



Trinity College Dublin

Coláiste na Tríonóide, Baile Átha Cliath

The University of Dublin

**Exploring Subclinical Giant Cell Arteritis in
Polymyalgia Rheumatica: A Novel
Phenotype in the GCA-PMR Disease
Spectrum.**

A thesis presented to the School of
Postgraduate Studies, Trinity College
Dublin, in fulfilment of the degree of
Medical Doctorate, 2026.

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Declaration, Online Access, and General Data Protection

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work, except where otherwise acknowledged.

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Dr Sharon Cowley

October 2024

Declaration and Statement of Plagiarism

I declare that this thesis is my work. Sources used to form hypotheses are cited in the references section. Full and informed consent was obtained from all the study participants. Ethical approval was granted by the Tallaght University and St. James's Hospitals Research Ethics Committee.

A handwritten signature in black ink, appearing to read 'SCowley', is positioned above a horizontal line.

Dr Sharon Cowley

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Abstract

Hypothesis

This study hypothesizes that patients with subclinical GCA in PMR have a distinct phenotype in the GCA-PMR disease spectrum.

Aim

This study aims to define the prevalence of subclinical GCA in PMR in a newly diagnosed PMR cohort, characterise the ultrasound pattern, natural history, and biomarker profile of this cohort, and compare with prospective PMR and GCA cohorts.

Objectives of the Research

1. To define the clinical manifestations of GCA in the context of the GCA-PMR Spectrum and examine the clinical impact of a GCA fast-track clinic on an Irish GCA cohort.
2. To examine the feasibility and clinical impact of establishing a novel fast-track PMR clinic, define patient characteristics, and establish the relapse rate over 12 months.
3. To assess the prevalence of subclinical GCA with temporal and axillary ultrasound in patients with newly diagnosed PMR and describe their clinical, ultrasound, and laboratory marker patterns.
4. To define the natural history of subclinical GCA in PMR including relapse, progression to GCA, and adverse events over 1 year follow-up and compare it to PMR and GCA cohorts.

5. To compare the Halo count, Halo score, and OMERACT score in patients with subclinical GCA in PMR with GCA.
6. To determine if analysis of serum biomarkers in PMR, subclinical GCA in PMR, and GCA may help differentiate between these related conditions.

Methods

This was a prospective study of consecutive patients with newly diagnosed PMR without signs or symptoms of GCA. All patients were seen in a novel PMR fast-track clinic and underwent clinical, laboratory, and ultrasound assessment of their temporal and axillary arteries. Patients with a positive vascular ultrasound, defined as the presence of a halo sign with increased intima-media thickness were considered to have subclinical GCA. Clinical and laboratory characteristics were compared with PMR patients without subclinical GCA. Ultrasound characteristics were compared with a consecutive cohort of newly diagnosed GCA patients recruited from a GCA fast-track clinic.

Results

We included 73 newly diagnosed PMR patients and 24 new GCA patients. 20.5% newly diagnosed PMR patients had ultrasound evidence of subclinical vasculitis. These patients were more likely to be male (80% vs 45%) but did not differ clinically at presentation. The mean time to relapse was statistically different between the three groups; 8.2 months for subclinical GCA in PMR, 9.2 months in PMR, and 11.4 months in GCA, $p=0.03$. PMR with subclinical GCA showed an increased propensity towards extracranial large vessel vasculitic involvement compared with classical GCA (47% vs 33%) without meeting statistical significance. While ultrasound scores steadily decreased over the first

6 months in GCA patients, there was a statistically significant increase in halo score in subclinical GCA from 3 to 12 months, $p=0.02$, and in OGUS score from 3 to 6 months, $p<0.001$. There was no statistical difference in the prevalence of cardiovascular risk factors including hypertension, hyperlipidaemia, diabetes mellitus and smoking status in patients with subclinical GCA in PMR. Subclinical GCA in PMR had a distinct biomarker profile to pure PMR. Angiopoietin-1 was significantly elevated in subclinical GCA in PMR compared with PMR patients at baseline at 25,548 [22,471.30-26468.36] versus 19,774.46 [18,051.58 -22140.71]; $p<0.001$. A cut-off of 21,408 pg/ml produced a sensitivity of 84.6% and a specificity of 70% for differentiating subclinical GCA in PMR from pure PMR. IL-17 levels were significantly more elevated in subclinical GCA in PMR compared with isolated PMR. ROC analysis demonstrated an AUC of 0.892, with a cut-off of 5pg/ml giving a sensitivity of 84.6%, and specificity of 79.2%. Osteopontin levels were significantly elevated in subclinical GCA in PMR compared with isolated PMR and ROC analysis found the AUC to be 0.814. A cut-off of 2766pg/ml gave a sensitivity of 84.6% and a specificity of 72.7%. GCA serum was significantly different from PMR serum at time of diagnosis, with GCA exhibiting significant elevations in angiopoietin-1 ($p<0.001$), angiopoietin-2 ($p<0.001$), CXCL-9 ($p<0.001$), osteopontin ($p<0.001$), IL-6 ($p=0.02$), and IL-17 ($p<0.001$) compared with PMR.

Conclusion

1 in 2 patients with suspected PMR in the community did not have PMR and 1 in 5 patients with confirmed PMR had subclinical GCA. Patients with subclinical GCA in PMR had a distinct phenotype. Their ultrasound pattern showed a predilection for extracranial artery involvement and unlike GCA ultrasound scores failed to resolve at

follow-up. Subclinical GCA were more likely to relapse earlier than their PMR or GCA counterparts and required significantly higher glucocorticoid treatment compared with PMR. Angiopoietin-1 IL-17, and osteopontin levels differentiate between subclinical GCA in PMR and pure PMR. Subclinical GCA in PMR is a distinct disease phenotype and biomarker signature in the GCA-PMR disease spectrum.

Lay Abstract

Background

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are two frequently overlapping diseases that occur in patients over 50 years. PMR presents with shoulder and hip pain and stiffness while GCA presents with a headache, pain chewing food, or new visual problems. Sometimes patients with PMR will go on to develop GCA and GCA patients may have shoulder or hip pain at the time of diagnosis. There is an emerging view that given the close links between these two conditions with similar, blood results, age group affected, and genetics, they should be considered as components of the same disease spectrum called GCA-PMR Spectrum Disease (GPSD). Scanning the arteries of patients with PMR without any headache or classic features of GCA may reveal silent vessel wall inflammation, which is usually only found in GCA. PMR patients do not have a routine ultrasound of their vessels to assess for GCA in current normal practice. This study aims to define how common silent or 'subclinical GCA in PMR' is in newly diagnosed PMR patients, describe the ultrasound pattern, natural history, and blood marker profile of this cohort, and compare it with both classic PMR and GCA patients.

Methods

This study included newly diagnosed PMR patients without signs or symptoms of GCA. All patients were seen in a novel PMR fast-track clinic and underwent clinical, laboratory, and ultrasound assessments of their head (temporal) and underarm (axillary) arteries. Patients with a positive scan but no symptoms of GCA were considered to have subclinical GCA. Clinical and laboratory features were compared with PMR patients

without subclinical GCA. Ultrasound characteristics were compared with newly diagnosed GCA patients recruited from a GCA fast-track clinic.

Results

We included 73 newly diagnosed PMR patients and 24 new GCA patients. One fifth of newly diagnosed PMR patients had ultrasound evidence of subclinical vessel inflammation. These patients were more likely to be male (80% vs 45%) but did not differ in their symptoms from regular PMR patients. The time to recurrence of symptoms in subclinical GCA in PMR was 8.2 months, 9.2 months in PMR, and 11.4 months in GCA. PMR with subclinical GCA had increased large vessel inflammation compared with classical GCA (47% vs 33%). While ultrasound scores steadily decreased over the first 6 months in GCA patients with treatment, there was an increase ultrasound scores in subclinical GCA at 6 months. There was no difference in the prevalence of cardiovascular risk factors including hypertension, hyperlipidaemia, diabetes mellitus and smoking status in patients with subclinical GCA in PMR.

Conclusion

1 in 2 patients with suspected PMR in the community did not have PMR and 1 in 5 patients with confirmed PMR had subclinical GCA. Patients with subclinical GCA in PMR are distinct. Their ultrasound pattern showed more large vessel involvement and unlike in GCA, ultrasound scores failed to resolve at follow-up. There was no correlation between cardiovascular risk and ultrasound scores suggesting subclinical GCA in PMR is not merely a finding related to increased cardiovascular risk. Subclinical GCA were more likely to relapse earlier than their PMR or GCA counterparts and required significantly

higher treatment doses with steroids compared with PMR. Subclinical GCA in PMR is a distinct subtype in the GCA-PMR disease spectrum.

List of Publications arising from thesis

Published:

1. The distinct phenotype of Subclinical Giant Cell Arteritis in Polymyalgia

Rheumatica: Evidence from a PMR Fast Track Clinic.

Cowley, S, Harkins, P, Kirby, C, Molloy, D, Conway, R, Kane, D. (2025) *EULAR*

Rheumatology Open, Volume 1, Issue 3, 157 – 164

<https://doi.org/10.1016/j.ero.2025.07.003>

2. A prospective cohort study evaluating the role of quantifying sonographic inflammatory changes in GCA.

Kirby C, Molloy D, **Cowley S**, Flood R, Gheta D, Mullan R, Murphy G, Kane D.

Rheumatology Advances in Practice. 2025 Aug 4;9(4):rkaf085. doi:

10.1093/rap/rkaf085.

3. Subclinical giant cell arteritis increases the risk of relapse in polymyalgia rheumatica.

De Miguel, E., Karalilova, R., Macchioni, P., Ponte, C., Conticini, E., **Cowley, S.**,

Tomelleri, A., Monti, S., Monjo, I., Batalov, Z., Klinowski, G., Falsetti, P., Kane, D. J.,

Campochiaro, C., & Hočevár, A. (2024). *Annals of the rheumatic diseases*, 83(3), 335–

341. <https://doi.org/10.1136/ard-2023-224768>

4. Should all patients with polymyalgia rheumatica have a vascular ultrasound assessment?

Cowley, S., Harkins, P., Kirby, C., Conway, R., & Kane, D. J. (2024). *Annals of the rheumatic diseases*, 83(8), 961–964. <https://doi.org/10.1136/ard-2024-225650>

5. Real-world outcomes of a dedicated fast-track polymyalgia rheumatica clinic.

Cowley, S., Harkins, P., Kirby, C., Conway, R., & Kane, D. (2024). *Rheumatology (Oxford, England)*, keae531. <https://doi.org/10.1093/rheumatology/keae531>

6. Polymyalgia rheumatica - an up-to-date review on diagnosis and management.

Harkins P, McCann L, Harrington R, **Cowley S**, Kane D, Conway R. *Vessel Plus*. 2024; 8:14. <http://dx.doi.org/10.20517/2574-1209.2023.137>

Accepted to print:

7. Elevated levels of serum angiopoietin-1, IL-17, osteopontin, and CXCL-9 as markers of vascular inflammation in newly-diagnosed PMR

Sharon Cowley, Patricia Harkins, Thomas J Butler, Colm Kirby, Danielle Molloy, Richard Conway, David Kane, (2025) *Rheumatology*, keaf603, <https://doi.org/10.1093/rheumatology/keaf603>

8. Prognostic Value of Quantifying Vascular Inflammation through Ultrasound in Patients with Giant Cell Arteritis: The MAGiCUS Study

Molina-Collada, J, **Cowley, S**, Kirby C et al. (2025) *The Lancet Rheumatology*

Abstract publications:

1. **Cowley S**, Kirby C, Harkins P, *et al*

POS0716 Differences in clinical and ultrasound characteristics of polymyalgia rheumatica patients with subclinical giant cell arteritis compared to those with clinical giant cell arteritis. *Annals of the Rheumatic Diseases* 2023;**82**:645.

2. **Cowley S**, Kirby C, Harkins P, Conway R, Kane D.

Clinical Phenotype of patients with subclinical giant cell arteritis in polymyalgia rheumatica [abstract]. *Arthritis Rheumatol.* 2023; 75 (suppl 9).

3. **Cowley S**, Kirby C, Harkins P, Conway R, Kane D. Baseline Vascular Ultrasound of Polymyalgia Rheumatica Patients at Time of Diagnosis Predicts Clinical Outcomes at 3 Months [abstract]. *Arthritis Rheumatol.* 2023; 75 (suppl 9).

4. **Cowley S**, Kirby C, Harkins P, Conway R, Murphy G, Kane D.

Effectiveness of Dose Spacing with Tocilizumab in Giant Cell Arteritis Treatment [abstract]. *Arthritis Rheumatol.* 2023; 75 (suppl 9).

5. Harkins P, **Cowley S**, Kane D, Conway R.

Frailty and Its Impact on Patient Reported Outcomes in Polymyalgia Rheumatica [abstract]. *Arthritis Rheumatol.* 2023; 75 (suppl 9).

6. Harkins P, **Cowley S**, Kane D, Conway R. Cognitive Function and Its Associated Factors in Polymyalgia Rheumatica [abstract]. *Arthritis Rheumatol.* 2023; 75 (suppl 9).

7. Patricia Harkins, **Sharon Cowley**, Robert Harrington, David Kane, Richard Conway.

P188 Frailty and its impact on patient-reported outcomes in polymyalgia rheumatica, *Rheumatology*, Volume 63, Issue Supplement_1, April 2024, keae163.227

8. **Cowley S**, Harkins P, Kirby C, *et al*

POS1426 Outcomes from a real-world dedicated fast-track polymyalgia rheumatica clinic. *Annals of the Rheumatic Diseases* 2024;**83**:1085-1086.

9. **Cowley S**, Harkins P, Kirby C, *et al*

POS0431 Baseline Ultrasound of PMR patients at time of diagnosis stratifies relapse risk at 6 months *Annals of the Rheumatic Diseases* 2024;**83**:440-441.

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1. **Cowley S**, Harkins P, Kirby C, Conway R, Kane, D. Baseline Vascular Ultrasound of PMR patients at diagnosis predicts clinical outcomes at 3 months. Oral Presentation Irish Society of Rheumatology annual meeting 2023, Dublin, Ireland
2. **Cowley S**, Kirby C, Harkins P, Conway R, Kane D. Clinical Phenotype of patients with subclinical giant cell arteritis in polymyalgia rheumatica. Oral Presentation American Society of Rheumatology Conference 2023, Imaging of Rheumatic Disease Session, San Diego, USA.
3. **Cowley S**, Kirby C, Harkins P, Conway R, Kane D. Baseline Vascular Ultrasound of Polymyalgia Rheumatica Patients at Time of Diagnosis Predicts Clinical Outcomes at 3 Months, Poster Presentation, American Society of Rheumatology Conference 2023, Imaging of Rheumatic Disease Session, San Diego, USA.
4. **Cowley S**, Kirby C, Harkins P, Conway R, Murphy G, Kane D. Effectiveness of Dose Spacing with Tocilizumab in Giant Cell Arteritis Treatment Poster Presentation, American Society of Rheumatology Conference 2023, Imaging of Rheumatic Disease Session, San Diego, USA.
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7. **Cowley S**, Harkins P, Kirby C, Conway R, Kane D. POS0431 Baseline Ultrasound of PMR patients at time of diagnosis stratifies relapse risk at 6 months. Poster presentation, EULAR conference 2024, Vienna, Austria.
8. **Cowley S**, Harkins P, Kirby C, Conway R, Kane D, Karalilova R, Macchioni P, Ponte C, Conticini E, Tomelleri A, Monti S, Monjo I, Batalov Z, Klinowski G, Falsetti P, Campochiaro C, Hocesvar A, De Miguel E. Subclinical Giant Cell Arteritis in Polymyalgia Rheumatica Has a Different Vascular Ultrasound Phenotype Than Giant Cell Arteritis, Poster Presentation, American College of Rheumatology Conference 2024, Washington, USA

Awards:

1. American College of Rheumatology “Emerging Investigator Excellence Award”,
2023 San Diego, USA.
2. Irish Society of Rheumatology “Best oral premier poster presentation” 2023,
Dublin, Ireland.

