6) Mean (SD)/ Median (IQR)/ N(%)	GCA and US+ (n=57) Mean (SD)/ Median (IQR)/ N(%)
Age (years)	75.00 (6.82)	73.0 (7.82)	74.4 (8.23)
Body Mass Index (kg/m ²)	34.1 (27.4-36.1) *	30.8 (27-36.1)	26.6 (24.4-31.2)
Sex (female)	2/5 (40.0%)	2/6 (33.3%)	24/57 (42.1%)
Months of Follow-up		12 (12)	8.18 (4.20)***
PTPS	10.20 (2.49)	9.33 (3.08)	12.84 (3.29) *
Any CV Risk Factor	5/5 (100.0%)	6/6 (100.0%)	48/57 (84.2%)
Number of CV Risk Factors	2.8 (1.30)	2.50 (1.38)	1.53 (1.05)
Smoker	1/4 (25.0%)	1/5 (20.0%)	7/55 (12.7%)
Established Vascular Disease	2/5 (40.0%)	3/6 (50.0%)	16/57 (28.1%)
Flare of GCA During Follow-up	5/5 (100%)	6/6 (100%)	20/51 (39.2%)
Ischaemia at Baseline (loss of vision, CVA etc)	0/5 (0.0%)	0/6 (0.0%)	14/57 (24.6%)
Ischaemia During Follow-up	0 (0.0%)	0 (0.0%)	3/51 (5.9%)
Ever Treated with Tocilizumab	2/6 (33.3%)	2/6 (33.3%)	31/57 (56.4%)
1990 ACR GCA Classification Criteria Fulfilled	0/5 (0.0%)***	0/6 (0.0%)	43/57 (75.4%)***
2022 ACR/EULAR Classification Criteria Fulfilled	5/5 (100.0%)	5/6 (83.3%)	56/57 (98.2%)*
2022 ACR/EULAR Classification Criteria Score	9.40 (1.34)	8.3 (2.87)	13.25 (3.25) ***
Initial Diagnosis PMR	5/5 (100.0%)***	6/6 (100.0%)	0/57 (0.0%)***
Final Diagnosis PMR	0/5 (0.0%)	0/6 (0.0%)	0/57 (0.0%)
Final Diagnosis GCA	5/5 (100.0%)	6/6 (100.0%)	57/57 (100.0%)
TAB Positive	0/3 (0.0%)	0/3 (0.0%)	19/44 (43.2%)
Time (days) from Initiation of GC to VUS	0 (0-0)	0 (0-18)	0 (0-2)
Time (days) from Initiation of GC to TAB	8 (1-21)	8 (1-21)	8 (4-14.5)

Table 4.13: Characteristics of those with Subclinical GCA vs patients with Clinical GCA who had positive baseline VUS. *p< 0.05, **p<0.005, ***p<0.0005.

Clinical Features	Subclinical GCA and US+ (n=5) Mean (SD)/ Median (IQR)/ N(%)	Subclinical GCA (n=6) Mean (SD)/ Median (IQR)/ N(%)	GCA and US+ (n=57) Mean (SD)/ Median (IQR)/ N(%)
Headache	0/5 (0.0%)***	0/6 (0.0%)***	47/57 (82.5%)
Scalp Tenderness	0/5 (0.0%)***	0/6 (0.0%)***	34/57 (59.6%)
Blurring of Vision	0/5 (0.0%)	0/6 (0.0%)	21/57 (36.8%)
Loss of Vision	0/5 (0.0%)	0/6 (0.0%)	13/57 (22.8%)
Jaw Claudication	0/5 (0.0%)	0/6 (0.0%)	17/57 (29.8%)
Shoulder PMR	5/5 (100.0%)*	5/6 (83.3%)	20/57 (35.1%)*
Hip PMR	2/5 (40.0%)	2/6 (33.3%)	12/57 (21.1%)
Fever	0/5 (0.0%)	0/6 (0.0%)	6/57 (10.5%)
Night Sweats	0/5 (0.0%)	0/6 (0.0%)	7/57 (12.3%)
Anorexia	0/5 (0.0%)	0/6 (0.0%)	15/57 (26.3%)
Weight Loss	1/5 (20.0%)	1/6 (16.7%)	16/57 (28.1%)
STA Pulse Impalpable, rt or lt	0/5 (0.0%)	0/6 (0.0%)	2/57 (3.5%)
STA Thickened on Palpation	0/5 (0.0%)	0/6 (0.0%)	9/57 (15.8%)
STA Tender on Palpation	0/5 (0.0%)	0/6 (0.0%)	8/57 (14.0%)
Any STA Exam Abnormality	0/5 (0.0%)	0/6 (0.0%)	16/57 (28.1%)

Table 4.14: Clinical features of those with Subclinical GCA vs patients with Clinical GCA who had positive baseline VUS. *p< 0.05, **p<0.005, ***p<0.0005.

Laboratory Results	Subclinical GCA and US+ (n=5) Mean (SD)/ Median (IQR)/ N(%)	Subclinical GCA (n=6) Mean (SD)/ Median (IQR)/ N(%)	GCA and US+ (n=57) Mean (SD)/ Median (IQR)/ N(%)
ESR or CRP elevated	4/5 (80.0%)	5/6 (83.3%)	47/57 (82.5%)
ESR (mm/hr)	31 (34-56)	27.5 (17-56)	54 (34-85)
CRP (mg/L)	14 (13 - 86)	13.5 (11-86)	43.5 (9-99.5)
IL-6 (pg/ml)	5.9 (3.7 -37.6)	5.9 (3.7-37.6)	4.9 (2.03-11.29)
Haemoglobin (g/dl)	13.26 (0.66)	13.55 (0.92)	12.92 (1.65)
White Blood Cells (x10 ⁹ /L)	10.26 (2.80)	9.98 (2.60)	9.97 (3.58)
Neutrophils (x10 ⁹ /L)	7.76 (2.60)	7.62 (2.35)	7.38 (3.37)
Lymphocytes (x10 ⁹ /L)	1.64 (0.62)	1.52 (0.63)	1.61 (0.78)
Monocytes (x10 ⁹ /L)	0.70 (0.31)	0.68 (0.28)	0.79 (0.34)
Eosinophils (x10 ⁹ /L)	0.10 (0.07)	0.10 (0.06)	0.16 (0.17)
Basophils (x10 ⁹ /L)	0.02 (0.04)	0.03 (0.05)	0.05 (0.05)
Platelets (x10 ⁹ /L)	267.40 (66.94)	248.50 (75.69)	353.35 (123.31)*

Table 4.15: Laboratory results for those with Subclinical GCA vs patients with Clinical GCA who had positive baseline VUS. *p< 0.05, **p<0.005, ***p<0.0005.

VUS Scores	Subclinical GCA and US+ (n=5) Mean (SD)/ Median (IQR)/ N(%)	Subclinical GCA (n=6) Mean (SD)/ Median (IQR)/ N(%)	GCA and US+ (n=57) Mean (SD)/ Median (IQR)/ N(%)
VUS Positive	5/5 (100.0%)	5/6 (83.3%)	57/57 (100.0%)**
Superficial Temporal Artery Halo Count	3 [1-4]	2.5 [0-4]	4 [0-6]
Axillary Artery Halo Count	0 [0-0]	0 [0-1]	0 [0-2]
Total Halo Count	2 [1-5]	2.5 [0-5]	4 [0-8]
Superficial Temporal Artery Halo Score	11 [7-14]	11 [1-14]	13[5-23]
Axillary Artery Halo Score	6[6-18]	10.5 [6-18]	15 [0-24]
Total Halo Score	20 [17-29]	19.5 [17-29]	26 [8-43]*

Table 4.16: VUS scores for those with Subclinical GCA vs patients with Clinical GCA who had positive baseline VUS. *p< 0.05, **p<0.005, ***p<0.0005.

VUS Results for Individual Vessels Branches	Subclinical GCA and US+ (n=5) Mean (SD)/ Median (IQR)/ N(%)	Subclinical GCA (n=6) Mean (SD)/ Median (IQR)/ N(%)	GCA and US+ (n=57) Mean (SD)/ Median (IQR)/ N(%)
Rt cSTA Halo	3/5 (60.0%)	3/6 (50.0%)	35/57 (61.4%)
Rt cSTA CS	3/5 (60.0%)	3/6 (50.0%)	35/57 (61.4%)
Rt cSTA IMTmax (mm)	0.45 (0.18)	0.42 (0.17)	0.56 (0.22)
Rt fSTA Halo	3/5 (60.0%)	3/6 (50.0%)	35/57 (61.4%)
Rt fSTA CS	3/5 (60.0%)	3/6 (50.0%)	36/57 (63.2%)
Rt fFTA IMTmax (mm)	0.37 (0.15)	0.33 (0.18)	0.43 (0.18)
Rt pSTA Halo	1/5 (20.0%)	1/6 (16.7%)	29/57 (50.9%)
Rt pSTA CS	1/5 (20.0%)	1/6 (16.7%)	29/57 (50.9%)
Rt pSTA IMTmax (mm)	0.24 (0.05)	0.22 (0.08)	0.32 (0.14)
Lt cSTA Halo	3/5 (60.0%)	3/6 (50.0%)	38/57 (66.7%)
Lt cSTA CS	3/5 (60.0%)	3/6 (50.0%)	38/57 (66.7%)
Lt cSTA IMTmax (mm)	0.47 (0.13)	0.43 (0.15)	0.50 (0.15)
Lt fSTA Halo	1/5 (20.0%)	1/6 (16.7%)	39/57 (68.4%)*
Lt fSTA CS	1/5 (20.0%)	1/6 (16.7%)	39/57 (68.4%)*
Lt fFTA IMTmax (mm)	0.29 (0.11)	0.28 (0.10)	0.43 (0.17)*
Lt pSTA Halo	3/5 (60.0%)	3/6 (50.0%)	31/57 (54.4%)
Lt pSTA CS	3/5 (60.0%)	3/6 (50.0%)	31/57 (54.4%)
Lt pSTA IMTmax (mm)	0.34 (0.10)	0.32 (0.11)	0.36 (0.17)
Rt Axillary Artery Halo	1/5 (20.0%)	1/6 (16.7%)	21/57 (36.8%)
Rt Axillary Artery IMTmax (mm)	0.72 (0.33)	0.75 (0.30)	0.98 (0.44)
Lt Axillary Artery Halo	0.5 (0.0%)	0/6 (0.0%)	21/57 (36.8%)
Lt Axillary Artery IMTmax (mm)	0.74 (0.11)	0.77 (0.12)	0.95 (0.40)

Table 4.17: VUS results in individual vessel branches of those with Subclinical GCA vs patients with Clinical GCA who had positive baseline VUS. *p< 0.05, **p<0.005, ***p<0.0005.