List of abbreviations:

ACPA	Anti-cyclic citrullinated peptide antibody
ACR/VF	American College of Rheumatology /Vasculitis Foundation
AION	Anterior ischaemic optic neuropathy
ALT	Alanine aminotransferase
ANCA	Anti-neutrophilic associated antibody
Anti-CCP	Anti-cyclic citrullinated peptide antibody
ASCVD	American Society Cardiology Cardiovascular Disease risk estimate
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
AST	Aspartate transferase
AUC	Area under curve
BAL	Bronchoalveolar lavage
BMI	Body mass index
CCL	C-C motif ligand
CRAO	Central retinal artery occlusion
CRP	C-reactive protein
CUH	Cork University Hospital
CXCL-9	Chemokine (C-X-C motif) Ligand 9
dB	Decibel
EFSUMB	European Federation of Societies for Ultrasound in Medicine and Biology
eGFR	Estimated glomerular filtration rate

EMS	Early morning stiffness
ESR	Erythrocyte sedimentation rate
EULAR	European Alliance of Associations for Rheumatology
FDG-PET	Fluorodeoxyglucose positron emission tomography
FTC	Fast-track clinic
GC	Glucocorticoid
GCA	Giant Cell Arteritis
GGT	Gamma-glutamyl transferase
GH	Glenohumeral
GM-CSF	Granulocyte-macrophage colony stimulating factor
GP	General Practitioner
GPSD	GCA-PMR Spectrum Disease
HC	Halo count
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HS	Halo score
ICAM-1	Intercellular Adhesion Molecule 1
ICU	Intensive Care Unit
IFN- γ	Interferon-gamma
IL-1	Interleukin 1
IL-10	Interleukin 10
IL-17A	Interleukin 17-A
IL-18	Interleukin 18

<i>IL-1Ra</i>	Interleukin 1 receptor antagonist
IL-1 β	Interleukin-1-beta
IL-2	Interleukin 2
IL-23	Interleukin 23
IL-4	Interleukin 4
IL-6	Interleukin 6
IL-8	Interleukin-8
IMT	Intima media thickness
JAK	Janus Kinase
JREC	Joint Research Ethics Committee
LDL	Low density lipoprotein
LHB	Long head of biceps
LRTI	Lower respiratory tract infection
LV-GCA	Large vessel giant cell arteritis
LVV	Large Vessel Vasculitis
MCP-3	Monocyte chemotactic protein-3
MFGE8	Milk fat globule-EGF factor 8 gene
MHz	Megahertz
MMP	Matrix metalloproteinase
MPA	Microscopic polyangiitis
MPO	Myeloperoxidase
MRI	Magnetic resonance imaging
NET	Neutrophil extracellular traps
NF-kB	nuclear factor kappa B

NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NHS	National Health Service (UK)
NICE	National Institute for Clinical Excellence
NK	Natural Killer cells
NSAID	Non-steroidal anti-inflammatory drug
NSTEMI	Non-ST Elevation myocardial infarction
OA	Osteoarthritis
OGUS	OMERACT Giant cell arteritis ultrasound score
OMERACT	Outcome measures in rheumatology
PET/CT	Positron emission tomography–computed tomography
PMR	Polymyalgia Rheumatica
PR3	Anti-Proteinase 3 Antibody
PRF	Pulse repetition frequency
RA	Rheumatoid Arthritis
RAPD	Relative afferent pupillary defect
RF	Rheumatoid factor
ROC	Receiver Operating Characteristic
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SASD	Subacromial subdeltoid bursitis
sCD206	Soluble Macrophage Mannose Receptor 206
SD	Standard deviation
SIA	Seronegative Inflammatory Arthritis
SJH	St James Hospital

SPSS	Statistical package for the social sciences
SPTPS	Southend pretest probability score
TA	Temporal arteritis
TAB	Temporal artery biopsy
TAUS	Temporal artery ultrasound
TENS	Toxic Epidermal Necrolysis Syndrome
TG	Triglyceride
TH1	T helper 1
TH17	T-helper 17
TIA	Transient ischaemic attack
TNF- α	Tumour necrosis factor-alpha
TUH	Tallaght University Hospital
US	Ultrasound
VEGF	Vascular Endothelial Growth Factor
VTN	Vitronectin
YKL-40/CHI3L1	Chitinase-3-like protein 1

Chapter 1:

General Introduction

1.1 Introduction

Giant cell arteritis (GCA) is the most common form of systemic vasculitis. The superficial temporal artery is the most classic site of involvement, but it may affect any medium or large artery and has a predilection for the aorta (Jennette et al., 2013). It occurs in patients over the age of 50 years and incidence increases with increasing age (Crowson et al., 2011). GCA occurs more frequently in women and those of Northern European descent (González-Gay and García-Porrúa, 2001). While the etiology remains largely unknown, both genetic and environmental factors likely initiate the inflammatory process. It may present with a variety of symptoms including vascular, rheumatic, ophthalmologic, or constitutional. The most feared complications are irreversible visual loss, stroke, and aortic dissection or rupture, which have potentially detrimental consequences.

The diagnosis of GCA remains a clinical one. Historically, temporal artery biopsy (TAB) was the gold standard of diagnosis. However, its sensitivity is impacted by inadequate sampling, skip lesions, and cumulative pre-operative glucocorticoid dose. In recent years, ultrasound, magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography (FDG-PET) have become an integral part of the diagnosis, supported by the 2018 EULAR recommendations for the use of imaging in large vessel vasculitis (LVV) (Dejaco et al., 2018).

Pathologically, the hallmark of GCA is granulomatous inflammation which infiltrates the vessel and results in intimal hyperplasia, which may ultimately lead to stenosis and occlusion (Weyand and Goronzy, 2013a). Both innate and adaptive immune mechanisms

likely contribute to abnormal T-cell migration and subsequent inflammatory release into the vascular layers (Bilton and Mollan, 2023).

While glucocorticoids remain the cornerstone of treatment in GCA, there has been progress in recent years in identifying pro-inflammatory cytokines and growth factors involved in the typical intima hyperplasia and vascular remodelling of GCA. Tocilizumab, an interleukin-6 receptor antagonist, is the first biological treatment to be approved for GCA due to its ability to reduce the rate of relapse and lower the cumulative glucocorticoid dose (Stone et al., 2017b). Several other agents have shown promise in the ongoing clinical trial phase (Venhoff et al., 2022, Cid et al., 2022b, Koster et al., 2022).

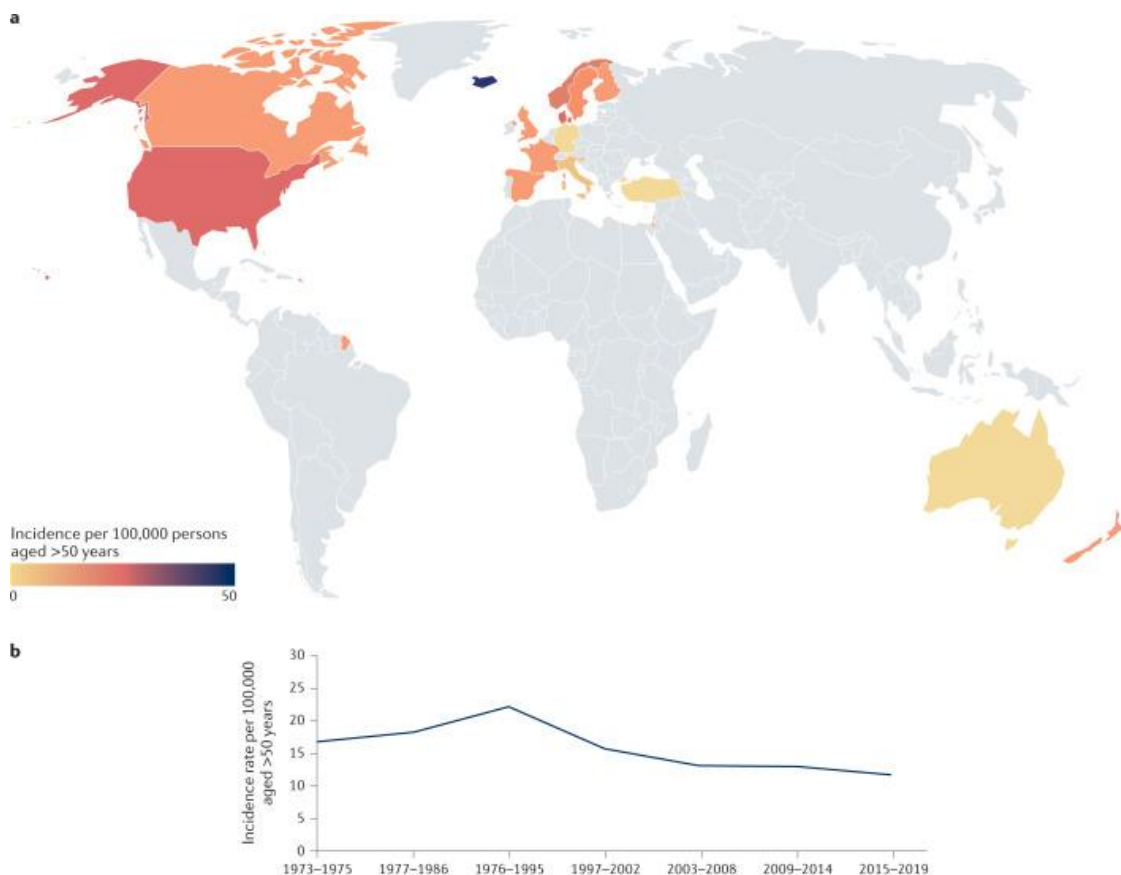
1.2 Epidemiology of GCA

1.2.1 Geographical Variations in GCA

GCA can be found in all geographical regions and ethnicities, however, it has a marked variation in incidence, the highest being in Northern Europe (Gonzalez-Gay et al., 2010), where reported incidence is over three-fold that reported elsewhere (Li et al., 2021). Most epidemiological studies on GCA over the past 25 years report increasing incidence in concordance with latitude in the Northern hemisphere, and conversely with the lowest incidence studies coming from Asia (Li et al., 2021, González-Gay and García-Porrúa, 2001). Scandinavian and North American populations of the same descent have the highest reported incidence rates of GCA (Salvarani et al., 2004, Boesen and Sørensen, 1987, Stamatis et al., 2021). A recently published study from Sweden reports an overall incidence of 13.3 per 100,000 population, with a higher incidence in females at 17.8 per 100,000 (Stamatis et al., 2021). In contrast, a Japanese epidemiological study reported a prevalence of GCA at 1.47 per 100,000 population (Wang et al., 2009).

Incidence in the United Kingdom is estimated at 11-22 per 100,000 (Smeeth et al., 2006, Petri et al., 2015). No Irish studies report on the incidence of GCA, and it is difficult to extrapolate incidence rates from other regions to apply to an Irish population. Genetically the Irish population over 50 years is largely homogenous with Celtic and Scandinavian origins, which is different to that of the United Kingdom. Cynthia Crowson and colleagues analysed a dataset with an unusually high GCA prevalence (the Olmsted County Minnesota dataset) and from this they estimated the lifetime risk of GCA as 1.0% for women (1/100) and 0.5% for men (1/200).

Figure 1.1: World map of GCA incidence



(Watts et al., 2022)

1.2.2 Seasonal alterations and viral triggers of GCA

The reasons for this variable incidence may have seasonal, genetic, or viral trigger origins. Some studies have seen cyclical variations in incidence, with the Minnesota study identifying 6 peaks in incidence from 1950 – 1999 (Salvarani et al., 2004). Other studies have found a seasonal variation in incidence, with a Danish study showing a higher occurrence in the summer months compared to Autumn (Kønig et al., 2021). However, a systematic review including 11 GCA studies and over 2800 patients did not identify any seasonal variation (Hysa et al., 2020). Environmental triggers are also hypothesized to be an activating event in genetically susceptible individuals. Infectious triggers have been investigated and shown a correlation between GCA incidence and epidemics of *Mycoplasma pneumonia*, *Varicella zoster virus*, and *Chlamydia pneumoniae* (Elling et al., 1996, Gilden et al., 2015, Wagner et al., 2000). However, subsequent larger studies have failed to replicate these results or identify these pathogens in temporal artery specimens from GCA patients (Njau et al., 2009, Helweg-Larsen et al., 2002). More recently, there has been interest in SARS-CoV-2-coronavirus as a causative agent in GCA with several studies showing an increased incidence of GCA during the COVID-19 pandemic (Moreno-Torres et al., 2023, Simão and Messias, 2021). Similarly, there has been concern regarding a temporal relationship between vaccination for SARS-CoV-2-coronavirus and a short duration of development of GCA symptoms (Jarrot et al., 2024). The mechanism of association between COVID-19 infection and GCA poses several questions, among them the hypotheses that SARS-CoV-2 infection might mimic a GCA presentation and result in misdiagnosis as well as the

theory that infection might directly induce GCA via COVID-19-associated endothelial dysfunction (Mackie et al., 2021).

1.2.3 Genetics of GCA

Given the predilection for certain populations, a strong genetic element is implicated in the development of GCA, which is independent of latitude. MHC class II molecules are strongly associated with GCA, most prominently, the HLA-DRB1*04 alleles (Weyand et al., 1992). HLA-DRB1*04 has been consistently replicated in multiple studies, spanning different geographical regions and ethnicities, and replicated in meta-analysis (Mackie et al., 2015c). It has also been implicated in resistance to glucocorticoid treatment of GCA (Rauzy et al., 1998), and shown to be a good predictor of ophthalmological adverse events (González-Gay et al., 2000a).

Other loci of significance, outside the HLA regions have also been associated with GCA. However, many have been implicated in small single studies and not replicated across different ethnicities. MFGE8 and VTN loci are related to angiogenesis pathways, and CCDC25 is related to neutrophil extracellular traps (NETs) (Borrego-Yaniz et al., 2024). All three have shown an association with GCA, highlighting the crucial role of angiogenesis in susceptibility. Other genes encoding cytokines or cytokine receptors have also been proposed as potential genetic risk factors for GCA. These include gene polymorphisms encoding interleukin 10 (IL-10 gene) implicated in the negative control of TH1 cytokines such as interferon-gamma (IFN- γ), regulation of B cell function, and repression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) activity (Rueda et al., 2007). Variants of the interleukin 4 (IL-4) gene have also been associated with GCA in HLA-DRB1*04 negative patients (Amoli et al., 2004). Interleukin

6 (IL-6) gene polymorphisms have been associated with GCA (Gonzalez-Gay et al., 2002) but was not replicated in subsequent studies (Salvarani et al., 2005). There are also reported associations between GCA and polymorphisms in interleukin 17-A (IL17A) (Márquez et al., 2014), interleukin 18 (IL-18) (Palomino-Morales et al., 2010) among several others.

1.2.4 The aging population and GCA

Susceptibility for GCA increases with chronological age in parallel with age-related changes in the immune system and remodelling of the vascular walls. GCA almost exclusively affects people over 50 years (Lyons et al., 2020), with peak incidence between 70 to 80 years (Mahr et al., 2017), standing out in this regard from other forms of vasculitis. Aging affects blood vessels by atherosclerosis resulting in low-grade inflammation on the endothelial surface of the vessel, while giant cell arteritis causes intense inflammation on the adventitial side (Watanabe and Hashimoto, 2022). This is mediated by migration of macrophages and subsequent intimal hyperplasia from vascular damage and macrophage-derived growth factors (Al-Mousawi et al., 2019). On a molecular level, elastic fibres in the vessel wall deteriorate and accumulate biochemical modifications. Aging also affects the immune system, and immunosenescence results in reduced T-cell pool numbers and diversity with impairment of innate immunity (Al-Mousawi et al., 2019). There may also be implications for the development of GCA in older individuals from increased infectious load in the context of impaired immunity. The exact mechanisms behind these processes remain to be fully defined.

1.2.5 Environmental pollutants and GCA

There is some emerging evidence that environmental pollutants, especially particulate matter with an aerodynamic diameter $\leq 10 \mu\text{m}$ (PM_{10}) may contribute towards the development of GCA. One recent study suggests that exposure to environmental PM_{10} in the preceding 60 days seems to be associated with an increased risk of developing GCA, especially in older individuals with prolonged exposure to high levels of air pollution (Bond et al., 2025). Noxious gases such as nitrogen dioxide and sulphur dioxide may also have a potential role as a non-specific inflammatory trigger in genetically predisposed hosts, potentially amplifying vascular immune activation. To date these noxious gases have been implicated in small vessel vasculitis (Pu and Hao, 2025) although confirmatory studies are required to elucidate its role in the development of other forms of vasculitis including GCA.

1.2.6 Vitamin D and GCA

Vitamin D insufficiency has been associated with several autoimmune rheumatic diseases (Pelajo et al., 2010). It is unclear if vitamin D insufficiency contributes to the pathogenesis of rheumatic disease or simply if it is a result of immobility indoors, confounded by poor diet and glucocorticoid use. Some studies suggest autoimmune diseases may also be associated with the development of anti-Vitamin D antibodies (Carvalho et al., 2007). Vitamin D deficiency has been sparsely studied in GCA. One very small study sample describes a high frequency of vitamin D deficiency in GCA and PMR cohorts (de Carvalho and Shoenfeld, 2021). The seasonal variation of GCA may also indirectly support an association.

1.3 Pathogenesis of GCA

The pathogenesis of GCA, remains to be fully determined however it is accepted to be an antigen-driven process (Weyand et al., 2012). The vessel wall pathology derives from a dysregulated interaction with the immune system principally through vessel dendritic cell activation by various antigens encountered. Dendritic cells in vasculitic lesions increase in number throughout the abnormal vessel wall and sustain the disease, resulting in formation of granulomas, intimal hyperplasia, and in certain cases end organ ischaemia (Weyand and Goronzy, 2003). Dendritic cells release cytokines (which stimulate two T-cell subsets T-helper 1 (TH1) and T-helper 17 (TH17)). TH1 cells produce IFN- γ and interleukin 1 (IL-1) which promote macrophage and neutrophil development (Weyand and Goronzy, 2013a) and are hypothesised to be responsible for the ischaemic complications of GCA. IFN- γ is the signature cytokine produced by the Th1 cell lineage and is relatively steroid-resistant in GCA (Weyand et al., 2011). IFN- γ is predominantly expressed by TH1 cells but may also be secreted by natural killer cells (NK) macrophages, B-cells, and dendritic cells (Schroder et al., 2004). IFN- γ promotes the differentiation of highly activated macrophages from multinucleated giant cells and these in turn release further growth factors and cytokines. The injured vessel wall cells have dysfunctional repair and result in media thickening, luminal occlusion, ischaemia, and end-organ damage. This TH1 / IFN- γ signature predominates in GCA patients with neuro-ophthalmic ischaemic complications driven by intimal hyperplasia. It may explain why those with ischaemic events have fewer constitutional symptoms and lower acute phase reactants than patients with a predominant interleukin 6 (IL-6) response which along with other cytokines induce a shift towards TH17 response (Cid et al., 1998, Ghoreschi et al., 2010).

TH17 cells produce IL-17A, interleukin 21 (IL-21), interleukin 22 (IL-22), interleukin 8 (IL-8), and interleukin 26 (IL-26) and these cytokines are deemed to be responsible for the constitutional, polymyalgia, and acute phase response of GCA. TH17 expression producing IL-17A in temporal arteries has been shown to correlate with a better response to glucocorticoid therapy and fewer relapses (Espígol-Frigolé et al., 2013).

Macrophages within the adventitia produce IL-6, interleukin 1 β (IL-1 β), and tumour necrosis factor-alpha (TNF- α) that amplify the inflammatory response (Esen et al., 2021). Within the media, they produce metalloproteinases which destroy elastic lamina and propagate intimal hyperplasia. They also produce reactive oxygen species that contribute to smooth muscle damage (Al-Mousawi et al., 2019).

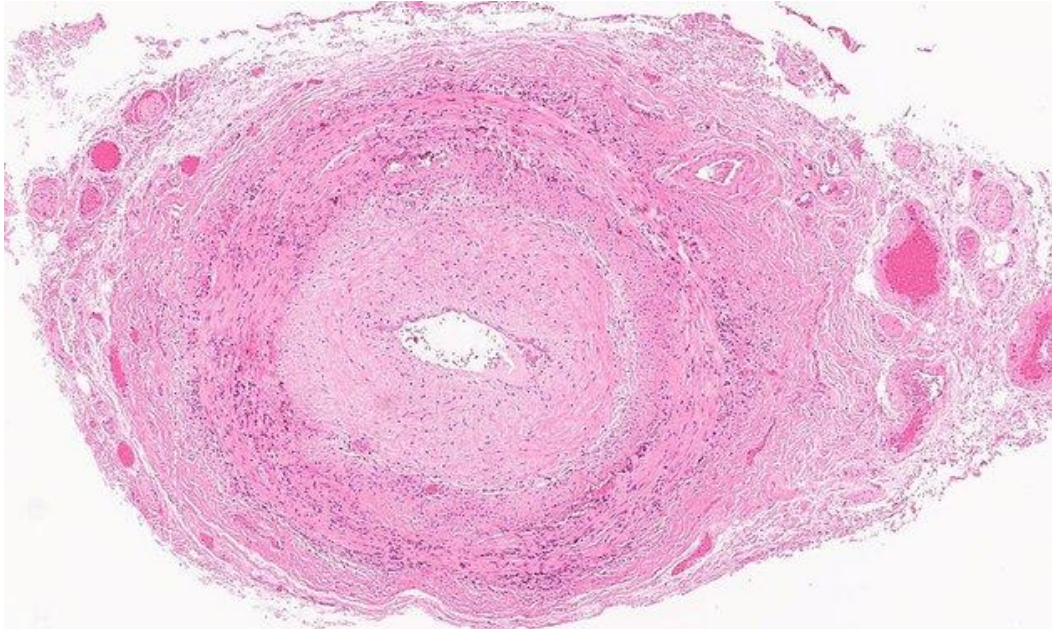
1.4 Histological features of GCA

GCA is characterised by a granulomatous inflammatory infiltrate of predominantly mononuclear cells (lymphocytes and plasma cells most commonly with neutrophils and eosinophils to a lesser extent), dendritic cells, macrophages, and necrotic tissue, and/or multinucleate giant cells. While all three layers of the vessel wall can be affected, this infiltrate is predominantly in the media near the internal elastic lamina, however inflammatory lesions may be confined to the adventitia (Galli et al., 2020). The burden of intimal cellularity can result in increased thickness and vessel lumen narrowing or occlusion with associated thrombus formation (Luqmani et al., 2016). Conversely, a normal arterial wall can also be the only finding on temporal artery biopsy (TAB) of patients ultimately diagnosed with GCA (Luqmani et al., 2016). However, this must be interpreted with caution and in conjunction with the overall clinical scenario, as TAB is not the perfect test with false negative results in up to half of cases (Galli et al., 2020).

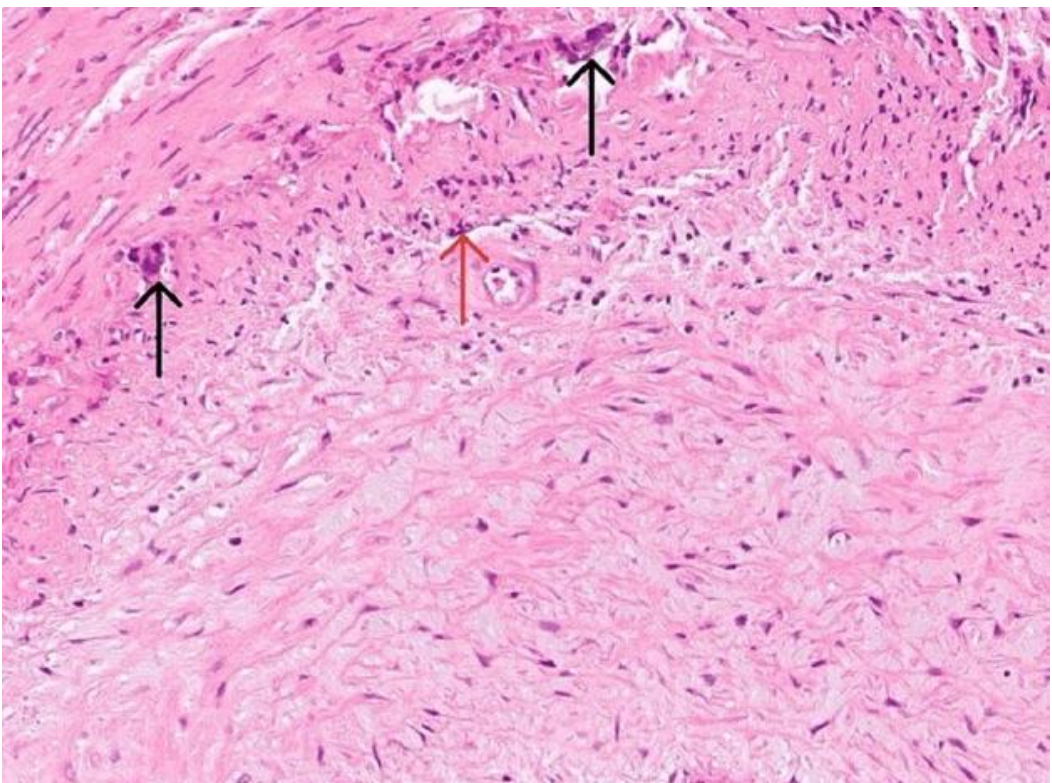
There are also considerations regarding the duration of glucocorticoid treatment before biopsy, the presence of skip lesions, number of sections taken, unilaterality or bilaterality of the biopsy, length of specimens.

Similarly, the presence of giant cells, despite the name 'giant cell arteritis' is not necessary to be present to reach a histological diagnosis of GCA. Reported presence of giant cells in a temporal artery biopsy deemed histologically positive is 39-73% (Roberts et al., 2013, Muniz Castro et al., 2022). There is no standardised definition of histological temporal arteritis and positive biopsies can have a variety of findings including irregular thickening, fibrosis, focal areas of chronic inflammation, neovascularisation of the media, loss of internal elastic media, and/or adventitial fibrosis (Muniz Castro et al., 2022). These features have also been described as having four patterns, adventitial, adventitial invasive, adventitial and intimal concentric involvement with media preservation, and pan-arteritic (Hernández-Rodríguez et al., 2016). Without the pathognomonic finding of giant cells, it is worth considering other forms of vasculitis which can affect the temporal artery and produce inflammatory histological findings including ANCA-associated vasculitis and polyarteritis nodosa (Hamidou et al., 2003), especially if the clinical exam or history is suspicious for these conditions.

Figure 1.2: Histological specimens of temporal arteritis



A:



B:

Legend: A: Temporal artery biopsy with giant cell arteritis, low-power magnification; B: Temporal artery biopsy, giant cell arteritis, high-power magnification with multinucleated giant cells (black arrowhead) and mononuclear cell infiltration (red arrowhead)..(Wan et al., 2024)

1.5 Clinical features of GCA

GCA is a heterogenous systemic disease that may affect the aorta and any of its major tributaries, as well as smaller arteries such as the ophthalmic artery and its branches leading to various clinical presentations (Lyne et al., 2023). GCA can present as predominant cranial GCA with headache and ischaemic symptoms of jaw claudication, scalp tenderness, or visual disturbance, while predominant large vessel GCA can present with constitutional symptoms of weight loss, fever, anorexia, lassitude, and polymyalgia rheumatica symptoms. Patients may also have a mix of both phenotypes.

1.5.1 Cranial GCA

Cranial GCA is the most characteristic presentation of 'temporal arteritis' with patients presenting with cranial ischaemic symptoms directly related to vascular inflammation and oedema. Headache is the predominant symptom in over two-thirds of patients and is the most common presenting symptom of cranial GCA (Hellmann, 2002). Classically, the headache is new, sudden, and severe in onset, and predominantly temporal. However, GCA headaches can be variable in location, intensity, and quality. Quite often the only distinguishing feature is that the headache is new in a person over 50 years old, or described as a 'different headache' in those accustomed to suffering from tension headaches or migraines previously (Hellmann, 2002). Characteristic involvement of the temporal artery leads to scalp tenderness, although this is an unreliable symptom in the clinical diagnosis of GCA, not corresponding to a positive TAB (Hayreh and Zimmerman, 2003). Jaw claudication occurs in up to half of GCA patients and is one of the strongest clinical predictors of GCA (Hayreh et al., 1997). It is ischaemic in nature, with reduced

masseter muscle blood flow on chewing resulting in pain or tiredness in the jaw, necessitating a break in eating to relieve it. Less commonly the arterial supply of the tongue can be implicated resulting in tongue claudication and interestingly smoking or other traditional cardiovascular risk factors are not associated with GCA claudication (Mackie et al., 2011). Ophthalmic problems in GCA are often some of the most feared complications due to the risk of irreversible visual loss. Amaurosis fugax occurs in 14% of GCA patients, with permanent visual loss preceded by amaurosis fugax in approximately half of cases (González-Gay et al., 2000a). Total or partial visual loss affects 14-20% of GCA patients (Lyne et al., 2023, Salvarani et al., 2012). Diplopia may occur in 5-12% of GCA patients due to disruption of the arterial supply of the extra-ocular muscles (González-Gay et al., 2000a, Mackie et al., 2011). In many cases, diplopia may be transient, with a resolution of extra-ocular muscle palsy at the time of examination. Strokes are less common ischaemic manifestations affecting 3% of GCA patients (Parreau et al., 2022) and tend to affect the vertebrobasilar territory preferentially (Larivière et al., 2014). The highest risk of stroke is at the time of disease onset, significantly decreasing once treatment is initiated (Gonzalez-Gay et al., 2009). Less commonly associated features of GCA include cough (10%) thought to be due to ischaemia of cough receptors (Salvarani et al., 2012), sore throat due to ischaemia of the ascending pharyngeal branches of the external carotid artery (Ling et al., 2012), and hoarseness (Ortner's syndrome) due to aortitis induced irritation of the recurrent laryngeal nerve (Edrees, 2012).

Table 1.1 Frequency of cranial GCA symptoms

Cranial Symptom	Frequency Range
Headache	60-85%
Jaw claudication	28-54%
Scalp tenderness	~50%
Amaurosis fugax	14%
Permanent visual loss	14-20%
Diplopia	5-12%
Stroke	3-7%

Legend: Occurs in up to (~) (Mackie et al., 2011, Salvarani et al., 2012, González-Gay et al., 2000b, Lyne et al., 2023, Parreau et al., 2022, Larivière et al., 2014)

1.5.2 Large Vessel GCA (LV-GCA)

GCA patients may present with symptoms related to involvement of the intrathoracic or intraabdominal arteries. These symptoms may be constitutional, arising from vessel inflammation or ischaemic. Constitutional symptoms are the most common presentation as only a minority suffer from localising large vessel ischaemic symptoms. LV-GCA symptoms can occur alongside cranial GCA or in isolation (van der Geest et al., 2024). Constitutional symptoms include weight loss, fatigue, and fever or night sweats which can present as pyrexia of unknown origin. Although fever associated with LV-GCA is usually low grade, a high-grade fever may be the presenting feature in up to 15% of patients (Calamia and Hunder, 1981). Patients with LV-GCA may present with limb claudication, with the upper limbs more frequently affected than the lower limbs (Berti

et al., 2015). Other symptoms include vascular bruits, decreased or absent pulses, and cold peripheries. Aortic dilatation has been reported both in the early and late course of GCA and it is not uncommon for dilatation and dissection to occur up to 5-10 years after the initial diagnosis (García-Martínez et al., 2014). These complications may be present in up to 22% of patients (García-Martínez et al., 2008). Aneurysm size is not a predictor of aortic dissection, rather the presence of active aortitis may be influential (Kermani et al., 2016).

Table 1.2 Frequency of large vessel GCA symptoms

LV-GCA Symptom	Frequency
Weight loss	37%
Fever	44%
Fatigue	72%
Limb claudication	7-15%
Aortic aneurysm	18-22%
Aortic dissection	5%

(Salvarani et al., 2012, Nuenninghoff et al., 2003, Tomelleri et al., 2022, García-Martínez et al., 2014, García-Martínez et al., 2008)

1.5.3 PMR symptoms in GCA

GCA patients frequently present with PMR symptoms including bilateral shoulder and/or pelvic girdle pain and early morning stiffness (Gonzalez-Gay, 2004, Buttgerit et al., 2016) with up to 50% of GCA patients with biopsy-proven disease exhibiting clinical features of PMR at diagnosis (Gonzalez-Gay et al., 2005). PMR is also the most frequent symptom of relapse in GCA, accounting for approximately 50% of disease relapses (Alba

et al., 2014). PMR associated with GCA is considered a more severe phenotype with frequent abnormality in laboratory variables including higher elevation of erythrocyte sedimentation rate and platelet counts, and lower values of haemoglobin (González-Gay et al., 1998).

Table 1.3 Clinical symptoms and signs in subtypes of GCA and PMR

Symptoms and signs	Cranial GCA	LV-GCA	PMR
Headache	++	–	-
Arterial tenderness/bruit	+	+	-
Jaw claudication/tongue pain	++	–	-
Visual symptoms/complications	++	–	-
Fever/ weight loss	+	++	++
Arm claudication	+	++	-
Polymyalgic symptoms	+	++	++
Acute phase reactants	++	++	++
Peripheral arthritis/RS3PE	+	+	++

Legend: ++: very common symptom/sign (>50% patients); +: common (10-50% patients); –: uncommon (<10% patients). RS3PE: remitting seronegative symmetric synovitis with pitting oedema (Dejaco et al., 2017)

1.6 Diagnosis and Classification of GCA

The diagnosis of GCA remains a clinical one, assessed by the clinician considering the clinical presentation, laboratory features, and other diagnostic aids such as imaging and/or biopsy. There are no diagnostic criteria to date for GCA.

Ultrasound (US) is recommended as the first line of investigation in the recent EULAR guidelines for imaging in LVV (Dejaco et al., 2023b). It has the advantage of enabling direct confirmation of a suspected diagnosis within the examination room without

further referrals to other clinics or specialists. It is ideally performed within one week of initiation of glucocorticoids to reduce the risk of false negative results in treated/partially treated patients (Hauenstein et al., 2012, Luqmani et al., 2016). Fast-track clinics for GCA incorporating US have led to a reduction in irreversible visual loss (Diamantopoulos et al., 2016). The 'halo' sign of temporal arteries is the most relevant ultrasound finding in GCA and is defined by OMERACT as homogenous, hypoechoic wall thickening of the lumen that is visible both in longitudinal and transverse planes, most commonly concentric in transverse scans (Dejaco et al., 2023a). The US halo sign is both sensitive and specific finding in GCA assessment (Sebastian et al., 2021). It has been shown to outperform TAB with a sensitivity for GCA at 54%, compared to 39% for biopsy, and specificity of 81% compared to 100% for TAB (Luqmani et al., 2016).

There does remain a role for TAB which was once considered the gold standard investigation for GCA (Salvarani et al., 2002). It is useful when clinical suspicion for GCA is high but the characteristic US findings are absent. In addition, TAB is useful where there has been a longer duration of corticosteroid exposure before assessment, with some evidence this can stay positive in over 70% of cases for up to 6 months with analysis of sufficient biopsy length of 3-4cm (Maleszewski et al., 2017). However, a negative TAB does not exclude GCA, with factors such as specimen length, skip lesions, and previous glucocorticoid exposure contributing to low sensitivity of TAB for GCA. Studies have also reported positive TABs in the setting of other systemic vasculitides such as ANCA-associated vasculitis and polyarteritis nodosa (Delaval et al., 2021, G  n  reau et al., 1999).

In 2022, the American College of Rheumatology (ACR) updated the 1990 classification criteria for GCA for research purposes (Figure 1.3). These criteria are not suitable for diagnosis, given that their design and focus are on differentiating GCA from other forms of vasculitis (Ponte et al., 2022a). They have an advantage over the 1990 classification criteria (Hunder et al., 1990) as imaging features are now included as well as PMR symptoms.

Figure 1.3 2022 American College of Rheumatology Classification Criteria for GCA

Classification requires: Age $\geq$ 50 years (mandatory) and a total score $\geq$ 6 points.

Domain	Item	Points
Clinical features	New-onset localized headache	+2
	Scalp tenderness or decreased temporal artery pulse	+2
	Jaw or tongue claudication	+2
	Morning shoulder/neck stiffness (PMR symptoms)	+1
Laboratory	ESR $\geq$ 50 mm/h or CRP $\geq$ 10 mg/L	+3
Imaging	Positive temporal artery ultrasound	+5
	Positive axillary artery ultrasound	+2
	CTA/MRA/PET-CT showing large-vessel vasculitis	+2
Biopsy	Positive temporal artery biopsy	+5

(Ponte et al., 2022a)

1.7 Treatment of GCA

The mainstay of treatment for GCA is high-dose glucocorticoids at a dose of 40-60mg, with preceding intravenous glucocorticoids if visual symptoms are present (Maz et al., 2021, Hellmich et al., 2020a). Glucocorticoids remain an important cornerstone of treatment, rapidly resolve symptoms and help to prevent GCA complications. However, they are associated with significant short and long-term morbidity from glucocorticoid-

induced side-effects, patients may continue to have subclinical disease progression, and relapse may still occur on glucocorticoid, particularly with dose tapering. Tocilizumab adjunctive treatment has shown improvement in sustained glucocorticoid-free remission in patients with giant-cell arteritis (Stone et al., 2017b) and is recommended from the outset of treatment in the American College of Rheumatology /Vasculitis Foundation (ACR/VF) guidelines and recommended by EULAR if the patient is at risk of glucocorticoid related adverse events to enable quicker corticosteroid taper (Maz et al., 2021, Hellmich et al., 2020b). There also may be a role for methotrexate as a treatment adjunct/ corticosteroid sparer in cases where tocilizumab is contraindicated. We await guidance on the role of emerging therapies in clinical trials including mavrilimumab (Cid et al., 2022a), secukinumab (Venhoff et al., 2021), and JAK inhibitors (Koster et al., 2022).