4.3.6 Study entry characteristic of those with GCA versus those with Subclinical GCA

In a comparison between those who presented with 'pure' PMR who were subsequently diagnosed with GCA (i.e. Subclinical GCA), and those who presented with GCA (both with positive and negative US), some differences were observed. Those presenting with GCA were more likely to be female, have higher PTPS, meet 1990 ACR GCA Classification Criteria and have higher 2022 ACR/EULAR GCA Classification Criteria scores, with an insignificantly higher proportion of these patients fulfilling 2022 ACR/EULAR GCA Classification Criteria. This group had a lower BMI and median number of CV risk factors and more prevalent baseline and future ischaemic complications, but these results did not reach statistical significance. This group had significantly more prevalent cranial symptoms and less prevalent shoulder PMR symptoms than the Subclinical GCA group. Platelets were significantly higher in this group. Median ESR and CRP and mean lymphocyte counts were higher while median IL-6 and mean Hb and neutrophil counts were lower in this group, but these results did not reach statistical significance. These patients were slightly more likely to have a positive VUS (86.4% v 83.3%) and insignificantly higher median HC and HS, despite a longer interval between commencing immunosuppressive therapy and performing VUS. Mean values for Halo, Compression Sign and IMTmax were also greater in this group, significantly so in the case of left fTA Halo and CS, with the exception of left pSTA HC and HS. Length of follow-up was shorter in the GCA group (7.06 vs 12 months) and flares were less prevalent (39.2% vs 100%). The GCA group had insignificantly higher values for TAB positivity and a greater requirement for biologic therapy (56.4% vs 33.3%).

Patient Characteristics	Subclinical GCA (n=6) Mean (SD)/ Median (IQR)/ N(%)	GCA (TP+FN US) (n=66) Mean (SD)/ Median (IQR)/ N(%)
Age (years)	73.0 (7.82)	73.30 (8.73)
Body Mass Index (kg/m ²)	30.8 (27-36.1)	27.1 (24.4-31.2)
Sex (female)	2/6 (33.3%)	30/66 (45.5%)
Length of Follow-up (months)	12 (12)	7.06 (4.82)
Pre-Test Probability Score	9.33 (3.08)	12.62 (3.19)*
Any CV Risk Factor	6/6 (100.0%)	57/66 (86.4%)
Number of CV Risk Factors	2.50 (1.38)	1.64 (1.08)
Smoker	1/5 (20.0%)	7/64 (10.9%)
Established Vascular Disease	3/6 (50.0%)	18/66 (27.3%)
Flare of GCA During Follow-up	6/6 (100%)	20/51 (39.2%)
Ischaemia at Baseline (loss of vision, CVA etc)	0/6 (0.0%)	15/66 (22.7%)
Ischaemia During Follow- up	0/6 (0.0%)	3/51 (5.9%)
Ever Treated with Tocilizumab	2/6 (33.3%)	31/57 (56.4%)
1990 ACR GCA Classification Criteria Fulfilled	0/5 (0.0%)	48/66 (72.7%)**
2022 ACR/EULAR Classification Criteria Fulfilled	5/6 (83.3%)	61/66 (92.4%)
2022 ACR/EULAR Classification Criteria Score	8.3 (2.87)	12.38 (3.89) *
Initial Diagnosis is PMR	6/6 (100.0%)	0/66 (0.0%)***
Final Diagnosis is PMR	0/6 (0.0%)	0/66 (0.0%)
Final Diagnosis is GCA	6/6 (100.0%)	66/66 (100.0%)
TAB Positive	0/3 (0.0%)	19/44 (43.2%)
Time (days) from Initiation of GC to VUS	0 (0-18)	1 (0-2)
Time (days) from Initiation of GC to TAB	8 (1-21)	8 (4-15)

Table 4.18: Characteristics of patients with Subclinical GCA vs Clinical GCA. *p< 0.05, **p<0.005, ***p<0.0005.

Clinical Features	Subclinical GCA (n=6) Mean (SD)/ Median (IQR)/ N(%)	GCA (TP+FN US) (n=66) Mean (SD)/ Median (IQR)/ N(%)
Headache	0/6 (0.0%)	54/66 (81.8%)***
Scalp Tenderness	0/6 (0.0%)	37/66 (56.1%)***
Blurring of Vision	0/6 (0.0%)	26/66 (39.4%)
Loss of Vision	0/6 (0.0%)	14/66 (21.2%)
Jaw Claudication	0/6 (0.0%)	18/66 (27.3%)
Shoulder PMR	5/6 (83.3%)	23/66 (34.8%)*
Hip PMR	2/6 (33.3%)	14/66 (21.2%)
Fever	0/6 (0.0%)	7/66 (10.6%)
Night Sweats	0/6 (0.0%)	9/66 (13.6%)
Anorexia	0/6 (0.0%)	16/66 (24.2%)
Weight Loss	1/6 (16.7%)	16/66 (24.2%)
STA Pulse Impalpable on Either Side	0/6 (0.0%)	1/66 (1.51%)
STA Thickened on Palpation	0/6 (0.0%)	9/66 (13.6%)
STA Tender on Palpation	0/6 (0.0%)	9/66 (13.6%)
Any STA Exam Abnormality	0/6 (0.0%)	17/66 (25.8%)

Table 4.19: Clinical features of patients with Subclinical GCA vs Clinical GCA. *p< 0.05, **p<0.005, ***p<0.0005.

Laboratory Results	Subclinical GCA (n=6) Mean (SD)/ Median (IQR)/ N(%)	GCA (TP+FN US) (n=66) Mean (SD)/ Median (IQR)/ N(%)
ESR or CRP elevated	5/6 (83.3%)	54/65 (83.1%)
ESR (mm/hr)	27.5 (17-56)	55 (35-82)
CRP (mg/L)	13.5 (11-86)	43.5 (11-995)
IL-6 (pg/ml)	5.9 (3.7-37.6)	4.9 (2.03-11.39)
Haemoglobin (g/dl)	13.55 (0.92)	12.86 (1.60)
White Blood Cells (x10 ⁹ /L)	9.98 (2.60)	10.13 (3.48)
Neutrophils (x10 ⁹ /L)	7.62 (2.35)	7.51 (3.29)
Lymphocytes (x10 ⁹ /L)	1.52 (0.63)	1.62 (0.76)
Monocytes (x10 ⁹ /L)	0.68 (0.28)	0.78 (0.33)
Eosinophils (x10 ⁹ /L)	0.10 (0.06)	0.17 (0.17)
Basophils (x10 ⁹ /L)	0.03 (0.05)	0.05 (0.04)
Platelets (x10 ⁹ /L)	248.50 (75.69)	354.68 (121.59) *

Table 4.20: Laboratory results for patients with Subclinical GCA vs Clinical GCA. *p< 0.05, **p<0.005, ***p<0.0005.

VUS Scores	Subclinical GCA (n=6) Mean (SD)/ Median (IQR)/ N(%)	GCA (TP+FN US) (n=66) Mean (SD)/ Median (IQR)/ N(%)
VUS Positive	5/6 (83.3%)	57/66 (86.4%)
Superficial Temporal Artery Halo Count	2.5 [0-4]	3 [2-5]
Axillary Artery Halo Count	0 [0-1]	9 [0-2]
Total Halo Count	2.5 [0-5]	4[0-8]
Superficial Temporal Artery Halo Score	11 [1-14]	12 [2-23]
Axillary Artery Halo Score	10.5 [6-18]	12 [0-24]
Total Halo Score	19.5 [17-29]	24 [8-43]

Table 4.21: VUS Scores for patients with Subclinical GCA vs Clinical GCA. *p< 0.05, **p<0.005, ***p<0.0005.

VUS Results for Individual Vessel Branches	Subclinical GCA (n=6) Mean (SD)/ Median (IQR)/ N(%)	GCA (TP+FN US) (n=66) Mean (SD)/ Median (IQR)/ N(%)
Rt cSTA Halo	3/6 (50.0%)	35/66 (53.0%)
Rt cSTA CS	3/6 (50.0%)	35/66 (53.0%)
Rt cSTA IMTmax (mm)	0.42 (0.17)	0.52 (0.23)
Rt fSTA Halo	3/6 (50.0%)	35/66 (53.0%)
Rt fSTA CS	3/6 (50.0%)	36/66 (54.5%)
Rt fFTA IMTmax (mm)	0.33 (0.18)	0.40 (0.18)
Rt pSTA Halo	1/6 (16.7%)	29/66 (43.9%)
Rt pSTA CS	1/6 (16.7%)	29/66 (43.9%)
Rt pSTA IMTmax (mm)	0.22 (0.08)	0.31 (0.14)
Lt cSTA Halo	3/6 (50.0%)	38/66 (57.6%)
Lt cSTA CS	3/6 (50.0%)	38/66 (57.6%)
Lt cSTA IMTmax (mm)	0.43 (0.15)	0.48 (0.15)
Lt fSTA Halo	1/6 (16.7%)	39/66 (59.1%)*
Lt fSTA CS	1/6 (16.7%)	39/66 (59.1%)*
Lt fFTA IMTmax (mm)	0.28 (0.10)	0.41 (0.17)
Lt pSTA Halo	3/6 (50.0%)	31/66 (47.0%)
Lt pSTA CS	3/6 (50.0%)	31/66 (47.0%)
Lt pSTA IMTmax (mm)	0.32 (0.11)	0.34 (0.16)
Rt Axillary Artery Halo	1/6 (16.7%)	21/66 (31.8%)
Rt Axillary Artery IMTmax (mm)	0.75 (0.30)	0.93 (0.43)
Lt Axillary Artery Halo	0/6 (0.0%)	21/66 (31.8%)
Lt Axillary Artery IMTmax (mm)	0.77 (0.12)	0.91 (0.40)

Table 4.22: VUS results in individual vessel branches for patients with Subclinical GCA vs Clinical GCA. *p< 0.05, **p<0.005, ***p<0.0005.

4.4 Discussion

PMR affects 0.5-1.5% of the population and shares considerable overlap with GCA (18). Symptoms, laboratory parameters and treatments are similar between the two groups and recently 'GCA PMR Spectrum Disease' has been described (41). PMR can be considered the mild end of this spectrum with GCA being on the more severe end. While the overlapping features of these two conditions are well recognised, means of distinguishing them from one another are needed. This is particularly true of Subclinical GCA i.e. patients who present with a pure PMR-like syndrome but actually have underlying vasculitis. The importance of early identification of this subset is clear given the ischaemic complications associated with the diagnosis (7, 40).

Traditionally, TAB has been used to confirm GCA diagnosis but it is invasive, expensive and has a high false-negative rate. While PET/CT is a sensitive tool for demonstrating large vessel inflammation in PMR, it involves high doses of ionising radiation, is costly to perform and access in most centres is poor. Therefore, with a growing number of rheumatologists becoming adept at musculoskeletal and VUS, VUS would appear to be most readily accessible diagnostic tool in daily routine practice. Only 8 published studies to date have specifically interrogated VUS in those presenting with PMR, 4 of which were published prior to 2003, when US technology was vastly inferior to that which is available today (47, 48, 67-69, 114, 149).

This study recruited only those patients with so-called 'Pure PMR' i.e. no cranial symptoms to suggest GCA. Comprehensive VUS was performed on the full length of all branches of STA and AA. VUS performed excellently in identifying Subclinical

GCA with an AUC 0.92. Those who later developed GCA in this cohort were older and more likely to meet 2022 ACR/EULAR Classification Criteria with higher scores by these criteria. Hip PMR was less prevalent in those who subsequently developed GCA while ESR/CRP elevations were more prevalent. All 6 of the Subclinical GCA cohort flared on initial PMR-dose steroid taper, with 2 ultimately requiring biologic therapy. None of the 19 PMR patients required biologic therapy during follow-up. Compared with another study cohort presenting with classical GCA (both with positive and negative VUS), the Subclinical GCA cohort had lower PTPS, 2022 ACR/EULAR Classification Criteria score and were less likely to fulfill 1990 ACR GCA Classification Criteria. They had less cranial symptoms, more shoulder PMR and lower platelets. There were no significant differences observed for VUS scores between these groups.

This study has many strengths. This is an induction cohort in which the median interval from initiation of glucocorticoids to performing ultrasound was 0 days. This is often a challenge when conducting research in PMR since it is a disease that is primarily managed in primary care prior to referral to rheumatology clinics and usually, the majority of patients have had some glucocorticoids before their rheumatology assessment. The investigators overcame this by advertising the rapid-access PMR clinic to all primary care physicians in the catchment area, offering clinical assessment within 24 hours. Secondly, the full length of all branches of STA and AA were examined. Some prior studies limited their ultrasound protocol to include STA assessment only. Thirdly, all patients were followed up at 12 months to ensure that the diagnosis was unchanged. This is important because PMR can mimic many other conditions in its earliest stages. Additionally, investigators were able to identify 1 patient who had a normal baseline

VUS but subsequently developed a clinical syndrome consistent with GCA. Another strength of this study is that patients were actively recruited from primary care physicians as well as from hospital departments meaning that this data reflects typical PMR and not a more severe/refractory disease subset that requires the input of a rheumatologist. Also, the results of this study are in line with those seen in a larger cohort of 346 patients reported by *De Miguel*, adding further validity to the findings (68).

This study has a number of weaknesses. Firstly, it couldn't be guaranteed that all patients were not treated with prior steroids. While this may have impacted results, it is known from other published studies that sonographic signs of vasculitis in GCA may persist for up to 6 months anyway (108, 139, 140). Secondly, this is a relatively small cohort but large studies in this area are lacking due to the relative infrequency of this illness and future efforts should be directed at collaborative studies between different centres. Thirdly, TAB could not be obtained on all patients with sonographic signs of vasculitis. While a positive TAB would have added another layer of certainty to the diagnosis, it is now abundantly clear from the literature that US is a more sensitive test anyway (5). A final weakness of this study is the predominant STA involvement, rather than predominant AA vasculitis. A PMR/GCA Working Group at the 2022 EULAR congress suggested that AA vasculitis should in theory be more common in those presenting with PMR, however the finding in this study is still supported elsewhere in the literature (48).

Future research should focus on the impact of CV risks on US parameters in this patient cohort. In this study, there was a non-significant higher mean number of CV risk factors in those presenting with PMR who had a positive VUS. Larger studies are needed, appropriately powered to assess this link, to further clarify whether or

not this is truly impacting on our interpretation of sonographic signs of vasculitis. This is of particular importance given the age-profile of patients who suffer from PMR and GCA. Additionally, this study suggests that the Subclinical GCA phenotype differs from that of classical GCA. Again, larger cohorts with longer follow-up are necessary to establish whether or not this truly is its own distinct subset of LVV. Lastly, studies are needed to directly compare VUS with other imaging modalities, in particular PET/CT, in terms of sensitivity and specificity for detecting Subclinical GCA.

4.5 Conclusions

This study showed that a single screening VUS of STA and AA accurately identified 83.3% of patients with Subclinical GCA in an inception PMR cohort, the prevalence of which was 24%. This adds to the accumulating evidence that approximately 1 in 5 patients presenting with PMR have underlying GCA (47, 67-69). Predominant STA involvement was observed. Relative to those with isolated PMR, those with subclinical GCA were older, likelier to meet 2022 ACR/EULAR GCA Classification Criteria, have less hip PMR, have elevated ESR/CRP and lower platelets. Additionally, over the course of 12 months follow-up, more of this group required biologic therapy. Relative to 66 GCA patients presenting in a more typical fashion to a rapid-access GCA clinic, those with subclinical GCA had lower PTPS, less prevalent fulfilment of GCA Classification Criteria, lower platelets and more prevalent shoulder PMR. VUS sensitivity and quantification score results were equivocal between these two groups.

The results suggest that VUS of STA and AA should be a routine investigation performed on all newly diagnosed PMR patients. VUS imaging will require adequate operator training using conventional US technology with standardised operational procedures and settings. Little is known at present about the longitudinal implications of a positive VUS in these patients. The results of this study indicate that these patients are likely to be resistant to PMR-dose steroids and ultimately may require biologic therapy but longer term follow up studies are awaited. As the understanding of the natural history of this subset of patients grows, it will become clearer whether or not there is justification for earlier use of GCA steroid protocols and/or conventional or biologic DMARDs. Resource limitations such as adequate training, operator expertise, access to appropriate US technology and associated costs will be the predominant factors limiting PMR VUS protocols.

Chapter 5: Discussion

Huge disparities exist in the literature with regard to the performance of VUS in diagnosing GCA. Studies have varied considerably in size and methodology with results showing wide discrepancies in sensitivities (9-100%), specificities (66-100%), positive predictive values (36-100%) and negative predictive values (33-100%). There is also a lack of studies assessing the utility of STA MRA for GCA diagnosis and few studies have compared VUS with STA MRA in GCA diagnosis. The 2022 ACR/EULAR GCA Classification Criteria have only been validated in three retrospective studies to date, demonstrating variable specificities, and the Southend PTPS appears to improve the performance of VUS but has only been validated in one prospective cohort where it demonstrated poor specificity. This research aimed to compare VUS of STA and AA in the diagnosis of GCA with TAB, MRA of STA and GCA Classification Criteria using confirmation of clinical diagnosis of GCA by two experienced rheumatologists after 6 months of treatment and follow-up as the reference standard. This study also aimed to externally validate the updated 2022 ACR/EULAR GCA Classification Criteria and examined whether or not the Southend Pre-Test Probability Score has a place in the initial assessment of suspected GCA.

Chapter 2 studied a cohort of 124 patients with suspected GCA and found that VUS was superior to TAB, 1990 and 2022 GCA Classification Criteria, as well as MRA STA for a clinical diagnosis of GCA. VUS had a sensitivity of 83% and a specificity of 85% while TAB sensitivity was poor at 40% and GCA Classification

Criteria lacked specificity. MRA demonstrated poor sensitivity and had a concerning high rate of false positive results. This study demonstrated that a model combining PTPS and VUS results outperformed both individual components with an AUC 0.91.

This study confirms that VUS is the best initial confirmatory test for evaluating suspected GCA and highlights the inappropriate use of TAB for this purpose. It shows that the Southend PTPS has a role in evaluating suspected GCA, achieving a sensitivity and specificity of 100% when used in combination with VUS.

Additionally, while 2022 ACR/EULAR GCA Classification Criteria have been shown to have better sensitivity than 1990 criteria in this cohort, they have no role in routine clinical practice due to their poor specificity for GCA diagnosis. MRA of STA has significant limitations including high cost, poor accessibility and patient tolerability and as demonstrated here, poor sensitivity and specificity for GCA diagnosis. However, this was not entirely a steroid-naïve cohort and importantly, there was a median interval of 8 days between commencing immunosuppressive treatment and performing MRA. Also, this study was not adequately powered to assess MRA and our results did not reach statistical significance. Future studies should be directed at evaluating MRA STA versus VUS in a larger steroid-naïve cohort, appropriately powered to properly define its place in a GCA diagnostic algorithm. However, for most rheumatologists, rapid access to VUS is more achievable than rapid access to MRI in daily clinical practice.