1.8 Polymyalgia Rheumatica

Polymyalgia Rheumatica (PMR) is the most common rheumatic disease in persons over the age of 50 years. It is characterised by severe pain and stiffness in the shoulders, proximal arms, neck, pelvic girdle, and proximal thighs (González-Gay et al., 2017). Patients typically have prolonged early morning stiffness, fatigue, malaise, and an elevation in acute phase reactants. ‘Polymyalgia arteritica’ was first coined in 1972 by Hamrin, recognizing that many cases of phenotypic PMR also had arteritis (Hamrin, 1972). GCA and PMR both have systemic inflammation, a predominant interleukin-6 signature, an excellent response to corticosteroids, and a tendency to a chronic relapsing course (Tomelleri et al., 2023b). The most common extra-cranial manifestation of GCA is PMR with studies reporting 45-61% incidence of PMR symptoms at the time of

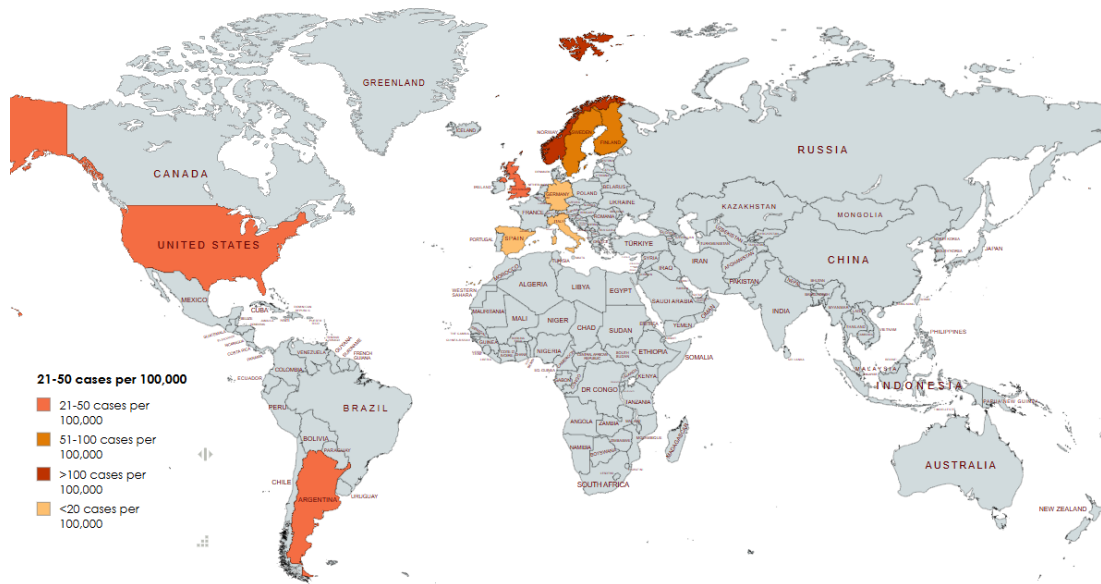
GCA diagnosis (Schmidt et al., 2008, González-Gay et al., 1998, Stone et al., 2017a). PMR is also the most frequent symptom of relapse in GCA, accounting for approximately 50% of disease relapses (Alba et al., 2014).

1.9 Epidemiology of PMR

1.9.1 Geographical variations of PMR

Like GCA, PMR has a high incidence in Scandinavian countries. The annual incidence of PMR in Sweden in people over 50 years is 50 per 100,000 population (Schaufelberger et al., 1995) and 68.3 per 100,000 in Denmark (Boesen and Sørensen, 1987). Notably, Minnesota, USA also has one of the highest incidence rates at 63.9 per 100,000 population over 50 years (Raheel et al., 2017), perhaps attributed to their prominent Scandinavian and northern European descent. A lower incidence has been found in southern Europe, with 12.7 per 100,000 in Italy and 18.7 per 100,000 in Spain (Salvarani et al., 1991, González-Gay et al., 1999). Incidence of PMR in the United Kingdom is high at 84-95.9 per 100,000 (Smeeth et al., 2006, Partington et al., 2018), highest in older women in the South of England. There are no Irish studies on PMR incidence to date, likely thwarted by significant PMR management in primary care, without rheumatology input and lack of disease registry data.

Figure 1.4 Geographical variations in the incidence of PMR



Legend: Map was made on mapchart.net/world from incidence data published Hysa et al.(E. Hysa, 2025)

1.9.2 Genetics of PMR

An association between genes that lie in the HLA-class II region has been described in both GCA and PMR (Weyand et al., 1992). Despite being consistently replicated in many GCA studies, HLA-DRB1 association in patients with PMR varies between populations (González-Gay et al., 2003). While PMR in the context of GCA is generally associated with HLA-DRB1*04 alleles, a Spanish study showed that patients with isolated PMR manifestations (without concomitant GCA) were associated with HLADRB1*13/14 alleles (Dababneh et al., 1998). Other allelic polymorphisms found to be associated with PMR include those in Intercellular Adhesion Molecule 1 (ICAM-1), and the interleukin-1 receptor antagonist (IL-1Ra) (González-Gay et al., 2003).

1.9.3 Infectious triggers of PMR

Infectious triggers may be implicated in the pathogenesis of PMR. A meta-analysis of over 5,000 PMR patients compared with 16.7 million age and sex-matched controls

found a significant and positive association between PMR and all-cause hospital-treated infections (Pacoureaux et al., 2023). Some studies have co-reported on infection in the context of both GCA and PMR and noted peaks in incidence in close concurrence with *Mycoplasma pneumoniae*, parvovirus B19, and *Chlamydia pneumoniae* infections (Elling et al., 1996), however parvovirus B19 infectious association with isolated PMR has not been replicated in other studies (Peris, 2003). There has also been considerable interest in both SARS-CoV-2 infection and vaccination in PMR, however a definitive link has not been established (Manzo et al., 2022, Chang et al., 2023). Infectious associations may simply reflect altered immunity in PMR patients, or indeed represent reverse-causation.

1.9.4 Aging and PMR

PMR is certainly a disease of the older person, with peak incidence at 70-75 years (Chang et al., 2023). The juxtaposition of low-grade systemic inflammation, cell senescence, and immunosenescence resulting in decreased T-cell output, increased glycolysis, and overproduction of oxygen free radicals appears to be implicated in PMR in the older patient (Coskun Benlidayi, 2024). Age-induced alterations in the HPA-axis are also thought to be a factor in the development of PMR (Cutolo et al., 2002). There are further theories of increased susceptibility to infectious triggers with age and gut dysbiosis leading to increased permeability and enhanced activity of Th1 and Th17 cells as well as decreased differentiation of Treg cells (Scrivo et al., 2018). Frailty, a syndrome characterised by reduced physiologic homeostasis, increased vulnerability to stressors, increased morbidity in the form of falls and hospitalisations, and increased mortality (Theou et al., 2013) has been associated with chronic low grade inflammation and

elevations in CRP and IL-6 referred to as 'inflammaging'. Higher levels of frailty and pre-frailty have been identified in PMR patients compared with older adults in the community without PMR (Sattui et al., 2022). Despite a recent revival in interest among researchers regarding aging and PMR, the exact mechanisms behind this process remain to be elucidated.

1.10 Clinical features of PMR

PMR typically presents with bilateral pain and stiffness in the shoulder and hip girdles with raised inflammatory markers. The cardinal feature of PMR is proximal girdle pain associated with restricted range of motion and stiffness. Shoulders are affected in up to 95% of cases the neck and pelvic girdle can also be involved (Mahmood et al., 2020). Symptoms are characteristically worse in the morning with significant early morning stiffness, improving as the day goes on, and worse after periods of inactivity. Constitutional symptoms are also a prominent feature of PMR, with fatigue, fever, and weight loss reported in up to 1/3 of patients (Lundberg et al., 2022). Less frequent manifestations include peripheral arthritis and lower back pain secondary to interspinous bursitis (Kermani and Warrington, 2013).

1.11 GCA in PMR

GCA frequently presents in a metachronous fashion in patients with a diagnosis of PMR. A recent retrospective study including 167 PMR patients showed 11% went on to develop typical cranial vasculitis symptoms or signs of vascular insufficiency in the upper

extremities during follow-up (Narváez et al., 2015). The median time to GCA diagnosis was 9 months and 50% of these patients experienced severe complications, including permanent vision loss, stroke, and limb claudication (Narváez et al., 2015). A recent systematic review also identified several studies in which GCA developed during follow-up of PMR patients. The incidence of new GCA in PMR varied at 2-77.7 per 1000 patient years (Nielsen et al., 2022) and the time of onset of GCA varied from 4.5 to 24 months (Nielsen et al., 2022). One Spanish study reported that 2% of patients with isolated PMR who did not exhibit any symptoms of GCA within the first 2 years, developed features of GCA during their extended follow-up (González-Gay et al., 1999). GCA patients who present initially as isolated PMR have the longest time to diagnosis and the lowest rate of overall steroid discontinuation (de Boysson et al., 2019). With regard the prevalence of ischemic complications in patients with GCA presenting with apparently isolated PMR, Narváez et al. reviewed 167 patients with PMR of whom, 18 (11%) developed GCA. Of these, 50% (9/18) developed transient or permanent disease-related ischemic complications (Narváez et al., 2015). These complications included jaw claudication in four patients (22%); visual manifestations in 7 (39%) patients, including five cases of amaurosis fugax and two cases of permanent visual loss; strokes in two patients (11%); and one case (6%) of upper limb claudication due to reversible stenosis of the axillary artery (Narváez et al., 2015). Indeed, this data highlights the close relationship between GCA and PMR and advocates for ongoing vigilance in PMR for the emergence of GCA.

1.12 Diagnosis and classification of PMR

The diagnosis of PMR remains a clinical one, predominantly based on the presence of characteristic clinical features. Elevated acute phase reactants are helpful, and ESR of >30-40mm/h has been described in many clinical studies; however, the optimal cut-off remains undefined (González-Gay et al., 1997, Dasgupta et al., 2012, Chuang et al., 1982). Conversely it is not uncommon to have minimal inflammatory rise in PMR with 20% of patients having ESR <40mm/h (González-Gay et al., 1997). A recent study noted that up to 14% of patients with PMR presented with entirely normal ESR and CRP (Marsman et al., 2021) which may add to diagnostic difficulty. These cases require rheumatology input and are more challenging for primary care diagnosis particularly as PMR has many mimics including rheumatoid arthritis (RA), seronegative inflammatory arthritis (SIA), myositis, ANCA-associated vasculitis and many non-inflammatory conditions including Parkinson's disease, rotator cuff disease and osteoarthritis (OA). Rapid resolution of symptoms within 24-48 hours initiation of glucocorticoids, is viewed by many clinicians as characteristic, but many inflammatory conditions respond to glucocorticoid in this manner, and it cannot be relied upon. Modern advances in imaging have also assisted PMR diagnosis and aided its differentiation from other similarly presenting conditions. McGonagle et al. first reported an anatomical difference in the distribution of inflammation on MRI compared with RA (McGonagle et al., 2001). The inflammatory change of PMR is extracapsular in nature, compared to the typical findings of RA with tenosynovitis, and joint effusions. Further PET studies have shown that the presence of abnormal ¹⁸F-FDG uptake adjacent to the ischial tuberosities, peri-articular shoulder or interspinous bursa on whole-body PET/CT is highly sensitive and specific for a diagnosis of PMR (Owen et al., 2020). Despite these diagnostic advances, there

remains no diagnostic criteria for PMR. ACR/EULAR has defined classification criteria for PMR in 2012, but these are not validated for use as diagnostic criteria in a clinical setting.

Table 1.4 2012 ACR/EULAR Classification Criteria for PMR

Characteristic	Points without US (0-6)	Points with US (0-8)
Morning stiffness >45 min	2	2
Hip pain or limited range of movement	1	1
Absence of other joint involvement	1	1
Absence of rheumatoid factor or anti-citrullinated protein antibodies	2	2
At least one shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis and at least one hip with trochanteric bursitis/synovitis	N/A	1
Both shoulders with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis	N/A	1

Legend: Requirements for entry into classification criteria are age 50 years or older, bilateral shoulder aching and abnormal CRP and/or ESR. A score of 4 or more is required without US and 5 or more with the use of US (Dasgupta et al., 2012).

1.13 Treatment of PMR

Like GCA, the cornerstone of PMR treatment relies on glucocorticoids, albeit at a much lesser dose than GCA. The 2015 ACR/EULAR PMR treatment recommendations advise a starting dose of 12.5-25mg, with an individualised tapering plan, aiming to be at a dose of 10mg after 4-8 weeks (Dejaco et al., 2015). Once remission is achieved the taper is reduced by 1mg every 4 weeks and discontinued. For relapses, increasing glucocorticoid doses to the pre-relapse dose is recommended. The early addition of methotrexate is also advocated for, especially in patients with high risk of relapse or at high risk from glucocorticoid side effects. Since the development of these guidelines, there has been FDA approval for sarilumab, an IL-6 receptor antagonist, for relapsing PMR after the success of the SAPHYR trial (Spiera et al., 2023). Tocilizumab has also been studied in both new and relapsing PMR in the PMR-Spare and SEMAPHORE trials, although formal approval is awaited (Bonelli et al., 2022, Izumi et al., 2021). Currently, several ongoing clinical trials are exploring potential treatments such as leflunomide, rituximab, abatacept, secukinumab, janus kinase inhibitors, low-dose IL-2, and selective inhibitors like SPI-62 and ABBV 154 in PMR (Iorio et al., 2024).

1.14 GCA/PMR Spectrum Disease (GPSD)

There is an emerging view that given the close links in between PMR and GCA including similar clinical presentation, acute phase response, age group affected, pathophysiology, genetics, immunology and anatomical sites of arterial and musculoskeletal inflammation that they should be approached as linked conditions, unified under the term GPSD (Tomelleri et al., 2022). Increased understanding of this

disease spectrum should prompt careful evaluation of patients with GCA for PMR symptoms and patients with PMR for underlying GCA given their commonalities. It is recommended by Dasgupta and colleagues that careful identification of all clinical features, targeted imaging, and meticulous review of laboratory markers in this cohort will assist with prognostication, monitoring, and management by stratifying their disease severity from the outset (Tomelleri et al., 2022). This is a new approach to these conditions, previously viewed as monolithic diseases. Advances in imaging have significantly contributed towards understanding of the GPSD spectrum, in particular the incorporation of bedside US into clinical rheumatology practice and increased accessibility to positron emission tomography (PET). A recent systematic review examining 13 studies with 566 PMR patients, which included TAB, US, and PET studies in this cohort, found that 23% of patients presenting solely with PMR without any cranial features of GCA had evidence of vasculitis on imaging or biopsy. This has been coined 'subclinical GCA in PMR' (sGCA/PMR) and presents many more currently unanswered questions for routine workup and management of PMR patients.

1.15 Subclinical GCA in PMR

Evidence from a recent meta-analysis has shown that inflammatory vascular involvement may be identified in PMR patients without any clinical symptoms of GCA, so-called 'subclinical GCA in PMR' (Hemmig et al., 2022). The lack of any specific clinical features of GCA in subclinical GCA in PMR is challenging in the clinical setting, with a high reported pooled prevalence in systematic review of 23% (Hemmig et al., 2022). There are few prospective studies on subclinical GCA in PMR with only two being

recently described in the literature (Burg et al., 2023). These have identified a similar prevalence of subclinical GCA in PMR at 22.8 and 22% respectively. The De Miguel group carried out a longitudinal study on these patients for up to two years and found that those with US-identified subclinical GCA in PMR were almost 4 times more likely to relapse compared to isolated PMR (De Miguel et al., 2023a, De Miguel et al., 2024). This has raised valid questions about whether rheumatologists should now include vascular imaging in management protocols for PMR to assess for vasculitis to accurately assess risk stratification, guide therapy, and optimise patient outcomes. The lack of evidence guiding risk stratification in GCA spectrum disease at the time of diagnosis to guide a personalised treatment plan is a major unmet need. Currently, the recommendations for PMR management do not advocate for routine imaging to assess for underlying vasculitis (Dejaco et al., 2015). Resource limitations such as adequate training, operator expertise, access to appropriate US technology, and associated costs will be the predominant limiting factors.

1.16 Hypothesis

This study hypothesizes that patients with subclinical GCA in PMR have a distinct phenotype from patients with 'pure PMR'. This study aims to define the prevalence of subclinical GCA in PMR in a newly diagnosed PMR cohort, characterise the ultrasound pattern, natural history, and biomarker profile of this cohort, and compare with prospective PMR and GCA cohorts.

1.17 Objectives of study

- To define the clinical manifestations of GCA in the context of the GCA-PMR Spectrum and examine the clinical impact of a GCA fast-track clinic on an Irish GCA cohort.
- To examine the feasibility and clinical impact of establishing a novel fast-track PMR clinic, define patient characteristics, and establish the relapse rate over 12 months.
- To assess the prevalence of subclinical GCA with temporal and axillary ultrasound in patients with newly diagnosed PMR and describe their clinical, ultrasound, and laboratory marker patterns.
- To define the natural history of subclinical GCA in PMR including relapse, progression to GCA, and adverse events over 1 year follow-up and compare it to PMR and GCA cohorts.
- To compare the Halo count, Halo score, and OMERACT GCA Ultrasound score in patients with subclinical GCA in PMR with GCA.
- To determine if analysis of serum biomarkers in PMR, subclinical GCA in PMR, and GCA may help differentiate between these related conditions.

1.18 Anticipated value of the research

This research will offer a real-world experience of a GCA fast-track clinic service. This will be useful for providing urgent patient care, validating ultrasound protocols, and planning future services. From the experience of running the GCA fast-track clinic, similar protocols can be implemented for a fast-track PMR service. There are few reports regarding fast-track PMR clinics in the literature to inform service provision. Recent

guidelines have recommended that suspected PMR patients should be reviewed by specialists. This requires information on the anticipated volume of referrals per 100,000 population, alternative diagnoses, number of follow-up appointments required, and clinical impact of providing this service. With growing evidence outlined in this thesis, the implementation of PMR fast-track clinics should offer a template from which to plan a PMR fast-track service and improve patient experience and outcomes.

This study will also define a cohort of PMR patients with subclinical GCA. Prospective longitudinal studies are required to clarify the prevalence of this finding, understand the natural history of these patients, provide recommendations on which PMR patients to screen, and offer insight into the most appropriate treatment protocol.

There are no currently published biomarker studies directly comparing PMR and GCA patients. The findings of this research have the potential to unravel the distinct profiles, and therefore the likely distinct pathophysiology, of PMR, subclinical GCA in PMR, and GCA. Shared immune pathways in GCA/PMR could also be targeted for treatment. The identified biomarkers have the potential to enhance the diagnostic process and facilitate targeted treatments in the future.

Chapter 2:

The Irish Fast-track GCA Clinic

Experience.

2.1 Abstract

Introduction

Fast-track clinics (FTC) in GCA have been a major success in improving GCA care and have been facilitated by incorporating ultrasound, usually performed by the clinician, into the diagnostic pathway. There is also increasing recognition that GCA should not be considered a disease in isolation due to its intricate links with PMR and the recent recognition of the GCA PMR Spectrum Disease (GPSD). There is a need for prospective inception cohort studies of GPSD, mapping of anatomical sites of inflammation, and monitoring the evolution of the disease course.

Methods

Primary care physicians were invited to refer patients with newly suspected GCA to the FTC. Referral criteria included new onset headache in patients over the age of 50 years with elevated inflammatory markers. All patients were seen within 24 hours of referral (Mon-Fri) and had clinical assessment, ultrasound of temporal and axillary arteries and laboratory blood work. Patients were followed up at 1-month, 3 months, 6-month, and 12-month timepoints.