The currently accepted definitions of normal IMT cut-off points have only been validated in one study to date and may be impacted by CV risk factors. Time-to-

regression for haloes, which is directly related to IMT, has varied from 2 days to 7 months after commencing immunosuppressive therapy for GCA and additionally it has been suggested that rising IMT may be predictive of future flares. Some evidence suggests that halo presence and distribution may correlate with GCA extent and severity but this data mostly comes from small studies. Novel VUS quantification scores have shown some prognostic value but lack external validation and nothing is yet known about their ability to monitor GCA over and above currently available biomarkers. This research aimed to define the optimal IMT cut-off values in each branch of STA and AA that can reliably identify the presence of vasculitis in that vessel. Sonographic signs of vasculitis were monitored over time to determine how early/late normalisation of IMT occurred. It evaluated what value, if any, exists in quantifying the degree of vasculitis observed sonographically and investigated whether or not this can help with disease prognostication. Lastly it looked for predictors of higher baseline VUS quantification scores and aimed to validate these scoring systems in an inception GCA cohort.

Chapter 3 provides insights into the optimal IMT cut-off values for STA and AA. In a cohort of 124 patients with suspected GCA, the AUC of various cut-off points are evaluated. The results differ from the currently accepted 'normal' values with regard the best cut-off IMT values to use for GCA diagnosis and they demonstrate that the presence of CV risks factors has no appreciable impact on IMT interpretation. Additionally, a framework that gives sonographers 100% sensitivity and specificity for a clinical diagnosis of GCA is outlined in Table 3.09. In this chapter, VUS quantification scoring is applied to the cohort as a means of monitoring changes in sonographic inflammation over time. Mean scores decreased over time with significant differences observed between each study time-point. Almost 25% of

GCA patients had not normalised OGUS by 6-month follow up but no association was seen with future adverse events in those who failed to normalise. Importantly, VUS quantification scores are shown to be superior to all other patient variables in predicting future adverse outcomes including future GCA flare and future biologic requirement. OGUS appears to perform best but further longitudinal studies are required to confirm this.

In defining optimal IMT cut-off points, this study cohort is substantially larger than that used by investigators who proposed the currently accepted normal values (Table 1.05) (86). Moving forward, larger studies across multiple centres, using a standardised scanning protocol, could definitively define the optimal IMT cut-off points to distinguish a normal vessel from a vasculitic vessel. This would additionally help to address the question of whether or not CV risk factors are an import factor in IMT interpretation as only 19% of this cohort did not have CV risk factors. The sample size was too small and thus had too few events to identify if VUS quantification scores were predictive of ischaemic complications, a key outcome variable in LVV studies. Additionally, cumulative steroid consumption in this cohort has not been accounted for, although the standard 'GiACTA' tapering regime was used in this study. Future studies need larger numbers in order to be adequately powered to identify associations between VUS quantification scores and ischaemic events. Also, while this study has shown that VUS outcome scores do not completely normalise by 6 months in almost 25%, one cannot determine for sure what long-term implications this has for individuals. 48 patients were followed up for 6 months and 27 patients for 12 months and while no association was seen between time-to-normalisation of haloes and adverse events, a larger cohort with longer follow-up may be necessary to address this question.

A close inter-relationship exists between GCA and PMR, highlighted by the recent description of GCA-PMR Spectrum Disease. An important distinction between the two is the relatively higher prevalence of vascular complications in those with GCA and so distinguishing Subclinical GCA from Isolated PMR is a priority for rheumatologists in those presenting with a 'pure' PMR-like syndrome. Prevalence rates of 5-54% for Subclinical GCA have been reported but evidence is lacking and little is known about the natural history of this subset of patients. This research sought to determine the prevalence of sonographically-defined, Subclinical GCA in an inception PMR cohort. It also investigated the natural history of Subclinical GCA to see how this clinical phenotype differs, if at all, from classical GCA.

In Chapter 4, in a cohort of 25 newly diagnosed PMR patients, without cranial or ischaemic symptoms, 5 had features of GCA on VUS at baseline, all 5 of whom flared over the following 12 months with a GCA-like syndrome and 2 of whom required biologic therapy. Only 1 of 19 patients with a normal baseline VUS developed clinical GCA over 12 months. VUS had a sensitivity of 83%, a specificity of 100% and an AUC of 0.92 for Subclinical GCA in this inception PMR cohort and identified a subgroup that was more resistant to steroids and likelier to require biologic therapy. Relative to those with isolated PMR, those with subclinical GCA were older, likelier to meet 2022 ACR/EULAR GCA Classification Criteria, have less hip PMR, have elevated ESR/CRP and lower platelets. Additionally, over the course of 12 months follow-up, more of this group required biologic therapy. Relative to 66 GCA patients presenting in a more typical fashion to a rapid-access GCA clinic, those with subclinical GCA had lower PTPS, less prevalent fulfilment of

GCA Classification Criteria, lower platelets and more prevalent shoulder PMR. VUS sensitivity and quantification scores were equivalent between these two groups.

The results of this study add to the accumulating evidence that approximately 1 in 5 patients presenting with PMR have underlying GCA, confirms the sensitivity of VUS for this purpose and highlights the presence of phenotypic differences between this subset of patients and those with Isolated PMR and classical GCA (47, 67-69). The results suggest that VUS of STA and AA should be a routine investigation performed on all newly diagnosed PMR patients. This was not an entirely steroid-naïve cohort however, and the sample size is small. Additionally, GCA diagnosis could not be confirmed histologically due to the lack of availability of TAB for this clinical phenotype. These investigators are currently undertaking a similar study in a substantially larger, steroid-naïve cohort which is expected to provide irrefutable evidence of the high prevalence of Subclinical GCA in those presenting with PMR and will further clarify the phenotypic distinction of this subset of patients.

In summary, VUS is the best initial confirmatory test for GCA and TAB should be reserved for those with a negative VUS in whom the diagnosis is thought to be likely. PTPS has a role in evaluating suspected GCA and while 2022 ACR/EULAR Classification Criteria are more sensitive than 1990 criteria, they lack the requisite specificity to have a meaningful clinical role. MRA of STA has a number of limitations and its diagnostic performance versus VUS should be compared in a larger study. Defining the optimal IMT cut-offs that distinguish a normal from a vasculitic vessel requires further investigation but this study shows that if certain IMT criteria are met, GCA diagnosis can be reliably excluded or confirmed. VUS

quantification scores can be used to monitor longitudinal changes in sonographic inflammation and higher baseline scores are more predictive of future adverse events than are all other patient variables. 20-25% of patients presenting with PMR have underlying vasculitis, so-called Subclinical GCA, and these patients represent a distinct phenotypic subset of GCA and are likely to require biologic therapy. A single screening baseline VUS can accurately identify these patients and should be adopted as routine care for all newly-diagnosed PMR patients.

Appendices

Appendix 1.1: All studies evaluating VUS in GCA 1995-2006.

Author	Year	Sample Size	Reference standard	Definition	Sens	Spec	PPV	NPV
Schmidt (63)	1995	10	Clinical	Halo	100%	100%	100%	100%
Puéchal (113)	1995	30	Histology	Stenosis	77%	80%	70%	85%
Schmidt (82)	1997	30	Clinical	Halo	73%	100%	100%	91%
Lauwerys (114)	1997	11	Clinical	Halo	9%	98%	50%	84%
Venz (209)	1998	6	Histology	Halo	100%	86%	75%	100%
Schmid (137)	2002	12	Histology	Halo	50%	100%		
			Clinical		40%	100%		
Nesher (210)	2002	12	Clinical/ Histology	Halo	86%	78%	50%	96%
Salvarini (211)	2002	86	Histology	Halo	40%	79%		
			Histology	Halo >1mm	40%	93%		
LeSar (212)	2002	8	Histology	Halo	86%	92.0%	75%	96%
			Histology	Halo+/- Stenosis	100%	80%	58.3%	100%
Schmidt (130)	2003	32	Histology	Halo	75%	100%	100%	33%
Murgatroyd (213)	2003	7	Histology	Halo	86%	68%	50%	93%
Pfadenhauer (115)	2003	27	Clinical	OA Halo	63%	100%		
				STA Halo	78%	94%		
			Histology	OA Halo	65%	100%		
				STA Halo	77%	82%		
Pfadenhauer (116)	2003	47	Clinical	STA Halo	78%	96%		
			Histology	STA Halo	91%	82%		
Reinhard (117)	2004	43	Histology	Halo Stenosis Occlusion	73%	93%	96%	58%
			Histology	Halo	67%	93%	96%	56%
			Clinical	Halo Stenosis Occlusion	65%	100%	100%	73%
			Clinical	Halo	60%	100%	100%	70%
Romera-Villegas (214)	2004	22	Histology	Halo	95.4%	91.3%	84%	97.6%
Karassa (119)	2005	2036	Clinical	Halo	55%	94%		
			Histology	Halo	69%	82%		
Karahaliou (118)	2006	22	Histology	Halo (U/L)	82%	95%	86%	93%
			Histology	Halo (B/L)	41%	100%	100%	80%

Appendix 1.2: All studies evaluating VUS in GCA 2007-2017.

Author	Year	Sample Size	Reference standard	Definition	Sens	Spec	PPV	NPV
Zaragozá-García (215)	2007	6	Histology	Halo Stenosis	100%	77%	62.5%	100%
Pérez López (139)	2009	30	Histology	STA Halo	72%	72%		
			Histology	STA Stenosis	41%	89%		
Stammeler (125)	2009	182	Clinical					
Aschwanden (108)	2010	72	Clinical	Halo Stenosis Occlusion	55%	100%	100%	66%
Maldini (216)	2010	32	Clinical/ Histology	Halo	10-17%	100%		
Singh (217)	2010	16	Clinical	Halo	67%		100%	
Suelves (146)	2010	10	Histology	Halo Stenosis Occlusion	100%	100%	100%	
Morinobu (218)	2010	8	Histology	Halo	100%			
Arida (120)	2010	204	Clinical	Halo	68%	91%		
Ball (121)	2010	998	Histology	Halo Stenosis Occlusion	75%	83%		
Habib (141)	2012	16	Clinical/ Histology	Halo (U/L)	81%	88%		
			Histology	Halo (B/L)	37%	100%		
Pfenninger (219)	2012	38	Histology		44%	90%	80%	
Aschwanden (83)	2012	43	Clinical	Halo, CS	79%	100%	100%	80%
Muratore (220)	2013		Clinical	CS	79%	100%	100%	80%
Black (221)	2013	50	Clinical	Halo	42%	94%		
			Histology	Halo	40%	81%		
Diamantopoulos (97)	2014	46	Clinical	Halo (STA/ AA/ CCA)	100%	91%	92%	100%
Croft (222)	2015	36	Clinical	Halo IMT	81%	98%	97%	88%
Lugmani (5)	2016	257	Clinical	Halo	54%	81%		
Aranda-Valera (223)	2017	451	Clinical	Halo	92%	96%		
Roncato (224)	2017	30	Histology	Halo (B/L)	80%	100%		
Czihal (225)	2017	25	Clinical	STA/ AA IMT cut-off of ≥ 0.7 mm/ 1.2 mm	85%	91%		

Appendix 1.3: All studies evaluating VUS in GCA 2018-2023.

Author	Year	Sample Size	Reference standard	Definition	Sens	Spec	PPV	NPV
Monti (136)	2018	118	Clinical	Halo and CS	63%	100%	100%	65%
Duftner (2)	2018	605	Clinical	Halo	77%	96%		
			Clinical	MRI STA	73%	88%		
			Clinical/ Histology	PET-CT	67- 77%	66- 100%		
Bilyk (207)	2018	14	Histology	Halo Stenosis Occlusion	29%	88%	36%	83%
			Histology	Halo	14%	97%	50%	82.1%
Rinagel (124)	2019	20 studies	Histology	Halo	68%	81%		
Conway (226)	2019	123	Clinical	Halo	53%	72%		
Sommer (227)	2019	15	Histology					
González Porto (149)	2020	21	Clinical	Halo	43%	66%		
			Clinical	Biopsy	73%	100%		
Mukhtyar (228)	2020	14	Clinical					
Hop (111)	2020	41	Clinical	STA Halo/ Occlusion	52%	93%		
			Clinical	Add AA Halo or Occlusion	71%	93%		
Nielsen (93)	2020	46	PET/CT +	AA Halo	76%	100%		
Molina Collada (190)	2020	15	Clinical	Halo	87%	95%	95%	87%
Sebastian (194)	2020	89	Clinical	Halo	94%	85%		
Gielis (229)	2021	24	Histology	Halo	53%	92%		
				Occlusion	20%,	100%		
Soares (123)	2021	91	Clinical	Halo	46%			
Hansen (230)	2023	35			63%	79%		

Appendix 1.4: All studies evaluating the role of STA MRI in the diagnosis and monitoring of GCA.

Author	Year	n=	Reference standard	Sens	Spec	PPV	NPV	Key findings
Bley (160)	2004	20	ACR	94%	100%	100%	75%	
Brannan (161)	2004	7	ACR	0%			43%	TAB: sensitivity 50%, specificity 100%, PPV 100%, NPV 60%
Bley (156)	2007	27	ACR	81%	97%	96%	84%	MR: more sensitive than TAB but sensitivity drops to 33.3% after 10 days of steroids
Bley (165)	2008	17						MR inflammation had normalised in all patients in clinical remission
Geiger (231)	2010	23						Non-contrast, T2-weighted radial MRI useful for STA
Hauenstein (169)	2012	36	ACR	69%	91%	93%	66%	Sensitivity of baseline US and MRI equivocal, both reduce rapidly on steroids
Klink (159)	2014	102	ACR	78.4-83.3%	85.5-90.4%	87.6-90.9%	77.3-80.7%	MR sensitivity declined rapidly in those on steroids
Siemonson (162)	2015	28	ACR	80%	80%	94%	50%	
Rhéaume (163)	2017	31	Histology	93.6%	77.9%	48.3%	98.2%	Normal MRI highly predictive of negative TAB
Yip (170)	2020	35	ACR					VUS and STA MRI equivocal
Junek (164)	2021	268						PTPS $\geq$ 50%, STA-MRA had PPV 93.0% PTPS <of 25%, NPV of 89.5%.

Appendix 1.5: All studies comparing VUS with other imaging modalities in assessing suspected GCA.

Author	Year	N=	Reference standard	Comparator	Sens	Spec (days of steroid therapy)	PPV	NPV
Bley (171)	2008	36	Clinical	Halo	67%	91%	92%	64%
			Clinical	MRI TA	69%	91%	93%	66%
			Histology	Halo	79%	59%	73%	67%
			Histology	MRI TA	83%	71%	80%	75%
Ghinoi (173)	2008	20	Clinical	Halo	77.7%	100%		
			Clinical	MRI TA	27.2%	88.9%		
			Histology	MRI TA	33.3%	87.5%		
Agard (107)	2009	20						
Czihal (232)	2010	8	Clinical	LV Halo	87.5%		100%	
			C LV-GCA	LV FDG+	100%		100%	
Pfadenhauer (205)	2011	46	PET-CT VA	VA halo	33%	90%	63%	74%
			PET-CT VA	TAB	70%		100%	
Morinobu (218)	2011	8	Histology	Halo	100%		100%	
			Histology	PET aortitis	100%		100%	
Förster (233)	2011							
Hauenstein (169)	2012	36	Histology	Halo	92%	(0-1 day)		
			Histology	MRI TA	90%	(0-1 day)		
			Histology	Halo	50%	(>4 days)		
			Histology	MRI TA	80%	(>4 days)		
			Clinical	Halo	88%	(0-1 day)		
			Clinical	MRI TA	85%	(0-1 day)		
			Clinical	Halo	50%	(>4 days)		
			Clinical	MRI TA	56%	(>4 days)		
Germanò (185)	2017	31	PET-CT	CCA CEUS	100%	92%		
Löffler (234)	2017	50	PET-CT	Halo	80%			
Imfeld (206)	2020	102	Clinical	Halo	71%	97%	98%	63%
			Clinical	PET CT	75%	85%	91%	63%
Yip (170)	2020	35						
Hop (111)	2020	28	Clinical	TAUS/AAUS	71%	93%		
			Clinical	PET-CT	71%	100%		
Nielsen (93)	2020	46	PET/CT	AA Halo	76%	100%		
Lecler (172)	2022	25	Clinical	MRI	100%	86%		
			Clinical	US	88%	84%		
			Clinical	Retinal Angio	94%	74%		

Appendix 3.1: Patient variables correlating with VUS outcome scores.