Results

84 patients were referred to the fast-track GCA clinic over 1 year. 24 patients (28.6%) met a clinical diagnosis of new GCA with agreement by two rheumatologists, while 60 (71.4%) patients had an alternative diagnosis. The Southend Pre-test probability score

(SPTPS) had a sensitivity of 100%, specificity of 73%, positive predictive value of 54%, and negative predictive value of 100% in this cohort. A significant number of GCA patients suffered adverse effects in the first year of treatment (41%) and 33% requiring hospitalisation.

Conclusion

This study outlines a training protocol in vascular ultrasound and its implementation into a GCA FTC. This FTC had a hit rate for GCA of 28%. Implementation of the STPTS had good sensitivity for GCA and good negative predictive value for non-GCA cases. Incorporating it into the screening process in the future would significantly reduce the workload in assessing low-risk GCA cases. GCA patients despite optimal management with regular follow-up, and treatment with glucocorticoid-sparing agents are susceptible to frequent adverse events. Careful management with service provision for ad hoc clinic slots for relapse cases are warranted.

2.2 Introduction

Early and accurate diagnosis of giant cell arteritis (GCA) is critical to prevent avoidable and irreversible complications including blindness, stroke, and death. Inaccurate diagnosis can lead to exposure to high dose glucocorticoids which can cause significant side-effects including infection, osteoporosis, and cardiovascular disease. However, early accurate diagnosis of GCA remains challenging due to the frequent lack of classic symptoms or a good biomarker to assist diagnosis. A positive TAB has previously been the gold standard for diagnosis. However, performing TAB is associated with problems

including diagnostic delay, unnecessary patient exposure to glucocorticoids, potential consequences from an invasive procedure, high costs, and frequent false negative results. Recent guidelines now recommended US as the first-line test in evaluating suspected GCA (Dejaco et al., 2018). A non-compressible 'halo' sign and increased arterial wall thickness are the ultrasound finding most suggestive of GCA. Ultrasound allows for evaluation of the entire length of the temporal vessels and their branches as well as other vessels including axillary, subclavian, carotid, and occipital arteries. It is non-invasive and the clinician performing the US has immediate access to the results to implement prompt clinical decision-making and reducing the need for return appointments for results.

Fast-track clinics (FTC) in GCA have been a major success in improving GCA care and have been facilitated by incorporating US, usually performed by the clinician, into the diagnostic pathway. FTCs have reduced the requirement for primary care to initiate glucocorticoid treatment for low probability suspected GCA, with many patients getting specialist review the same working day, thus avoiding unnecessary exposure to glucocorticoids in non-GCA diagnosis. Rapid assessment avoids the obscuration of clinical, laboratory, or imaging findings with glucocorticoids in those with true GCA. However, in cases of high suspicion for GCA, glucocorticoid therapy should not be delayed and should be initiated before confirmation of the diagnosis, with diagnostic evaluation ideally within the first 3 days of treatment (Schmidt et al., 2024). FTCs have also heralded a relative risk reduction of 88% in permanent visual impairment secondary to GCA (Diamantopoulos et al., 2016). Best practice guidelines recommend that patients are seen within 24 hours of referral by a specialist with expertise in GCA (Schmidt et al.,

2024). Despite this, delays are still reported in the time from symptom onset to FTC review (van Nieuwland et al., 2024).

There is also increasing recognition that GCA should not be considered a disease in isolation due to its intricate links with PMR and the recent recognition of the GCA PMR Spectrum Disease (GPSD). There are clear similarities between both conditions relating to patients' age, genetics, clinical presentation, complications, and treatment. A recent review paper has proposed a stratification of both GCA and PMR patients into 1) Cranial GCA, 2) Ischaemic GCA, 3) Large-vessel GCA (with either GCA on its own with constitutional symptoms or with cranial GCA and/or relapsing PMR), 4) Isolated PMR, and 5) PMR with peripheral arthritis and/or distal involvement such as RS3PE (Tomelleri et al., 2023b). It has also recommended the need for prospective inception cohort studies of GPSD, mapping of anatomical sites of inflammation, and monitoring the evolution of the disease course (Tomelleri et al., 2023b). The overarching objective of this study was to establish a fast-track GCA clinic, validate vascular ultrasound protocols for the temporal artery and axillary artery for the diagnosis of GCA in our cohort, and establish a cohort of GCA patients as a control group to compare with our polymyalgia / GCA cohort (details of which are described in chapter 3 in depth).

2.3 Objectives

The objectives of this study were:

1. To describe the time from onset of symptoms to diagnosis and treatment in GCA-suspected patients in a fast-track clinic (FTC)

2. To determine the accuracy of clinical features and erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) in establishing the diagnosis of TA.
3. To validate temporal and axillary vascular US performed by Dr Sharon Cowley.
4. To define the alternative diagnoses arising from a GCA fast-track clinic.
5. To define the clinical manifestations of GCA in the context of the GCA-PMR Spectrum.
6. To determine the rate of GCA relapse at 12 months.
7. To determine the rate of glucocorticoid remission at 12 months.
8. To examine the clinical impact of a GCA fast-track clinic on an Irish GCA cohort.

2.4 Methods

2.4.1 Design and study population

This project aims to build upon earlier work at TUH and Cork University Hospital (CUH) which established the validity of grayscale and power Doppler ultrasound in the diagnosis of GCA. The first Irish clinician-sonographer-led fast-track GCA clinic was established in August 2020 by Professor David Kane and Dr Colm Kirby at TUH and with Prof Grainne Murphy at CUH. This multicentre prospective longitudinal cohort study was conducted by continuing the GCA FTC at TUH and extending it to involve St James Hospital (SJH), Dublin.

Primary care physicians in our catchment area with a population of 600,000 were invited to refer patients over 50 years with suspicion of new GCA to our fast-track clinic. Engagement with primary care included attending local GP meetings to remind GPs about the clinic and sending an email-based flyer to GPs in the catchment area to capture those not at the meeting.

Inclusion criteria included new onset headache in patients aged above 50 years or new ocular symptoms including transient visual loss, visual fatigue, or visual field loss with a suspicion of GCA. Exclusion criteria included patients on glucocorticoids for >4/52 weeks and patients on glucocorticoid-sparing agents for another reason. Referrals were accepted via email to a dedicated GCA clinic address, and included details of the patient's history, GP laboratory results, and contact details. The patients were contacted by telephone on the same working day with an appointment time arranged within 24 hours (same or next working day).

All patients had a full clinical history and examination performed. Laboratory investigations completed included baseline ESR, CRP, full blood count, liver profile, renal function, fibrinogen, Hba1c, and lipid profile. Additional serum was bio-banked in the Meath Foundation Research Laboratory at TUH for later cytokine analysis. All patients had a baseline vascular ultrasound of their cranial and axillary arteries. The diagnosis of GCA was a clinical one, made in agreement by two rheumatologists. All GCA patients had follow-up at 1 month, 3-month, 6-month, and 12-month time points. Each follow-up review was carried out in the same format as the initial FTC assessment with clinical

review accompanied by US evaluation, laboratory marker analysis, and serum bio-banking. All patients gave informed written consent and received a patient information booklet.

Figure 2.1 GCA Fast-track clinic flyer for primary care.

Fast-track GCA Clinic

**Tallaght University Hospital**
Ospidéal Ollscoile Thamhlachta
An Academic Partner of Trinity College Dublin

Key Messages:

- Giant Cell Arteritis is known to cause permanent visual impairment and stroke
- Urgent assessment and treatment is required to reduce this risk

Who to refer?

1. Age **50 years** or older
2. **New-onset** headache (especially <6 weeks)
3. **Elevated inflammatory markers** particularly if ESR>50mm/hr and CRP >10mg/dl

About the clinic:

- Patients will be contacted immediately and seen the same or the next working day
- All patients will get access to temporal artery ultrasound at this appointment
- Prompt treatment will be initiated in those with GCA

How to refer? Email: sharon.cowley@tuh.ie
or for urgent queries call: 0877120040

2.4.2 Ultrasound training and validation

In preparation for running the FTC ultrasound training was required. The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) Level 1 training programme for vascular ultrasound was followed. This required attending at least two half-day ultrasound clinics per week over a six-month period with approximately 4-6 examinations performed at each session under supervision, with maintenance of a record of scans. This practical training was performed in advance of

this research, at two clinical sites, with the supervision Dr Colm Kirby at TUH and Prof Grainne Murphy at CUH. After sufficient training over a six-month period, a validation exercise was subsequently performed at TUH with assessment by Prof David Kane. This consisted of performing three standard vascular ultrasound assessments of all branches of the temporal arteries and the axillary arteries in three different patients. An US report including details regarding the presence or absence of a halo sign, vessel compressibility, vessel blood flow/stenosis/occlusion, and measurement of the intima-media thickness (IMT) was completed for the temporal vessels. For the axillary vessels, the reports included comments on the appearance of the artery including the presence or absence of the halo sign and the slope sign, vessel blood flow/stenosis/occlusion, and measurement of the IMT. This was performed in a blinded fashion and compared against scans performed on the same patients by Dr Colm Kirby. Dr Colm Kirby had previously validated his temporal artery ultrasound (TAUS) technique along with TAB, the ACR classification criteria and MRI temporal artery, against temporal artery biopsy as the gold standard. In this validation, TAUS outperformed other diagnostic techniques with sensitivity of 86% and specificity of 82%. Our independent US results achieved 95% concurrence in IMT figures and validated my competence to perform the scans independently.

2.4.3 Ultrasound protocols

All vascular ultrasound scanning was performed on a GE Logiq P9 machine. Temporal arteries were assessed with a GE L8-18i hockey stick probe with a 5-9 MHz frequency range. The axillary vessels were assessed with an 18MHz transverse linear array probe.

All images observed were saved on the machine. Sonographic assessment of the full length of the superficial temporal artery and its branches including common, frontal, and parietal branches and both axillary arteries was performed in all patients. Each artery was interrogated in both longitudinal and transverse planes, with an assessment of vessel compressibility and blood flow.

B-mode settings for this study were adapted from the British Medical Ultrasound Society guidelines on vascular ultrasound scanning in GCA (R Brinley, 2021). For temporal artery scanning the frequency was $\geq 15\text{MHz}$, depth starting at 1-2cm, then adjusted for the patient habitus, gain was set at 35-45dB and adjusted so the halo appeared hypoechoic not anechoic, and focus was 0.5cm and then adjusted to the level of the artery. Doppler settings consisted of use of steer on the box at <60 degrees towards the flow, pulse repetition frequency (PRF) of 2-3.5kHz, frequency of 7-12.5MHz, and enough gain to fill the lumen without blooming.

The axillary artery settings in B-mode consisted of a frequency of 10-15MHz, depth of 3-4cm initially, then adjusted to the patient habitus, focus of 2cm, then adjusted to the artery and gain of 35-45dB so the halo is hypoechoic not anechoic. Regarding doppler settings for the axillary artery box steer was at <60 degrees towards the flow, PRF of 3-4kHz, and a frequency of 5-8MHz with enough gain to fill the lumen without blooming.

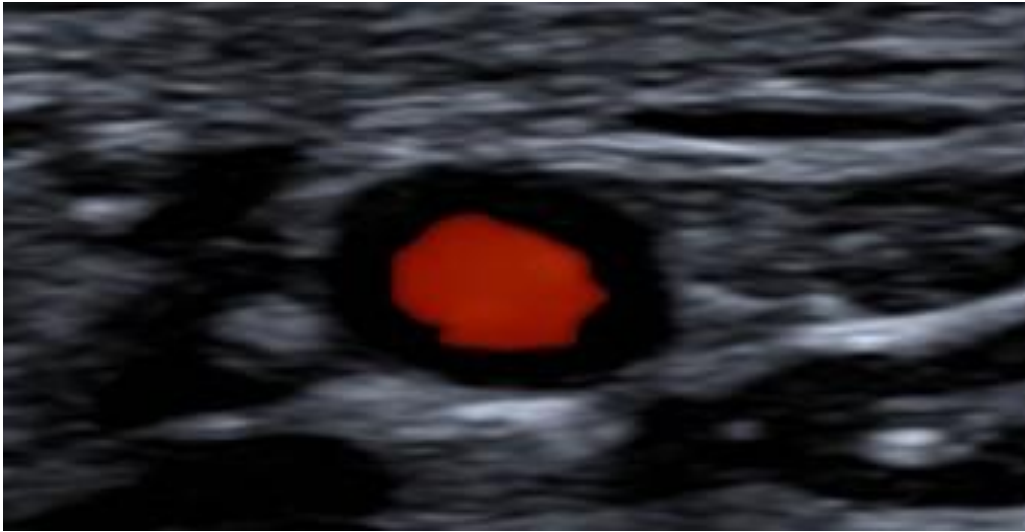
Abnormalities deemed to indicate the presence of vasculitis included the halo sign (see figure 2.2), compression sign (see figure 2.3), and abnormal IMT measurements above existing pre-determined thresholds (see table 2.1). The halo sign is a pathological

thickening of the intima media complex characterised by a hyperechoic rim around the artery lumen that contrasts with the hypoechoic surrounding tissue. The compression sign is a failure to obliterate the artery with downward pressure, or a lack of normal compression.

Axillary arteries were assessed for the slope sign. This is a newer US finding of the axillary artery vasculitis with a long thickened segment of inflamed arterial wall that slides down to a normal intima-media structure (Dasgupta et al., 2019). This is distinct from atherosclerotic deposits which tend to be more focal with a discrete raised portion on top of the intima-media complex.

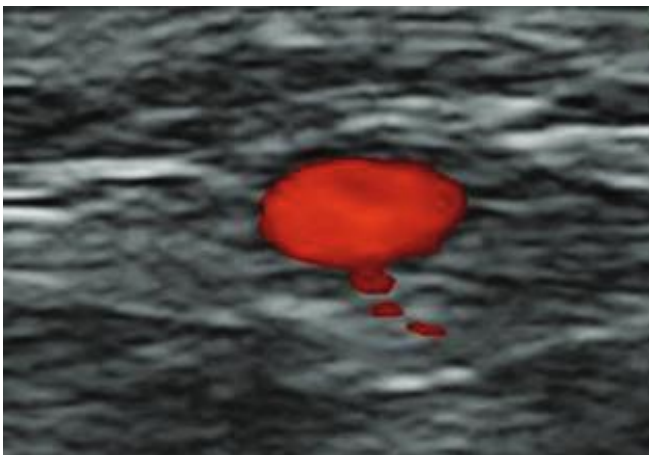
IMT measurements were deemed normal/abnormal by previously determined thresholds by Schäfer et al, which employed a case-control study design comparing GCA patients with patients who had other rheumatic diseases. Cut-off values were 0.42mm for the common temporal artery, 0.34mm for the frontal artery, 0.29mm for the parietal artery, and 1.0mm for the axillary artery (Schäfer et al., 2017). While these cut-offs have been reported to achieve 100% sensitivity and specificity for the common superficial temporal artery, frontal branch of the temporal artery, and the axillary artery and sensitivities and specificities of 97.2% and 87.5% respectively for the parietal artery, this study has noted there may have been 'spectrum bias' artificially inflating these cut-offs from the case-control design (Schäfer et al., 2017). All images were scored by the lead investigator. Images were also reviewed by a second expert ultrasonographer blinded to the clinical details of the case. In the case of a discordant diagnosis, a joint score was made by agreement.

Figure 2.2 Halo sign



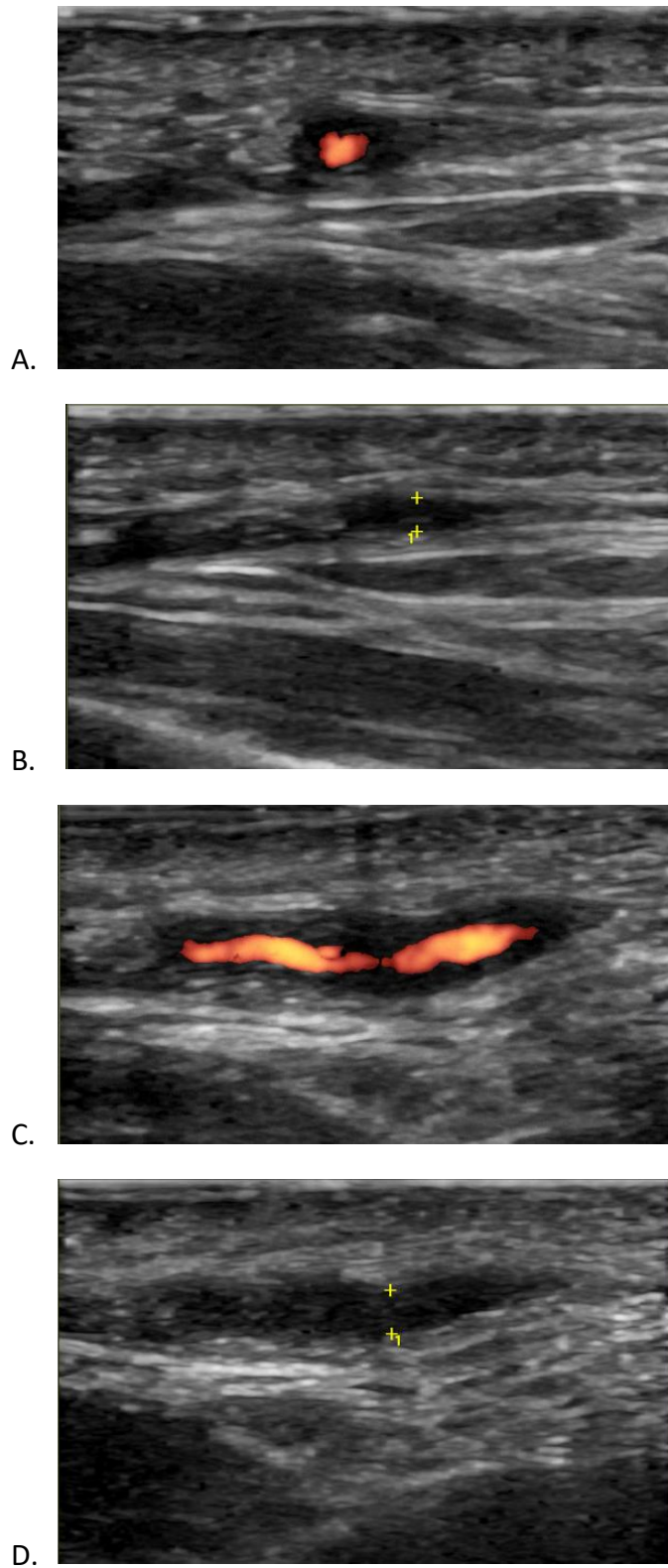
Legend: Transverse temporal artery frontal branch with halo sign (image from our Fast-track GCA clinic).

Figure 2.3 Normal temporal artery



Legend: Normal temporal artery ultrasound with doppler filling to the edge of the vessel wall (images from fast-track GCA clinic).

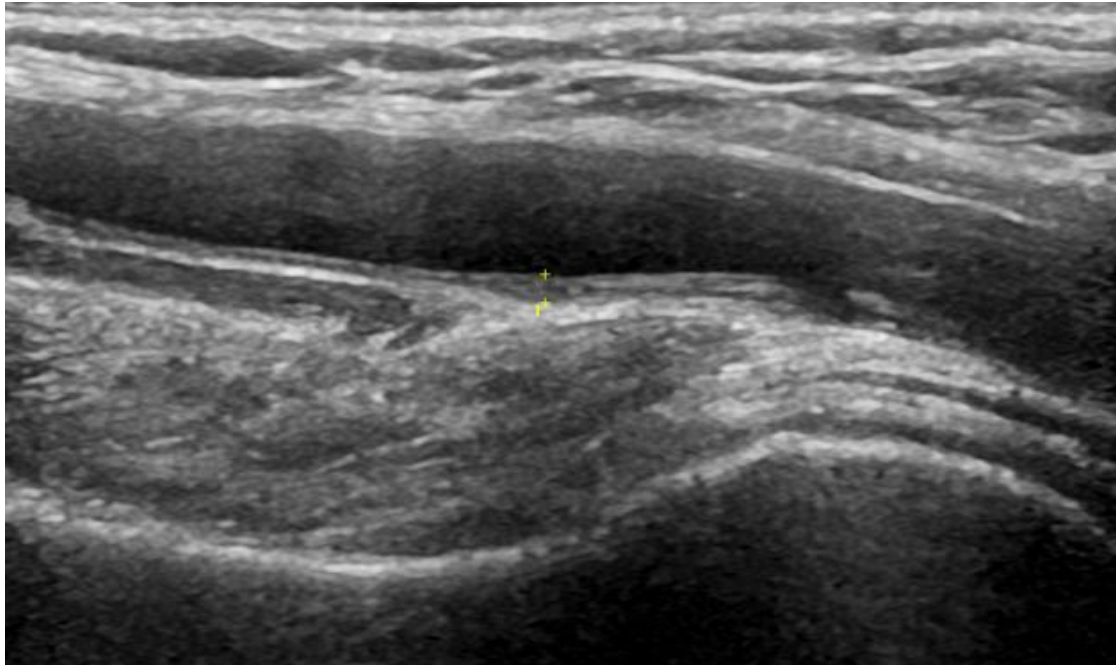
Figure 2.4 Abnormal compression sign



Legend: A: Transverse view of superficial temporal artery before compression; B: Transverse view with compression sign; C: Longitudinal view of superficial temporal

artery before compression; D: Longitudinal view of superficial temporal artery with compression sign (images from our Fast-track GCA clinic).

Figure 2.5 Slope sign



Legend: Axillary artery with slope sign, yellow crosses mark area of transition to abnormal thickness IMT branch (image from our Fast-track GCA clinic)

Table 2.1 Arterial Branch intima-media thickness thresholds for distinguishing a vasculitic artery from a normal artery.

Artery	IMT Cut-off (mm)	Sensitivity	Specificity
Common branch of superficial temporal artery	0.42	100%	100%
Frontal branch of superficial temporal artery	0.34	100%	100%
Parietal branch of superficial temporal branch	0.29	97.2%	98.7%
Axillary artery	1.0	100%	100%

(Schäfer et al., 2017)

2.4.4 Ethical approval

Full ethical approval was obtained from the Joint Research Ethics Committee for Tallaght University Hospital and St James Hospital, Dublin, Ireland (see appendix 3). All patients gave fully informed written consent to participate in the fast-track clinic study.

2.4.5 Statistical Analysis

Descriptive analysis of the data was performed using SPSS. Data were expressed as the mean $\pm$ standard deviation (SD) for normally distributed continuous variables, as median (interquartile range) for non-normally distributed variables, and as percentages and frequencies for categorical variables. Continuous variables were compared using the independent t-test. Categorical variables are summarised by frequency and percentage (%) and compared using the chi-square test or Fisher's exact test. P values <0.05 were considered statistically significant.

2.5 Results

2.5.1 Demographics

Between July 2022 and July 2023, a total of 84 patients were referred to the fast-track GCA clinic. 24 patients (28.6%) met a clinical diagnosis of new GCA with agreement by two rheumatologists, while 60 (71.4%) patients had an alternative diagnosis. This figure of about a quarter of cases referred to a GCA FTC resulting in GCA diagnosis is in keeping with other cohorts (Luther et al., 2020, Sebastian et al., 2020). Age was normally distributed in both GCA and non-GCA cohorts at the time of diagnosis. The mean age of those with a GCA diagnosis was 71.6 years [± 8.2], while those with a non-GCA diagnosis

were slightly younger with a mean age of 67.3 years [± 12.2]. There was no statistically significant difference in age between the GCA and non-GCA groups, $p=0.06$. The GCA group consisted of 13 males (54.2%) and 11 females (45.8%), while the non-GCA group consisted of 23 males (38.3%) and 37 females (61.7%). The GCA cohort had a mean BMI of 27.28 [± 5.76] with the average patient classified as overweight. The BMI breakdown was 0% underweight (BMI <18.5), 37% normal weight (BMI 18.5 to 24.9), 29% overweight (BMI 25 to 29.9), and 33% obese BMI (>30).

Table 2.2: Demographics of GCA and non-GCA patients

Variable	GCA (n = 24)	Non-GCA (n = 60)	P-value
Age (years)	M = 71.6, SD = 8.2, 95% CI [68.3, 74.9]	M = 67.3, SD = 12.2, 95% CI [64.2, 70.4]	.06
Male gender	54.2%, 95% CI [35.1%, 72.1%]	38.3%, 95% CI [27.1%, 50.9%]	.18
Female gender	45.8%, 95% CI [27.9%, 65.0%]	61.7%, 95% CI [49.0%, 72.9%]	.18
BMI < 18.4	0%, 95% CI [0.0%, 13.8%]	—	—
BMI 18.5–24.9	37%, 95% CI [21.2%, 57.3%]	—	—
BMI 25–29.9	29%, 95% CI [14.9%, 49.2%]	—	—
BMI > 30	33%, 95% CI [18.0%, 53.3%]	—	—

2.5.2 Estimating Irish Incidence of GCA

There are currently no published studies estimating the Irish incidence of GCA. It remains difficult to extrapolate incidence rates from other regions to apply to an Irish population. Genetically the Irish population >50 years is largely homogenous with Celtic

and Scandinavian origins, which is different to that of the United Kingdom and our other European neighbours. This study aimed to provide estimated incidence data.

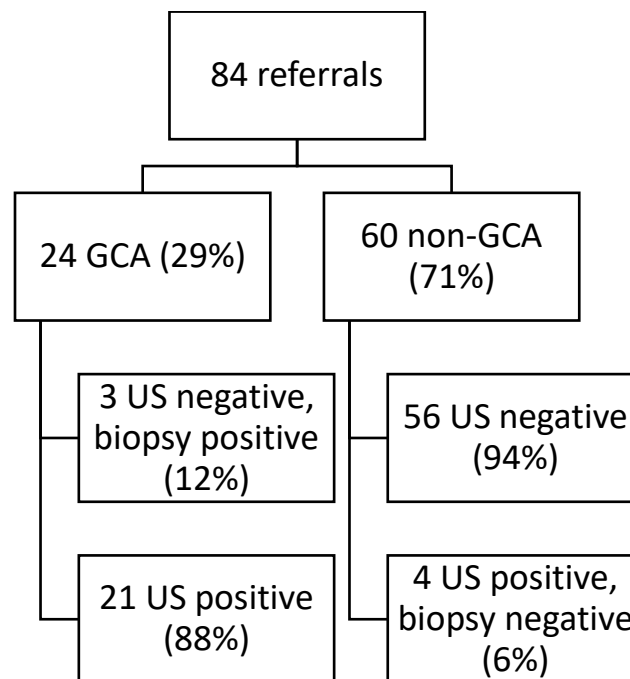
In the TUH catchment of 600,000 people, there were in total 21 cases of GCA diagnosed between July 2022- July 2023. 32.9% of the Irish population is over 50 years, according to the 2022 Irish census (CSO, 2023). With approximately 197,400 patients over the age of 50 in our catchment area, this gives an incidence of 10.6 new cases of GCA per 100,000 in those over 50 years. A recent meta-analysis has calculated the pooled European incidence at 7.26/100000 and the Scandinavian incidence of 21.57/100000 (Li et al., 2021) although it must be noted that this is in a population over 50 years. This data suggests that there is a higher incidence of GCA in Ireland than the European average. This is likely an underestimation as approximately 40% of patients in our catchment area have private health insurance and may have sought diagnosis and treatment in the private healthcare setting.

2.5.3 Non-GCA Diagnoses

60 patients (71.4%) had an alternative diagnosis to GCA. The commonest alternative diagnosis was migraine (10), followed by trigeminal neuralgia (8), sinusitis (7), and cervicogenic headache (6). There were several serious diagnoses including stroke/TIA (5), malignancy (4) with 2 lung cancers, one presenting with superior vena cava obstruction and the other with metastasis, 1 breast cancer with metastasis, and 1 prostate cancer with metastasis. Other diagnoses included obstructive sleep apnoea (3), lower respiratory tract infection with headache (3), cellulitis with headache (2), microvascular ischaemia with cranial nerve palsy (2), pre-syncopal episodes (2), multiple

sclerosis with visual symptoms (2), temporomandibular joint dysfunction (1), chronic daily headache (1), MRI overcall of GCA with no clinical features (1), facial shingles (1), viral labyrinthitis (1), and a head injury (1) (see table 2.3). A GCA FTC diagnosed not only GCA but a variety of other diagnoses; many with serious pathology. This prevented unnecessary glucocorticoid exposure and potential delayed diagnoses in these cases.

Figure 2.6 Flow diagram of referrals to GCA clinic



2.5.4 Temporal Artery Biopsy

3 patients in the GCA group had a negative baseline ultrasound in the setting of high clinical suspicion for GCA for which TAB confirmed the diagnosis of GCA.

1. The first patient presented with a new temporal headache and tenderness with no inflammatory markers checked before glucocorticoid was initiated in the

community. The patient had 4 days of 40mg prednisolone before review. ESR and CRP were normal at the time of FTC review, as was the vascular US. A clinical decision was made for TAB to be performed due to the lack of a better explanation for symptoms, previous diagnosis of PMR, and the potential masking effect of glucocorticoids on US and inflammatory markers.

2. The second patient with a negative US was referred from an ophthalmology hospital. This patient had new visual loss treated with intravenous pulsed glucocorticoid followed by high-dose oral glucocorticoid for two weeks. Both temporal artery ultrasound and TAB were positive before intravenous glucocorticoid, completed at the Royal Victoria Eye and Ear Hospital before referral to our FTC.
3. The third patient presented with right facial and jaw pain in the context of no new headache and highly elevated inflammatory markers. The patient was on high-dose oral glucocorticoids at 60mg for 7 days before FTC assessment. High clinical suspicion for GCA, lack of an alternative diagnosis, and concerns over glucocorticoid-induced resolution of US findings lead to TAB which was positive.

There were 4 patients with very low clinical suspicion of GCA who had a positive ultrasound. To exclude false positive results, which have been reported in previous studies, these patients were sent for TAB (Fernández-Fernández et al., 2020). All TABs were negative for GCA findings.

Table 2.3 Alternative diagnoses from the GCA fast-track clinic.

Alternative Diagnosis (Total 60)	Number (n)
Neurological (19)	
Migraine	10
Trigeminal Neuralgia	7
Multiple Sclerosis	2
Ischaemic (8)	
Stroke	3
Transient Ischaemic Attack (TIA)	2
Microvascular ischaemia with cranial nerve palsy	3
Infective (14)	
Sinusitis	7
LRTI	3
Cellulitis	2
Shingles	1
Viral labyrinthitis	1
Malignant (4)	
Lung cancer	2
Breast cancer	1
Prostate cancer	1
Degenerative (7)	
Cervical spine osteoarthritis/spondylosis	6
Temporomandibular joint dysfunction	1
Others (8)	
Obstructive sleep apnoea	3

Postural hypotensive episode	2
MRI overcall	1
Head injury	1
Chronic daily headache	1

2.5.5 Classification Criteria

The 1990 ACR GCA classification criteria (Hunder et al., 1990) and the newer 2022 ACR/EULAR GCA classification criteria (Ponte et al., 2022b) were calculated on all referrals (see tables 2.4 and 2.5). The 1990 criteria require 3/5 of the following criteria to be present to classify a patient with GCA: age ≥ 50 years, new headache, temporal artery abnormality including tenderness, reduced or absent pulse, elevated ESR $>50\text{mm/hr}$, and abnormal temporal artery biopsy. In comparison the updated 2022 criteria have included ultrasound features which were absent from the 1990 criteria and requires age ≥ 50 years as an absolute requirement for entry into the classification criteria. In studies in real life cohorts, it outperforms the 1990 criteria (Narváez et al., 2023, Molina-Collada et al., 2023). The components required to fill the 2002 criteria include a positive temporal artery biopsy or temporal artery halo sign on ultrasound (+5); erythrocyte sedimentation rate ≥ 50 mm/hour or C-reactive protein ≥ 10 mg/l (+3); sudden visual loss (+3); morning stiffness in shoulders or neck, jaw or tongue claudication, new temporal headache, scalp tenderness, temporal artery abnormality on vascular examination, bilateral axillary involvement on imaging, and fluorodeoxyglucose-positron emission tomography activity throughout the aorta (+2 each). A patient may be classified as having GCA with a cumulative score of ≥ 6 points (Ponte et al., 2022a).

In our GCA cohort, (20/24) 83% of patients fulfilled the 1990 criteria while 100% fulfilled the 2022 criteria. Regarding the non-GCA diagnosis, 15/60 (25%) met the 1990 criteria while 8/60 (13%) met the 2022 criteria. This accounted for a sensitivity and specificity of 83.3% and 75% respectively for the 1990 criteria, and 100% and 86.7% for the 2022 criteria. The superior performance of the 2022 criteria over the 1990 criteria replicated in our cohort is in keeping with the validation of the criteria and the results from real-world cohorts (Narváez et al., 2023, van Nieuwland et al., 2023). Our cohort exhibited a slightly higher sensitivity and specificity for both scores than reported in their validation studies.

Table 2.4 1990 ACR Classification Criteria for GCA

Feature	Points
Age $\geq$ 50 years	+1
New, localised headache	+1
Temporal artery tenderness or loss of pulsation	+1
ESR >50mm/h	+1
Vasculitis on biopsy, with granulomatous inflammation or mononuclear infiltration	+1

Legend: A score of $\geq$ 3 points is required to classify a patient with GCA

Table 2.5 2022 ACR/EULAR Classification Criteria for GCA

Absolute requirement: Age ≥ 50 years

Feature	Points
Morning stiffness in the shoulders/neck	+2
Sudden visual loss	+3
Jaw or tongue claudication	+2
New temporal headache	+2
Scalp tenderness	+2
Abnormal examination of the temporal artery	+2
Maximum ESR ≥ 50 mm/h or maximum CRP ≥ 10 mg/l	+3
Positive temporal artery biopsy or halo sign on temporal artery ultrasound	+5
Bilaterally axillary involvement	+2
FDG-PET activity throughout aorta	+2

Legend: These classification criteria should be applied to classify the patient as having giant cell arteritis when a diagnosis of medium-vessel or large-vessel vasculitis has been made. Alternative diagnoses mimicking vasculitis should be excluded prior to applying the criteria. A score of ≥ 6 points is required for the classification of GCA.

2.5.6 GCA Pre-test Probability Score

Screening of referrals is a crucial component of the GCA FTC. It is vital to have reliable screening of referrals so that urgent suspected GCA patients have access to the service promptly, and the service is not incapacitated with cases with a low level of suspicion for GCA. Unfortunately, in real-world practice, clinical presentations with GCA are diverse and may be characterised by a mix of cranial, ischaemic, constitutional, or

polymyalgia symptoms. Equally many non-GCA diagnoses may present with elevated inflammatory markers including malignancy, infection, trauma, and to a lesser degree ESR may be elevated in older age and obesity.

Recently, the Southend pre-test probability score (SPTPS) has been developed to aid GCA assessment. It is devised as a probability-based algorithm to guide diagnostic tests in suspected cases of GCA. The scoring system from 0-30 classifies patients into three distinct groups: low risk (<9), intermediate risk, (9-12), and high risk (>12) of having GCA. It is a composite score combining patient demographics, examination, symptoms, and laboratory markers with the reference standard being a diagnosis of GCA using US (see table 2.6). In the validation cohort, the overall prevalence of GCA was 25% (Sebastian et al., 2020). The prevalence of GCA in each of the three pre-test probability groups was 0% (low-risk group), 24% (intermediate-risk group), and 80% (high-risk group) (Sebastian et al., 2020).

In this study, we calculated the SPTPS in all patients referred to the FTC. For patients diagnosed with GCA 0% had a low-risk score, 8/24 (33%) had an intermediate-risk score, and 16/24 (67%) had a high-risk score. For the non-GCA diagnoses, 44/60 (73%) were classified as low-risk, 16/60 (27%) as intermediate-risk, and none as high-risk. This equates to a sensitivity of 100%, specificity of 73%, positive predictive value of 54%, and negative predictive value of 100% in this cohort, which is comparable to the validation study. It is important to note that information regarding the presence of infection, malignancy, systematic rheumatic disease, head/neck pathology or other diagnoses is needed to be provided by the referring clinician in order to stratify for ultrasound. In this study, this information was not always known at the time of referral which is important

for real-world clinical practice. Nonetheless, future implementation of this screening tool for our FTC referrals will enable a more efficient service. The Southend PTPS stratified referrals and excluded mimics, offering a reliable stratification of which patient required a temporal artery ultrasound (see table 2.7).