Variable	Outcome	Correlation Coefficient	95% CI	p-value
22 ACR/EULARcc Score	Total HC	0.79	0.71-0.84	<0.0005
22 ACR/EULARcc Score	OGUS	0.76	0.69-0.82	<0.0005
22 ACR/EULARcc Score	STA HC	0.76	0.69-0.82	<0.0005
22 ACR/EULARcc Score	STA HS	0.74	0.66-0.80	<0.0005
22 ACR/EULARcc Score	Total HS	0.69	0.60-0.77	<0.0005
22 ACR/EULARcc Score	LtFTA IMTmax	0.67	0.58-0.75	<0.0005
22 ACR/EULARcc Score	RtCSTA IMTmax	0.63	0.52-0.72	<0.0005
22 ACR/EULARcc Score	RtFTA IMTmax	0.63	0.52-0.72	<0.0005
22 ACR/EULARcc Score	STA HC	0.61	0.50-0.71	<0.0005
22 ACR/EULARcc Score	Total HC	0.61	0.50-0.70	<0.0005
22 ACR/EULARcc Score	LtCSTA IMTmax	0.61	0.50-0.70	<0.0005
22 ACR/EULARcc Score	STA HS	0.60	0.48-0.69	<0.0005
22 ACR/EULARcc Score	OGUS	0.58	0.47-0.68	<0.0005
22 ACR/EULARcc Score	Total HS	0.57	0.45-0.67	<0.0005
PTPS	Total HC	0.56	0.44-0.66	<0.0005
PTPS	STA HC	0.54	0.41-0.64	<0.0005
22 ACR/EULARcc Score	AA HC	0.54	0.41-0.64	<0.0005
22 ACR/EULARcc Score	LtPTA IMTmax	0.54	0.41-0.64	<0.0005
PTPS	OGUS	0.52	0.40-0.63	<0.0005
TAB Positive	OGUS	0.52	0.32-0.68	<0.0005
PTPS	STA HS	0.51	0.38-0.62	<0.0005
22 ACR/EULARcc Score	LtFTA IMTmax	0.50	0.37-0.61	<0.0005
22 ACR/EULARcc Score	RtCSTA IMTmax	0.50	0.36-0.61	<0.0005
22 ACR/EULARcc Score	RtPTA IMTmax	0.49	0.35-0.60	<0.0005
22 ACR/EULARcc Score	RtFTA IMTmax	0.49	0.35-0.60	<0.0005
PTPS	Total HS	0.49	0.35-0.60	<0.0005
PTPS	LtFTA IMTmax	0.48	0.35-0.60	<0.0005
22 ACR/EULARcc Score	LtAA IMTmax	0.48	0.35-0.60	<0.0005
TAB Positive	RtFTA IMTmax	0.48	0.27-0.65	<0.0005
Age	Total HS	0.48	0.34-0.59	<0.0005
ESR	AA HC	0.47	0.33-0.59	<0.0005
22 ACR/EULARcc Score	LtCSTA IMTmax	0.46	0.33-0.58	<0.0005
PTPS	RtFTA IMTmax	0.46	0.33-0.58	<0.0005
22 ACR/EULARcc Score	AA HS	0.46	0.32-0.58	<0.0005
22 ACR/EULARcc Score	RtAA IMTmax	0.45	0.31-0.57	<0.0005
1990 ACRcc Score	LtFTA IMTmax	0.43	0.28-0.57	<0.0005
1990 ACRcc Score	OGUS	0.42	0.27-0.56	<0.0005
Age	STA HC	0.42	0.28-0.55	<0.0005
Age	AA HS	0.42	0.28-0.54	<0.0005
PTPS	RtCSTA IMTmax	0.42	0.28-0.54	<0.0005
Age	Total HC	0.42	0.27-0.54	<0.0005
Jaw claudication	LtFTA IMTmax	0.41	0.27-0.54	<0.0005
Age	STA HS	0.41	0.27-0.54	<0.0005
1990 ACRcc Score	RtFTA IMTmax	0.41	0.25-0.54	<0.0005
ESR	Total HC	0.41	0.26-0.54	<0.0005
ESR	LtAA IMTmax	0.40	0.26-0.53	<0.0005
22 ACR/EULARcc Score	LtPTA IMTmax	0.39	0.25-0.52	<0.0005
22 ACR/EULARcc Score	AA HS	0.39	0.25-0.52	<0.0005
PTPS	AA HC	0.39	0.25-0.52	<0.0005
Age	OGUS	0.39	0.24-0.52	<0.0005
1990 ACRcc Score	Total HC	0.39	0.23-0.53	<0.0005
22 ACR/EULARcc Score	RtPTA IMTmax	0.38	0.24-0.51	<0.0005
1990 ACRcc Score	STA HS	0.38	0.22-0.52	<0.0005
22 ACR/EULARcc Score	LtAA IMTmax	0.38	0.23-0.51	<0.0005
Age	RtCSTA IMTmax	0.37	0.23-0.51	<0.0005
PTPS	LtCSTA IMTmax	0.37	0.22-0.50	<0.0005
1990 ACRcc Score	STA HC	0.36	0.20-0.51	<0.0005
1990 ACRcc Score	Total HS	0.36	0.20-0.50	<0.0005
PTPS	LtPTA IMTmax	0.35	0.21-0.49	<0.0005
22 ACR/EULARcc Score	AA HC	0.35	0.20-0.49	<0.0005
Jaw claudication	Total HC	0.35	0.20-0.48	<0.0005
Platelets	AA HC	0.35	0.19-0.48	<0.0005
PTPS	RtPTA IMTmax	0.34	0.19-0.48	<0.0005
Jaw claudication	STA HC	0.34	0.19-0.48	<0.0005
22 ACR/EULARcc Score	RtAA IMTmax	0.34	0.19-0.48	<0.0005
ESR	RtAA IMTmax	0.34	0.18-0.48	<0.0005
PTPS	LtAA IMTmax	0.34	0.19-0.48	<0.0005
Jaw claudication	STA HS	0.34	0.19-0.47	<0.0005
ESR	Total HS	0.34	0.18-0.48	<0.0005
PTPS	AA HS	0.34	0.19-0.47	<0.0005
Jaw claudication	OGUS	0.34	0.19-0.47	<0.0005
ESR	OGUS	0.34	0.18-0.48	<0.0005
ESR	STA HC	0.33	0.18-0.47	<0.0005
Age	LtPTA IMTmax	0.32	0.17-0.46	<0.0005
Jaw claudication	RtFTA IMTmax	0.32	0.17-0.46	<0.0005
Weight Loss	Total HC	0.31	0.16-0.45	<0.0005

Appendix 3.2: AUC for all patient variables and future adverse events.

Variable	Outcome	AUC	95% CI	p-value	Variable	Outcome	AUC	95% CI	p-value
STA HS	Ischaemia	0.95	0.84-0.95		Monocytes	Ischaemia	0.64	0.03-0.64	
LtPTA IMTmax	Ischaemia	0.93	0.86-0.93		IL6	Biologic	0.63	0.48-0.63	
IL6	Ischaemia	0.92	0.75-0.92		WBC	Biologic	0.63	0.52-0.63	
OGUS	GCA	0.91	0.86-0.91	<0.0005	RtPTA IMTmax	Flare	0.62	0.47-0.62	
Total HC	GCA	0.89	0.84-0.89	<0.0005	WBC	GCA	0.62	0.53-0.62	
STA HS	GCA	0.89	0.83-0.89	<0.0005	Blurred vision	Biologic	0.61	0.51-0.61	
STA HC	GCA	0.88	0.82-0.88	<0.0005	Fever	Ischaemia	0.61	0.29-0.61	
Total HC	Biologic	0.88	0.82-0.88	<0.0005	Neutrophils	Biologic	0.61	0.50-0.61	
OGUS	Biologic	0.87	0.81-0.87	<0.0005	Fever	Flare	0.60	0.51-0.60	
Total HS	GCA	0.86	0.80-0.86	<0.0005	Night Sweats	Ischaemia	0.60	0.27-0.60	
RtPTA IMTmax	Ischaemia	0.84	0.64-0.84		Monocytes	Flare	0.60	0.44-0.60	
STA HC	Biologic	0.83	0.76-0.83	<0.0005	Jaw claudication	GCA	0.59	0.54-0.59	
Total HS	Biologic	0.83	0.75-0.83	<0.0005	Weight Loss	Biologic	0.59	0.50-0.59	
LtCSTA IMTmax	GCA	0.83	0.76-0.83	<0.0005	CRP	Ischaemia	0.59	0.12-0.59	
Blurred vision	Ischaemia	0.83	0.77-0.83		IL6	GCA	0.59	0.46-0.59	
STA HS	Biologic	0.82	0.75-0.82	<0.0005	Scalp tenderness	GCA	0.58	0.50-0.58	
LtCSTA IMTmax	Ischaemia	0.82	0.52-0.82		Blurred vision	Flare	0.58	0.47-0.58	
RtAA IMTmax	Ischaemia	0.81	0.59-0.81		Loss of vision	Biologic	0.58	0.50-0.58	
LtAA IMTmax	Ischaemia	0.81	0.53-0.81		Night Sweats	Flare	0.58	0.49-0.58	
STA HC	Ischaemia	0.80	0.47-0.80		Weight Loss	GCA	0.58	0.52-0.58	
Total HC	Flare	0.80	0.71-0.80	<0.0005	Hb	Ischaemia	0.58	0.17-0.58	
RtCSTA IMTmax	GCA	0.80	0.73-0.80	<0.0005	Lymphocytes	GCA	0.57	0.47-0.57	
LtFTA IMTmax	GCA	0.80	0.73-0.80	<0.0005	Basophils	Ischaemia	0.57	0.15-0.57	
AA HC	Biologic	0.79	0.70-0.79	<0.0005	Platelets	GCA	0.57	0.47-0.57	
RtFTA IMTmax	GCA	0.79	0.72-0.79	<0.0005	LtPTA IMTmax	Flare	0.56	0.44-0.56	
RtAA IMTmax	Biologic	0.79	0.68-0.79	<0.0005	Scalp tenderness	Flare	0.56	0.45-0.56	
LtFTA IMTmax	Biologic	0.78	0.68-0.78	<0.0005	Blurred vision	GCA	0.56	0.49-0.56	
LtPTA IMTmax	GCA	0.77	0.70-0.77	<0.0005	Loss of vision	GCA	0.56	0.51-0.56	
OGUS	Flare	0.77	0.68-0.77	<0.0005	Loss of vision	Flare	0.56	0.46-0.56	
Lymphocytes	Ischaemia	0.77	0.56-0.77		Anorexia	GCA	0.56	0.50-0.56	
RtPTA IMTmax	Biologic	0.76	0.65-0.76	<0.0005	Anorexia	Ischaemia	0.56	0.23-0.56	
LtAA IMTmax	Biologic	0.76	0.65-0.76	<0.0005	Anorexia	Biologic	0.56	0.48-0.56	
ESR	Biologic	0.76	0.66-0.76	<0.0005	Abnormal STA exam	Biologic	0.56	0.47-0.56	
STA HC	Flare	0.75	0.65-0.75	<0.0005	Hb	Flare	0.56	0.40-0.56	
AA HS	Biologic	0.75	0.64-0.75	<0.0005	Headache	GCA	0.55	0.48-0.55	
Total HS	Flare	0.75	0.63-0.75	<0.0005	Headaches	Flare	0.55	0.46-0.55	
RtCSTA IMTmax	Biologic	0.75	0.65-0.75	<0.0005	Anorexia	Flare	0.55	0.45-0.55	
RtFTA IMTmax	Biologic	0.75	0.65-0.75	<0.0005	Weight Loss	Flare	0.55	0.45-0.55	
LtCSTA IMTmax	Biologic	0.75	0.65-0.75	<0.0005	Hb	Biologic	0.55	0.43-0.55	
LtFTA IMTmax	Ischaemia	0.75	0.32-0.75		Lymphocytes	Biologic	0.55	0.44-0.55	
LtAA IMTmax	Flare	0.75	0.61-0.75	<0.0005	Eosinophils	Flare	0.55	0.41-0.55	
AA HC	Flare	0.74	0.63-0.74	<0.0005	Platelets	Flare	0.55	0.39-0.55	
AA HS	GCA	0.74	0.66-0.74	<0.0005	Loss of vision	Ischaemia	0.54	0.21-0.54	
LtFTA IMTmax	Flare	0.74	0.61-0.74	<0.0005	Fever	Biologic	0.54	0.48-0.54	
LtAA IMTmax	GCA	0.74	0.67-0.74	<0.0005	Lymphocytes	Flare	0.54	0.40-0.54	
RtPTA IMTmax	GCA	0.73	0.65-0.73	<0.0005	Eosinophils	GCA	0.54	0.45-0.54	
AA HC	Ischaemia	0.72	0.54-0.72		Eosinophils	Biologic	0.54	0.42-0.54	
RtAA IMTmax	GCA	0.72	0.63-0.72	<0.0005	AA HS	Ischaemia	0.53	0.08-0.53	
CRP	GCA	0.72	0.63-0.72	<0.0005	Shoulder PMR	GCA	0.53	0.45-0.53	
STA HS	Flare	0.71	0.60-0.71		Fever	GCA	0.53	0.49-0.53	
RtFTA IMTmax	Flare	0.71	0.58-0.71		Abnormal STA exam	Flare	0.53	0.42-0.53	
WBC	Ischaemia	0.71	0.43-0.71		Scalp tenderness	Ischaemia	0.52	0.19-0.52	
RtCSTA IMTmax	Ischaemia	0.70	0.56-0.70		Shoulder PMR	Flare	0.52	0.40-0.52	
LtPTA IMTmax	Biologic	0.70	0.59-0.70	<0.0005	Night Sweats	GCA	0.52	0.47-0.52	
RtAA IMTmax	Flare	0.70	0.56-0.70		Night Sweats	Biologic	0.52	0.45-0.52	
ESR	GCA	0.70	0.62-0.70	<0.0005	Abnormal STA exam	GCA	0.52	0.45-0.52	
CRP	Biologic	0.70	0.59-0.70		Hb	GCA	0.52	0.42-0.52	
Total HC	Ischaemia	0.69	0.38-0.69		Eosinophils	Ischaemia	0.52	0.00-0.52	
AA HS	Flare	0.69	0.55-0.69		Basophils	GCA	0.52	0.43-0.52	
LtCSTA IMTmax	Flare	0.69	0.57-0.69		Jaw claudication	Ischaemia	0.51	0.18-0.51	
Neutrophils	Ischaemia	0.69	0.53-0.69		Shoulder PMR	Biologic	0.51	0.41-0.51	
Monocytes	Biologic	0.69	0.57-0.69		Abnormal STA exam	Ischaemia	0.51	0.18-0.51	
Platelets	Biologic	0.69	0.57-0.69		IL6	Flare	0.51	0.32-0.51	
OGUS	Ischaemia	0.68	0.36-0.68		Basophils	Flare	0.51	0.36-0.51	
Scalp tenderness	Biologic	0.68	0.59-0.68	<0.0005	Basophils	Biologic	0.51	0.39-0.51	
ESR	Flare	0.68	0.54-0.68		Headache	Biologic	0.50	0.40-0.50	
CRP	Flare	0.68	0.55-0.68		Shoulder PMR	Ischaemia	0.49	0.16-0.49	
RtCSTA IMTmax	Flare	0.67	0.54-0.67		Hip PMR	Biologic	0.48	0.39-0.48	
Jaw claudication	Biologic	0.67	0.57-0.67	<0.0005	Total HS	Ischaemia	0.47	0.17-0.47	
WBC	Flare	0.67	0.56-0.67		Hip PMR	GCA	0.47	0.40-0.47	
AA HC	GCA	0.66	0.60-0.66	<0.0005	Hip PMR	Flare	0.43	0.34-0.43	
Jaw claudication	Flare	0.66	0.55-0.66	<0.0005	Platelets	Ischaemia	0.42	0.01-0.42	
Neutrophils	Flare	0.66	0.53-0.66		Headache	Ischaemia	0.41	0.08-0.41	
ESR	Ischaemia	0.64	0.20-0.64		RtFTA IMTmax	Ischaemia	0.40	0.21-0.40	
Neutrophils	GCA	0.64	0.55-0.64		Hip PMR	Ischaemia	0.40	0.34-0.40	
Monocytes	GCA	0.64	0.54-0.64		Weight Loss	Ischaemia	0.36	0.30-0.36	