Table 2.6 Southend Pre-Test Probability Scoring System

	-3	0	1	2	3
Age		<50	50-60	61-65	>65
Gender			Male	Female	
Symptom duration (weeks)		>24	12-24	6-16	<6
CRP (mg/L)		0-5	6-10	11-25	>25
Headache		No	Yes		
PMR symptoms		No		Yes	
Constitutional symptoms		No	Single		>1
Ischaemic symptoms		No			Yes
AION/CRAO/Field loss/RAPD		No			Yes
Temporal artery abnormality		No	Tender	Thick	No pulse
Extracranial artery abnormality		No	Tender	Thick	No pulse
Cranial nerve palsy		No			Yes
Infection	Yes				
Cancer	Yes				

Systemic rheumatic disease	Yes				
Head/neck pathology	Yes				
Other diagnosis	Yes				

Legend: Low risk <9, Intermediate risk 9-12, High risk >12. AION: Anterior ischaemic optic neuropathy, CRAO: Central retinal artery occlusion, RAPD: Relative afferent pupillary defect

Table 2.7 Stratification of SPTPS for non-GCA diagnoses in our fast-track clinic

Alternative diagnosis	Number (n)
High risk (SPTPS >12)	
No cases	0
Total	0
Intermediate risk (SPTPS (9-12))	
Migraine	4
Trigeminal neuralgia	3
Stroke	2
Viral labyrinthitis	1
LRTI	1
Multiple sclerosis	1
Obstructive sleep apnoea	1
Cellulitis	1
Head injury	1
Lung cancer	1

Total	16
Low Risk (STPTS <9)	
Sinusitis	7
OA c-spine/ spondylosis	6
Migraine	6
Trigeminal neuralgia	4
Microvascular ischaemia with CN palsy	3
Postural hypotension	2
TIA	2
LRTI	2
Obstructive sleep apnoea	2
Multiple sclerosis	1
Cellulitis	1
Chronic daily headache	1
MRI overcall	1
Shingles	1
Breast cancer	1
Lung cancer	1
Prostate cancer	1
Stroke	1
Temporomandibular joint dysfunction	1
Total	44

2.5.7 Clinical characteristics

Regarding clinical presenting symptoms of GCA 20/24 (83%) presented with headache, 15/24 (62.5%) had temporal tenderness, 8/24 (33%) had blurred vision, 3/24 had visual loss, 8/24 had jaw claudication, 6/24 had shoulder PMR symptoms, 6/24 had hip PMR symptoms, 2/24 presented with fevers, 8/24 with night sweats, 12/24 with anorexia, 8/24 with weight loss, and 9/24 had temporal artery thickening, 1 with an absent temporal pulse and 1 patient presented with stroke (see table 2.8).

For the patients classified as non-GCA, their clinical presentation included 44/60 (73%) with headache, 11/60 (18%) with temporal tenderness, 12/60 (20%) with blurred vision, 6/60 (10%) with visual loss, 3/60 (with jaw claudication, 3 with shoulder PMR symptoms, 0 with hip PMR symptoms, 0 with fever or night sweats, 3/60 with anorexia, and 3/60 with weight loss. None had temporal artery thickening or absent temporal pulse.

Regarding clinical symptoms most associated with GCA in this cohort, no single clinical feature was a good differentiator between GCA and non-GCA diagnoses. Similarly, no single clinical feature was a good predictor of a positive temporal artery US. Previous studies with larger numbers of patients have shown jaw claudication, temporal artery thickening, and loss of temporal artery pulse to be the best predictors of an eventual diagnosis of GCA (Grossman et al., 2016, van der Geest et al., 2020c). Our cohort is likely underpowered with smaller numbers to reproduce these findings. While those larger

studies are interesting, no single symptom or physical sign is sufficient to completely rule in or exclude GCA.

Classification of the clinical spectrum of GCA-PMR disease identified our cohort consisted of 10/24 (41.6%) patients with a purely cranial GCA presentation, 5/24 (20.8%) with overlapping cranial and large vessel vasculitis (LVV) symptoms, 8/24 (33.3%) with GCA-PMR overlap, and 1/24 (4.2%) with LVV alone. This highlights diversity in the clinical presentation of GCA, which can further add to diagnostic difficulty.

GCA patients were symptomatic for a mean of 29.5 days [14-47.75] before assessment in the FTC. A third of patients were glucocorticoid naïve at the time of referral to the FTC (8/24). The median time between the onset of symptoms and the first GP visit was 14 days [5.5-32.5]. The median time from symptom onset to referral of steroid-naïve GCA patients was 20 days [10.5-32.5]. The mean time from symptom onset to glucocorticoid treatment was 19.3 [$\pm$ 17.1] days in patients presenting with pure cranial GCA, compared to 29.6 [$\pm$ 31.6] for all other presentations, $p=0.38$. Diagnostic delay still occurs despite offering a FTC for GCA diagnosis (see figure 2.7). Patients with purely cranial symptoms had a quicker time to glucocorticoid treatment than those other presentations of the GCA-PMR spectrum.

Table 2.8 Clinical features and inflammatory markers of GCA and non-GCA diagnoses

Clinical Feature	GCA (n=24)	Non-GCA (n=60)	p-value
Headache	83%, 95% CI [64.1%, 93.3%]	73%, 95% CI [61.0%, 82.9%]	.17
Temporal tenderness	62%, 95% CI [42.7%, 78.8%]	18%, 95% CI [10.6%, 29.9%]	.38
Temporal thickening	38%, 95% CI [21.2%, 57.3%]	0%, 95% CI [-0.0%, 6.0%]	—
Absent temporal pulse	4%, 95% CI [0.7%, 20.2%]	0%, 95% CI [-0.0%, 6.0%]	—
Blurred vision	33%, 95% CI [18.0%, 53.3%]	20%, 95% CI [11.8%, 31.8%]	.56
Loss of vision	12%, 95% CI [4.3%, 31.0%]	10%, 95% CI [4.7%, 20.1%]	.65
Jaw claudication	33%, 95% CI [18.0%, 53.3%]	5%, 95% CI [1.7%, 13.7%]	.66
Shoulder PMR	25%, 95% CI [12.0%, 44.9%]	5%, 95% CI [1.7%, 13.7%]	.40
Hip PMR	25%, 95% CI [12.0%, 44.9%]	0%, 95% CI [-0.0%, 6.0%]	.75
Fever	8%, 95% CI [2.3%, 25.8%]	0%, 95% CI [-0.0%, 6.0%]	—
Night sweats	33%, 95% CI [18.0%, 53.3%]	0%, 95% CI [-0.0%, 6.0%]	—
Anorexia	50%, 95% CI [31.4%, 68.6%]	5%, 95% CI [1.7%, 13.7%]	.50
Weight loss	33%, 95% CI [18.0%, 53.3%]	5%, 95% CI [1.7%, 13.7%]	.33
Stroke	4%, 95% CI [0.7%, 20.2%]	5%, 95% CI [1.7%, 13.7%]	.87
ESR (mm/h)	66.4, SD = 31.3, 95% CI [53.9, 78.9]	31.5, SD = 24.6, 95% CI [25.3, 37.7]	<.001
CRP (mg/L)	57.2, SD = 50.3, 95% CI [37.1, 77.3]	11.9, SD = 25.0, 95% CI [5.6, 18.2]	<.001

Figure 2.7 Time from symptom onset to GP visit and FTC referral

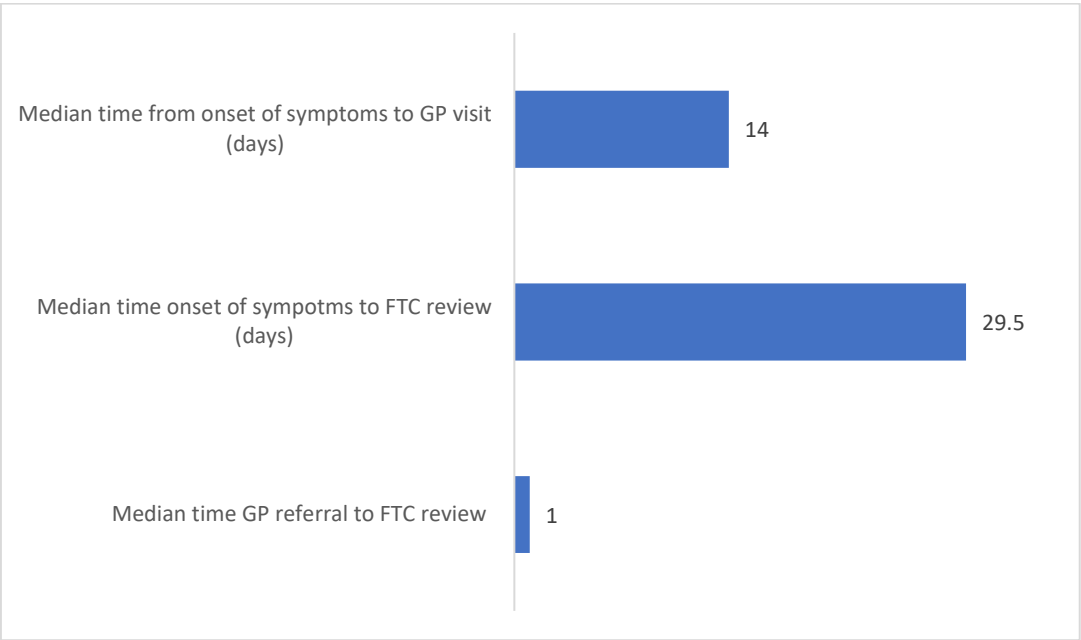
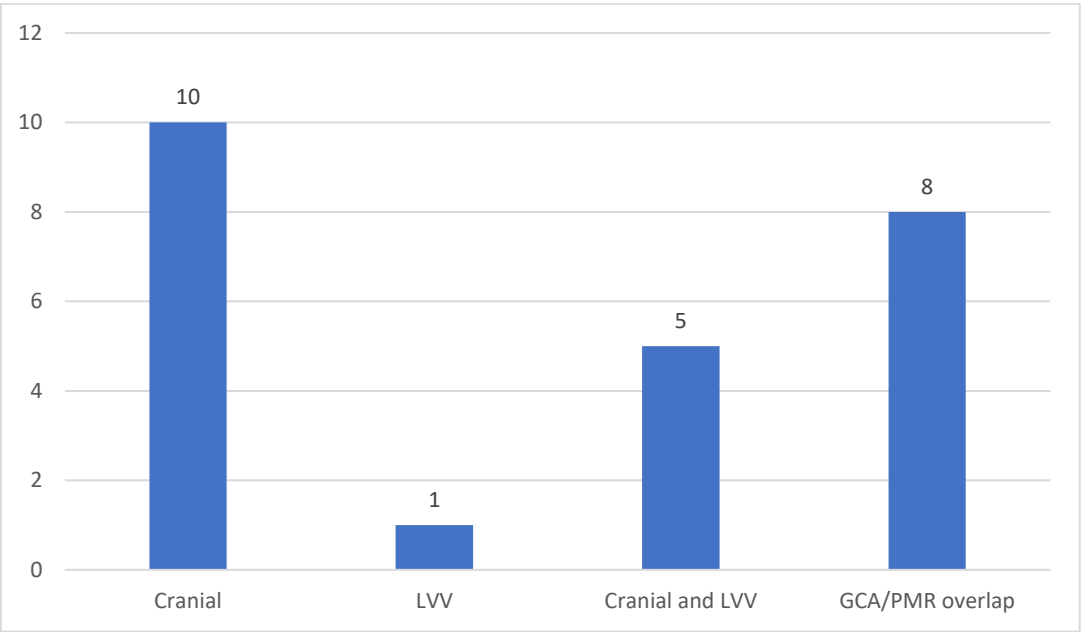


Figure 2.8 Clinical spectrum of disease



2.5.8 Laboratory characteristics

2.5.8.1. Inflammatory markers

Both ESR and CRP helped discriminate GCA from non-GCA diagnoses in this cohort with higher ESR associated with GCA diagnosis. The median baseline ESR in patients with GCA was 64 mm/h [51-83.5] compared to 25.5mm/hr [13-48] in those with an alternative diagnosis to GCA, $p<0.001$. 19/24 (79%) of patients with GCA had an initial ESR ≥ 50 mm/h, rising to 96% of steroid naïve cases at presentation. This compares with only 22% of non-GCA diagnoses having an ESR ≥ 50 mm/h at baseline. ROC analysis produced an AUC of 0.81 (see figure 2.9) and a cut off ESR of 51.5mm/h gave a sensitivity of 75% and specificity of 80% for GCA. Median baseline CRP levels in GCA patients were 55.5mg/l [11.5-93] compared with 4.5 mg/l [1-12] in those with non-GCA diagnoses, $p<0.001$. ROC analysis gave an AUC of 0.849. A cut-off of 18.5mg/l gave a sensitivity of 71% and specificity of 85% for GCA. These cut-offs are comparable with a previously published study which determined the estimated optimal cut-off levels were confirmed at 50 mm/hour for ESR, and 20 mg/L for CRP (Chan et al., 2019).

Figure 2.9 ROC curve of ESR in GCA and Non-GCA diagnoses

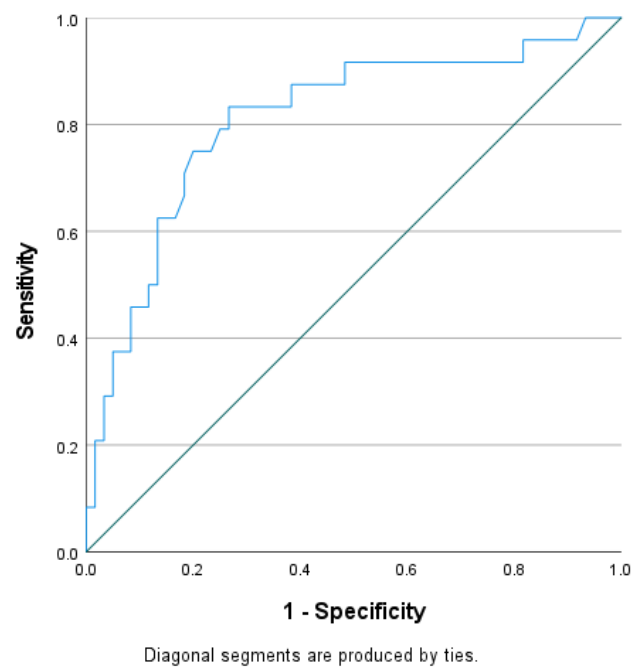
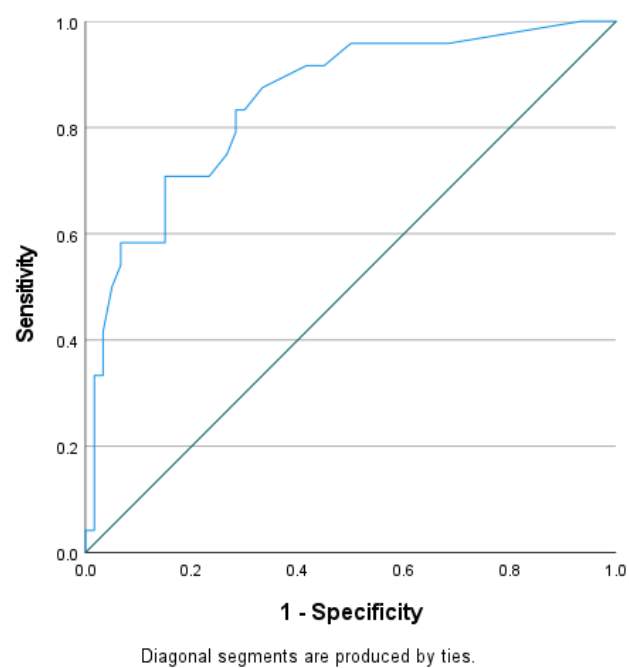


Figure 2.10 ROC curve of CRP in GCA and non-GCA diagnoses



2.5.8.2 Haematological markers

Haematological markers which helped differentiate GCA from non-GCA diagnoses included absolute neutrophil count, neutrophil: lymphocyte ratio, and platelet count. The mean absolute neutrophil count for GCA patients at baseline was $9.03 \times 10^9/\text{l}$ [± 3.66], compared with $6.28 \times 10^9/\text{l}$ [± 1.16] in non-GCA diagnoses, $p < 0.001$. When adjusted for glucocorticoid exposure before FTC assessment, this was still significant with a glucocorticoid-naïve mean absolute neutrophil count of $8.05 \times 10^9/\text{l}$ [± 3.03], $p < 0.001$. The neutrophil: lymphocyte ratio was also helpful in differentiating GCA from non-GCA, with ratios of 6.34 and 3.62 respectively, $p < 0.001$. Finally, platelet count was significantly different between GCA and non-GCA diagnoses at baseline, reflecting its elevation in states of inflammation. The mean baseline platelet count in GCA patients was $402.18 \times 10^9/\text{l}$ [± 222.6] compared with a count of $173.41 \times 10^9/\text{l}$ [± 85.7] for non-GCA diagnoses, $p < 0.001$.

Table 2.9 Haematological markers in GCA and non-GCA diagnosis

Laboratory Parameter	GCA (n=24)	Non-GCA (n=60)	p-value
Hemoglobin (g/dL)	12.69, SD = 1.29, 95% CI [12.16, 13.22]	13.11, SD = 1.71, 95% CI [12.67, 13.55]	.28
Neutrophils ($\times 10^9/\text{L}$)	9.03, SD = 3.66, 95% CI [7.47, 10.59]	6.28, SD = 1.16, 95% CI [6.03, 6.53]	<.001
Lymphocytes ($\times 10^9/\text{L}$)	1.92, SD = 1.05, 95% CI [1.48, 2.36]	2.08, SD = 1.16, 95% CI [1.83, 2.33]	.55

Neutrophil: Lymphocyte ratio	6.34	3.62	<.001
Monocytes ($\times 10^9/L$)	0.68, SD = 0.28, 95% CI [0.56, 0.80]	0.70, SD = 0.23, 95% CI [0.64, 0.76]	.73
Platelets ($\times 10^9/L$)	402.18, SD = 222.6, 95% CI [309.0, 495.3]	173.41, SD = 85.7, 95% CI [151.5, 195.3]	<.001

2.5.8.3 Biochemical markers

Biochemical parameters were not a good discriminator between GCA and non-GCA diagnoses. There were statistical differences between the estimated glomerular filtration rate (eGFR) and corrected calcium between GCA and non-GCA groups, with higher eGFR and lower corrected calcium in the GCA group (see table 2.10). This result is of unclear significance.