Appendix 3.3: Correlation coefficients for all patient variables and future adverse events.

Variable	Outcome	Correlation Coefficient	95% CI	p-value
Total HC	GCA	0.65	0.55-0.73	<0.0005
STA HC	GCA	0.65	0.55-0.73	<0.0005
STA HS	GCA	0.64	0.53-0.72	<0.0005
OGUS	GCA	0.63	0.52-0.72	<0.0005
Total HS	GCA	0.62	0.51-0.71	<0.0005
AA HC	Biologic	0.60	0.47-0.70	<0.0005
Total HC	Biologic	0.58	0.45-0.68	<0.0005
OGUS	Biologic	0.55	0.41-0.66	<0.0005
LtCSTA IMTmax	GCA	0.54	0.41-0.64	<0.0005
LtFTA IMTmax	GCA	0.52	0.39-0.63	<0.0005
Total HS	Biologic	0.52	0.38-0.63	<0.0005
RtCSTA IMTmax	GCA	0.52	0.39-0.63	<0.0005
RtFTA IMTmax	GCA	0.50	0.37-0.61	<0.0005
RtAA IMTmax	Biologic	0.50	0.36-0.62	<0.0005
STA HC	Biologic	0.49	0.35-0.61	<0.0005
STA HS	Biologic	0.48	0.34-0.60	<0.0005
LtAA IMTmax	Biologic	0.48	0.34-0.60	<0.0005
LtFTA IMTmax	Biologic	0.46	0.31-0.59	<0.0005
LtPTA IMTmax	GCA	0.46	0.32-0.58	<0.0005
RtPTA IMTmax	Biologic	0.43	0.28-0.56	<0.0005
AA HS	GCA	0.43	0.29-0.55	<0.0005
RtPTA IMTmax	GCA	0.42	0.28-0.54	<0.0005
RtFTA IMTmax	Biologic	0.40	0.24-0.53	<0.0005
ESR	Biologic	0.39	0.23-0.53	<0.0005
LtAA IMTmax	GCA	0.39	0.25-0.52	<0.0005
AA HC	Flare	0.39	0.23-0.53	<0.0005
AA HS	Biologic	0.39	0.23-0.52	<0.0005
AA HC	GCA	0.39	0.24-0.52	<0.0005
LtAA IMTmax	Flare	0.38	0.22-0.52	<0.0005
Jaw claudication	Biologic	0.38	0.22-0.51	<0.0005
RtCSTA IMTmax	Biologic	0.37	0.22-0.51	<0.0005
RtAA IMTmax	GCA	0.37	0.22-0.50	<0.0005
Total HC	Flare	0.37	0.21-0.51	<0.0005
RtAA IMTmax	Ischaemia	0.36	0.09-0.58	<0.05
ESR	GCA	0.35	0.20-0.49	<0.0005
CRP	GCA	0.35	0.20-0.49	<0.0005
LtPTA IMTmax	Biologic	0.35	0.20-0.49	<0.0005
LtCSTA IMTmax	Biologic	0.34	0.18-0.48	<0.0005
Total HS	Flare	0.34	0.17-0.48	<0.0005
Blurred vision	Ischaemia	0.32	0.05-0.55	<0.05
Jaw claudication	Flare	0.32	0.15-0.46	<0.0005
CRP	Biologic	0.31	0.15-0.46	<0.0005
LtFTA IMTmax	Flare	0.31	0.15-0.46	<0.0005
IL6	Flare	0.31	0.09-0.51	<0.05
Scalp tenderness	Biologic	0.31	0.15-0.46	<0.0005
RtAA IMTmax	Flare	0.31	0.15-0.46	<0.0005
STA HC	Flare	0.31	0.15-0.46	<0.0005
LtAA IMTmax	Ischaemia	0.31	0.04-0.54	<0.05
OGUS	Flare	0.31	0.14-0.46	<0.0005
Platelets	Biologic	0.30	0.14-0.46	<0.005
Monocytes	Biologic	0.30	0.13-0.45	<0.005
Fever	Flare	0.29	0.12-0.44	<0.005
AA HS	Flare	0.27	0.10-0.42	<0.005
Jaw claudication	GCA	0.26	0.10-0.40	<0.005
STA HS	Flare	0.26	0.09-0.41	<0.005
CRP	Flare	0.25	0.08-0.41	<0.05
ESR	Flare	0.25	0.07-0.41	<0.05
RtCSTA IMTmax	Flare	0.24	0.08-0.40	<0.05
Monocytes	GCA	0.24	0.08-0.39	<0.005
IL6	Biologic	0.23	-0.01-0.44	
RtFTA IMTmax	Flare	0.22	0.05-0.38	<0.05
Weight Loss	GCA	0.22	0.06-0.37	<0.05
LtCSTA IMTmax	Flare	0.22	0.05-0.38	<0.05
Neutrophils	GCA	0.22	0.05-0.37	<0.05
WBC	GCA	0.20	0.04-0.36	<0.05
Blurred vision	Biologic	0.20	0.03-0.36	<0.05
Night Sweats	Flare	0.20	0.03-0.36	<0.05
Weight Loss	Biologic	0.20	0.03-0.36	<0.05
Loss of vision	Biologic	0.20	0.03-0.36	<0.05
Loss of vision	GCA	0.19	0.03-0.34	<0.05
WBC	Biologic	0.19	0.02-0.35	<0.05
Lymphocytes	Ischaemia	0.18	-0.1-0.44	
Fever	Ischaemia	0.17	-0.1-0.42	
AA HC	Ischaemia	0.17	-0.1-0.42	
Scalp tenderness	GCA	0.16	0.00-0.31	<0.05
Monocytes	Flare	0.16	-0.02-0.33	

Variable	Outcome	Correlation Coefficient	95% CI	p-value
Anorexia	GCA	0.16	0.00-0.31	
Neutrophils	Biologic	0.15	-0.02-0.32	
Eosinophils	Ischaemia	0.15	-0.1-0.42	
WBC	Flare	0.15	-0.03-0.32	
Platelets	GCA	0.14	-0.02-0.30	
Night Sweats	Ischaemia	0.14	-0.1-0.40	
RtPTA IMTmax	Flare	0.14	-0.03-0.31	
Blurred vision	GCA	0.14	-0.02-0.29	
Blurred vision	Flare	0.14	-0.04-0.30	
Anorexia	Biologic	0.14	-0.03-0.30	
Fever	Biologic	0.13	-0.04-0.30	
ESR	Ischaemia	0.13	-0.20-0.39	
IL6	GCA	0.13	-0.10-0.34	
Monocytes	Ischaemia	0.13	-0.16-0.40	
Loss of vision	Flare	0.13	-0.05-0.29	
Neutrophils	Flare	0.12	-0.06-0.29	
WBC	Ischaemia	0.12	-0.17-0.39	
Abnormal STA exam	Biologic	0.12	-0.05-0.28	
Fever	GCA	0.12	-0.05-0.27	
Headaches	GCA	0.11	-0.05-0.27	
Anorexia	Flare	0.10	-0.07-0.27	
Weight Loss	Flare	0.10	-0.07-0.27	
Eosinophils	Biologic	0.10	-0.08-0.27	
Scalp tenderness	Flare	0.09	-0.08-0.26	
Headache	Flare	0.09	-0.09-0.26	
Platelets	Flare	0.08	-0.10-0.25	
Night sweats	GCA	0.08	-0.08-0.24	
Hb	Flare	0.08	-0.10-0.25	
Platelets	Ischaemia	0.08	-0.21-0.35	
Anorexia	Ischaemia	0.07	-0.21-0.34	
Eosinophils	GCA	0.07	-0.10-0.23	
Lymphocytes	Flare	0.07	-0.11-0.24	
Eosinophils	Flare	0.06	-0.11-0.24	
Lymphocytes	Biologic	0.06	-0.11-0.23	
Neutrophils	Ischaemia	0.06	-0.20-0.34	
Night Sweats	Biologic	0.06	-0.11-0.23	
LtPTA IMTmax	Flare	0.06	-0.11-0.23	
Shoulder PMR	GCA	0.05	-0.10-0.21	
Abnormal STA exam	GCA	0.0	-0.11-0.21	
Abnormal STA exam	Flare	0.05	-0.13-0.22	
Loss of vision	Ischaemia	0.04	-0.23-0.32	
Basophils	Flare	0.04	-0.14-0.21	
Shoulder PMR	Flare	0.03	-0.14-0.20	
Basophils	Biologic	0.02	-0.15-0.19	
Scalp tenderness	Ischaemia	0.02	-0.26-0.29	
Jaw claudication	Ischaemia	0.01	-0.27-0.29	
Abnormal STA exam	Ischaemia	0.01	-0.27-0.29	
Shoulder PMR	Biologic	0.01	-0.16-0.18	
AA HS	Ischaemia	0.00	-0.27-0.28	
Headaches	Ischaemia	-0.00	-0.18-0.16	
Shoulder PMR	Ischaemia	-0.01	-0.29-0.27	
Total HS	Ischaemia	-0.02	-0.29-0.26	
Hb	GCA	-0.02	-0.19-0.14	
Basophils	GCA	-0.02	-0.19-0.14	
CRP	Ischaemia	-0.04	-0.31-0.24	
Hip PMR	Biologic	-0.04	-0.20-0.13	
Hb	Biologic	-0.05	-0.23-0.12	
IL6	Ischaemia	-0.06	-0.37-0.26	
Hip PMR	GCA	-0.07	-0.23-0.09	
Basophils	Ischaemia	-0.08	-0.35-0.21	
Hb	Ischaemia	-0.09	-0.36-0.20	
RtFTA IMTmax	Ischaemia	-0.10	-0.36-0.18	
Lymphocytes	GCA	-0.11	-0.27-0.05	
Hip PMR	Flare	-0.11	-0.28-0.06	
Headache	Ischaemia	-0.12	-0.38-0.16	
Hip PMR	Ischaemia	-0.12	-0.39-0.16	
Weight Loss	Ischaemia	-0.15	-0.40-0.13	
Total HC	Ischaemia	-0.16	-0.41-0.12	
OGUS	Ischaemia	-0.16	-0.42-0.12	
RtCSTA IMTmax	Ischaemia	-0.17	-0.43-0.11	
LtFTA IMTmax	Ischaemia	-0.24	-0.48-0.04	
LtPTA IMTmax	Ischaemia	-0.26	-0.50-0.02	
STA HC	Ischaemia	-0.27	-0.51-0.00	
LtCSTA IMTmax	Ischaemia	-0.28	-0.52-(-0.01)	<0.05
RtPTA IMTmax	Ischaemia	-0.31	-0.54-(-0.04)	<0.05
STA HS	Ischaemia	-0.38	-0.60-(-0.11)	<0.05

Appendix 3.4: DeLong test comparing ROC for OGUS to that of Halo Count, Halo Score and IMTmax for predicting future adverse events.

Predictor	Outcome	OGUS ROC	Predictor ROC	p-Value	Adjusted p-value	Comment
STA HC	GCA	0.91	0.88			
STA HC	Ischaemia	0.68	0.80			Pred> OGUS
STA HC	Biologic	0.87	0.83			
STA HC	Flare	0.77	0.75			
STA HC	Biologic	0.87	0.83			
AA HC	GCA	0.91	0.66	<0.0005	<0.0005	
AA HC	Ischaemia	0.68	0.72			Pred> OGUS
AA HC	Biologic	0.87	0.79			
AA HC	Flare	0.77	0.74			
AA HC	Biologic	0.87	0.79			
Total HC	GCA	0.91	0.89			
Total HC	Ischaemia	0.68	0.69			Pred> OGUS
Total HC	Biologic	0.87	0.88			Pred> OGUS
Total HC	Flare	0.77	0.80			Pred> OGUS
Total HC	Biologic	0.87	0.88			Pred> OGUS
STA HS	GCA	0.91	0.89			
STA HS	Ischaemia	0.68	0.95			Pred> OGUS
STA HS	Biologic	0.87	0.82	<0.05		
STA HS	Flare	0.77	0.71	<0.05		
STA HS	Biologic	0.87	0.82	<0.05		
AA HS	GCA	0.91	0.74	<0.0005	<0.005	
AA HS	Ischaemia	0.68	0.53			
AA HS	Biologic	0.87	0.75	<0.05		
AA HS	Flare	0.77	0.69			
AA HS	Biologic	0.87	0.75	<0.05		
Total HS	GCA	0.91	0.86	<0.05		
Total HS	Ischaemia	0.68	0.47			
Total HS	Biologic	0.87	0.83			
Total HS	Flare	0.77	0.75			
Total HS	Biologic	0.87	0.83			
RtCSTA IMTmax	GCA	0.91	0.80	<0.0005	<0.005	
RtCSTA IMTmax	Ischaemia	0.68	0.70			Pred> OGUS
RtCSTA IMTmax	Biologic	0.87	0.75	<0.005	<0.05	
RtCSTA IMTmax	Flare	0.77	0.67	<0.05		
RtCSTA IMTmax	Biologic	0.87	0.75	<0.005	<0.05	
RtFTA IMTmax	GCA	0.91	0.79	<0.0005	<0.005	
RtFTA IMTmax	Ischaemia	0.68	0.40			
RtFTA IMTmax	Biologic	0.87	0.75	<0.05	<0.05	
RtFTA IMTmax	Flare	0.77	0.71			
RtFTA IMTmax	Biologic	0.87	0.75	<0.05	<0.05	
RtPTA IMTmax	GCA	0.91	0.73	<0.0005	<0.0005	
RtPTA IMTmax	Ischaemia	0.68	0.84			Pred> OGUS
RtPTA IMTmax	Biologic	0.87	0.76	<0.05		
RtPTA IMTmax	Flare	0.77	0.62	<0.05		
RtPTA IMTmax	Biologic	0.87	0.76	<0.05		
LtCSTA IMTmax	GCA	0.91	0.83	<0.005	<0.05	
LtCSTA IMTmax	Ischaemia	0.68	0.82			Pred> OGUS
LtCSTA IMTmax	Biologic	0.87	0.75	<0.005	<0.05	
LtCSTA IMTmax	Flare	0.77	0.69			
LtCSTA IMTmax	Biologic	0.87	0.75	<0.005	<0.05	
LtFTA IMTmax	GCA	0.91	0.80	<0.005	<0.005	
LtFTA IMTmax	Ischaemia	0.68	0.75			Pred> OGUS
LtFTA IMTmax	Biologic	0.87	0.78	<0.05		
LtFTA IMTmax	Flare	0.77	0.74			
LtFTA IMTmax	Biologic	0.87	0.78	<0.05		
LtPTA IMTmax	GCA	0.91	0.77	<0.0005	<0.005	
LtPTA IMTmax	Ischaemia	0.68	0.93			Pred> OGUS
LtPTA IMTmax	Biologic	0.87	0.70	<0.005	<0.05	
LtPTA IMTmax	Flare	0.77	0.56	<0.0005	<0.005	
LtPTA IMTmax	Biologic	0.87	0.70	<0.005	<0.05	
RtAA IMTmax	GCA	0.91	0.72	<0.0005	<0.0005	
RtAA IMTmax	Ischaemia	0.68	0.81			Pred> OGUS
RtAA IMTmax	Biologic	0.87	0.79			
RtAA IMTmax	Flare	0.77	0.70			
RtAA IMTmax	Biologic	0.87	0.79			
LtAA IMTmax	GCA	0.91	0.74	<0.0005	<0.005	
LtAA IMTmax	Ischaemia	0.68	0.81			Pred> OGUS
LtAA IMTmax	Biologic	0.87	0.76	<0.05		
LtAA IMTmax	Flare	0.77	0.75			
LtAA IMTmax	Biologic	0.87	0.76	<0.05		

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