Table 2.10 Biochemical markers in GCA and non-GCA diagnosis

Biochemical Parameter	GCA (n=24)	Non-GCA (n=60)	p-value
Creatinine (45–104 mmol/L)	78.5, SD = 22.2, 95% CI [69.6, 87.4]	96.19, SD = 44.07, 95% CI [85.0, 107.3]	.06
eGFR (66–143 mL/min)	74.95, SD = 13.22, 95% CI [69.7, 80.2]	65.83, SD = 20.36, 95% CI [60.7, 71.0]	.04

Sodium (136–145 mmol/L)	137.95, SD = 2.87, 95% CI [136.8, 139.1]	138.41, SD = 3.58, 95% CI [137.5, 139.3]	.57
Potassium (3.5–5.3 mmol/L)	4.18, SD = 0.42, 95% CI [4.0, 4.3]	4.16, SD = 0.37, 95% CI [4.1, 4.3]	.83
Corrected Calcium (2.15–2.50 mmol/L)	2.41, SD = 0.12, 95% CI [2.4, 2.5]	3.89, SD = 0.37, 95% CI [3.8, 4.0]	<.001
Alkaline phosphatase (40–129 U/L)	90.05, SD = 33.93, 95% CI [76.5, 103.6]	85.02, SD = 38.4, 95% CI [75.3, 94.7]	.53
GGT (10–71 IU/L)	39.45, SD = 43.21, 95% CI [22.2, 56.7]	47.31, SD = 54.52, 95% CI [33.5, 61.1]	.38
ALT (0–41 IU/L)	19.05, SD = 8.93, 95% CI [15.5, 22.6]	22.06, SD = 12.38, 95% CI [18.9, 25.2]	.28

2.5.9 Treatment of GCA

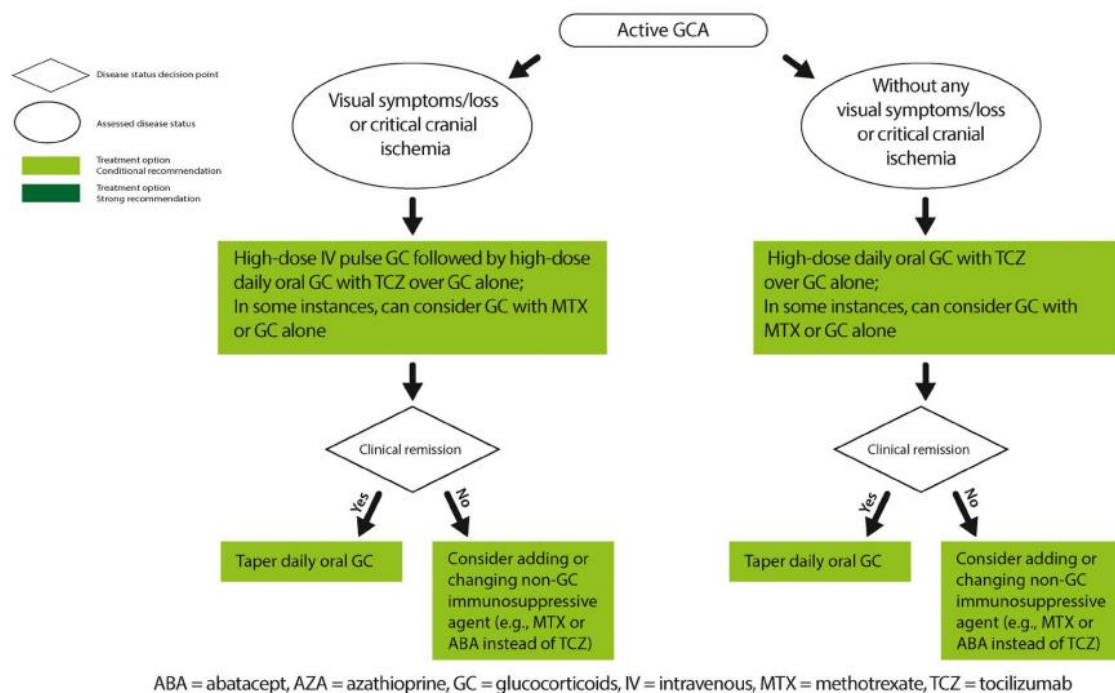
Patients with GCA were treated following the 2021 American College of Rheumatology / Vasculitis Foundation (ACR/VF) guidelines. This recommends high-dose intravenous pulsed glucocorticoids for those with visual symptom/loss or critical cranial ischaemia followed by a high-dose oral daily glucocorticoid taper and tocilizumab. For those without visual symptoms/loss or critical cranial ischaemia a high dose oral glucocorticoid taper plus tocilizumab is the recommended starting protocol.

3 patients had high-dose pulsed methylprednisolone in this cohort due to visual loss followed by a 60mg prednisolone taper. The other 21 patients were commenced on 40–60mg of oral prednisolone taper. The mean oral glucocorticoid starting dose was 51.9mg [± 11.67]. 20/24 patients, (80%) were initiated on tocilizumab within one month of diagnosis. 4/24 (12.5%) were not; 2 for previous severe diverticulitis requiring hospitalisation, and 1 that declined due to personal preference after requiring intensive

care admission for severe toxic epidermal necrolysis (TENS) secondary to bisphosphonate initiated for bone protection, and 1 patient who developed a haematological malignancy and could not attend follow up due to a lengthy admission in another hospital including chemotherapy and bone marrow transplant. All patients were commenced on a bisphosphonate for bone protection at the outset. For the patient who developed TENS this was stopped, and denosumab was then commenced. All patients had proton pump inhibitor cover for gastric ulcer prophylaxis.

Glucocorticoid taper was performed in all patients, aiming for a target dose of 15-20mg within 2-3 months, to be entirely tapered by 26 weeks for those receiving tocilizumab plus glucocorticoid and by 52 weeks for those on glucocorticoid monotherapy in a manner emulating the GiACTA trial (Stone et al., 2017a). Total glucocorticoid exposure was 1470mg [± 384.88] at 1-month 2603.14mg [± 440.84] at 3 months, 3235.74mg [± 869.15] at 6 months, and 3844.31mg [± 1420.89] at 12 months. 21/24 patients reached the 12-month follow-up assessment (2 passed away and 1 discontinued follow-up due to a lengthy admission for treatment of haematological malignancy in another hospital). 16/21 (76%) were in glucocorticoid-free remission at 12 months of treatment.

Figure 2.11 ACR/VF GCA treatment algorithm



(Maz et al., 2021)

2.5.10 Adverse events

GCA patients suffered a high rate of adverse events in the first 12 months of treatment. 8/24 (33%) required hospital admission for infections or complications. Hospitalisations included 1 for pulmonary embolism, 1 with ICU admission for TENS, 1 lower respiratory tract infection (LRTI), 2 hospitalisations for cellulitis, 1 for cholecystitis, and 2 for workup of a new malignancy (1 lung cancer and 1 leukaemia). A further 4 cases did not require hospitalisation but were treated in the community for infection including 2 cases of herpes zoster, 1 case of herpes ophthalmicus, and 1 for a LRTI. In total 11/24 (41.6%) patients suffered 12 adverse events.

Glucocorticoids and tocilizumab exerted an interesting effect on glycaemic control in this cohort. The mean baseline Hba1c for all patients was 46.36mmol/mol [± 15.18], increasing to 51.47 mmol/mol [± 19.88] at 1 month, then reducing to 43.05 mmol/mol [± 11.6] at 6 months, and 40.93 mmol/mol [± 10.3] at 12 months. While the 5 patients with diabetes mellitus at the outset had their diabetes treatment escalated after elevations in the first month, we observed a reduction in hba1c with tocilizumab treatment in pre-diabetic patients despite significant doses of glucocorticoid treatment, $p=0.005$ (see table 2.11). IL-6 receptor blockage has been previously shown to exert a rapid beneficial effect on insulin resistance and insulin sensitivity in non-diabetic rheumatoid arthritis patients (Castañeda et al., 2019).

Table 2.11 Changes in Hba1c with glucocorticoid and tocilizumab treatment

Group	Baseline HbA1c (mmol/mol)	12-month HbA1c (mmol/mol)	p-value
Diabetes	71, SD = 15.37, 95% CI [57.5, 84.5]	63.3, SD = 12.82, 95% CI [52.1, 74.5]	.51
Pre-diabetes	44, SD = 1.63, 95% CI [42.4, 45.6]	39.3, SD = 0.58, 95% CI [38.7, 39.9]	.005
Non-diabetic	38.25, SD = 2.59, 95% CI [36.9, 39.6]	38, SD = 2.12, 95% CI [36.9, 39.1]	.82

Table 2.12 Adverse events in GCA

Adverse Events (12)	Number (n)	Hospitalisations (n)
Infectious		
Herpes Zoster	2	0
Herpes Ophthalmicus	1	0
LRTI	2	1
Cellulitis	2	2
Cholecystitis	1	1
Non-infectious		
Pulmonary Embolism	1	1
Lung cancer	1	1
TENS	1	1
Leukaemia	1	1
Total	12	8

2.5.11 Relapse of GCA in the first 12 months

In total 4/24 (16.7%) patients suffered a relapse of GCA in the first 12 months of treatment. Relapses were defined by definitions in the 2018 Update to the EULAR recommendations for the treatment of large vessel vasculitis (Hellmich et al., 2020c). Major relapse was defined as a recurrence of active disease with either clinical features of ischaemia (including jaw claudication, visual symptoms, visual loss attributable to

GCA, scalp necrosis, stroke, and/or limb claudication) or evidence of active aortic inflammation resulting in progressive aortic or large vessel dilatation, stenosis, or dissection. Minor relapse was defined as the recurrence of active disease, not fulfilling the criteria for a major relapse. This cohort included 2 major relapses, and 2 minor relapses (see table 2.13).

The median time to relapse was 6.5 months [3-11]. Both patients with minor relapses (one with PMR symptoms and one with return of headache without ischaemia) were on glucocorticoid treatment alone at time of relapse. These patients were treated with escalation of glucocorticoid doses and the introduction of ustekinumab (anti-IL12/23) for one and secukinumab (anti-IL-17) in the second. Conventional disease-modifying agents were not utilized due to patients' comorbidities and wishes.

There were some useful trends in laboratory markers comparing remission and relapse. Our cohort had small numbers (n=4) of patients who relapsed in the first year, which restricted this analysis. 50% of patients who relapsed were on tocilizumab treatment which blunted the inflammatory response and seriously impacted the analysis. We did observe a numerical elevation in ESR, CRP, fibrinogen, absolute neutrophil count, and neutrophil: lymphocyte ratio in GCA relapse, but these were not statistically significant (see table 2.14).

Table 2.13 Relapse in GCA

Relapse	Baseline disease characterisation	Timepoint (months)	Major/Minor relapse	Treatment at the time of relapse
Patient 1	Cranial + PMR	6	Minor	15mg prednisolone
Patient 2	Cranial	6	Minor	9mg prednisolone
Patient 3	Cranial	7	Major	Tocilizumab weekly plus 6mg prednisolone
Patient 4	Cranial + LVV	11	Major	Tocilizumab weekly

Table 2.14 Laboratory markers in GCA relapse

Laboratory Parameter	Pre-relapse (n=4)	In-relapse (n=4)	p
Mean ESR (mm/h)	13.75, SD = 15.56, 95% CI [-1.5, 29.0]	22.5, SD = 19.05, 95% CI [3.8, 41.2]	.5
Mean CRP (mg/l)	4.25, SD = 5.85, 95% CI [-1.5, 10.0]	19.75, SD = 23.9, 95% CI [-3.7, 43.2]	.25
Mean Fibrinogen (g/l)	3.03, SD = 1.2, 95% CI [1.9, 4.2]	3.75, SD = 1.59, 95% CI [2.2, 5.3]	.49
Monocytes ($\times 10^9/l$)	0.77, SD = 0.27, 95% CI [0.5, 1.0]	0.7, SD = 0.25, 95% CI [0.5, 0.9]	.71
Neutrophils ($\times 10^9/l$)	6.97, SD = 4.42, 95% CI [2.6, 11.3]	8.4, SD = 4.92, 95% CI [3.6, 13.2]	.68
N: L Ratio ($\times 10^9/l$)	2.7, SD = 1.89, 95% CI [0.8, 4.6]	4.5, SD = 3.35, 95% CI [1.2, 7.8]	.38

2.6 Discussion

This study showed that despite offering a GCA FTC equipped to see patients within one working day, there was still a significant time interval between onset of GCA symptoms and assessment in the FTC. There was a median of 14 days from symptom onset to GP review, possibly indicative of waiting time to access a GP appointment. Further delays occurred from GP review to FTC referral reaching our clinic, resulting in 29.5 days from symptom onset to FTC review, possibly reflective of failure of treatment of other causes of headache or delays in the turnaround of bloodwork in the community. Appointments in the FTC occurred within a median of 1 day after the GP referral. Similar lengthy time intervals between symptom onset and FTC review have been identified in other studies (van Nieuwland et al., 2024). This suggests it may be useful to have regular GP communication reminders on the fast-track pathway for GCA and to advocate for improved GP turnaround of ESR and CRP blood tests.

We identified that clinical features alone are a poor differentiator of GCA from non-GCA diagnoses. Several mimics may present with a similar clinical presentation including cancers, other rheumatological and neurological conditions. ESR and CRP are much more useful markers, particularly if very elevated. In this study, we identified that all our steroid naïve GCA cases had an ESR ≥ 50 mm/h at baseline. ROC analysis showed high sensitivity and specificity for a diagnosis of GCA with cut-offs of 18.5mg/L for CRP and 51.5mm/h.

This study has shown that the SPTPS is an excellent stratification tool for GCA FTC referrals into low-risk, intermediate risk, and high-risk of a GCA diagnosis. It achieved a sensitivity of 100%, specificity of 73%, positive predictive value of 54%, and negative predictive value of 100% in this cohort, which is comparable to the validation study. It outperformed both the 1990 and 2022 GCA classification criteria, highlighting the known limitations of relying on these criteria to be met to accept patients for FTC referral. If we had adopted the SPTPS as a screening tool to decide which patients with GP suspected GCA warranted evaluation with temporal artery ultrasound we would have eliminated the need to see 44/80 patients with a stratified low risk of GCA, which would have reduced our overall workload in the GCA FTC by over 50%. The SPTPS is an extremely useful tool in real-world practice, particularly when resources are limited.

The protocol followed in this study for vascular ultrasound training with performance of over 200 scans and objective validation of technique will allow this training schedule to be replicated in other centres hoping to establish an FTC. My predecessor Dr Colm Kirby followed the same training protocol and validated it against temporal artery biopsy. My successor will also follow this protocol enabling a seamless transition of GCA FTC care at TUH. We hope to provide this as a template to other Irish rheumatology centres to be replicated and facilitate growing a GCA FTC service on a national level. There are plans for a national GCA FTC study day to educate colleagues in other Irish centres in December 2024.

This study highlighted the multitude of alternative non-GCA diagnoses referred to the GCA FTC. The high negative predictive value of the SPTPS suggests it is particularly helpful in ruling out GCA. If we had implemented the SPTPS as a screening tool, this would have eliminated 73% of the non-GCA referrals. This may also allow for faster assessment of cases with higher suspicion of GCA. This approach would also be more cost-effective. Ongoing studies externally validating this score in larger cohorts will validate this further and guide adaptation as a standard screening tool for GCA FTCs. Non-GCA diagnoses were referred back to primary care for expectant management should any new features of GCA develop. This approach worked well as treatment of non-GCA diagnosis would have been beyond the scope of this clinic. It also would have taken valuable resources of time and manpower away from new referrals with suspected GCA.

There was a significant number of adverse events in this GCA cohort at 41%, with 33% of patients requiring hospitalisation. Despite careful clinical management and regular follow-up at 1-, 3-, 6-, and 12-month intervals, as well as ad-hoc reviews in the event of a relapse, patients still had a complicated treatment course. Similarly, despite 80% of patients being initiated on glucocorticoid plus tocilizumab from diagnosis, relapses still occurred. This is a sick population where adverse events and relapsing disease occur despite optimal clinical management. We advocate for regular follow-up and patient access to ad hoc review slots in the event of relapse which should be factored into service provision.

In summary, we have established a GCA FTC protocol for vascular US training and validation, and successfully implemented a FTC clinical service. This study adds to the literature on FTCs and highlights their critical role in the provision of high-quality care for the GCA patient. We have also contributed towards externally validating the SPTPS, adding to other real-world validation studies by Scottish (Melville et al., 2022) and Australian (Mathake et al., 2022) colleagues. Use of this probability score would have made the clinic much more efficient and significantly reduced the workload associated with reviewing low-risk GCA referrals. Also presented is the very high rate of complications in GCA patients, even when glucocorticoid-sparing biological agents are prescribed, highlighting the necessity for close follow-up of these patients. With this validated protocol, we have further implemented it in a novel fast-track polymyalgia rheumatica clinic (described in detail in chapter 3).

Chapter 3:

The Irish Fast-track PMR Clinic

Experience.

3.1 Abstract

Introduction

PMR is treated predominantly in the community, but patients frequently relapse and have lengthy waiting times on the general rheumatology outpatient waiting list. There is currently no capability for community monitoring of emerging GCA in this patient group. Patients also have significant steroid morbidity and significant variation in their steroid doses. We aimed to establish the first Irish or UK-based PMR fast-track clinic. A streamlined clinic will ensure all patients have the correct diagnosis, get the correct steroid dose, are evaluated for subclinical GCA, and have closer follow-up than in current practice.

Methods

Primary care physicians were invited to refer patients with newly suspected PMR to the first Irish fast-track clinic. Referral criteria included new onset shoulder and/or pelvic girdle pain with stiffness. All patients were seen within 72 hours of referral. Patients with a rheumatology diagnosis of PMR had an ultrasound (US) of both their temporal and axillary arteries, and a subset of patients had a bilateral shoulder US.

Results

157 patients were referred from primary care over 12 months. 40% of patients referred with suspected PMR had an alternative diagnosis for which PMR regimen glucocorticoid treatment was inappropriate, many with serious inflammatory rheumatic or malignant disease. Only 20% of patients referred from primary care and started on glucocorticoids were commenced on bone protection. PMR patients were co-morbid with a mean of 2.5 other conditions. 75% of PMR patients experienced a glucocorticoid-related adverse event in the first 12 months of treatment. 20% of patients with new PMR had ultrasound features of subclinical giant cell arteritis.

Conclusion

A fast-track PMR clinic is feasible when a dedicated clinician has funding and sufficient clinical space to provide this service. There is a clinical need for such a clinic being part of mainstream rheumatology services as almost 40% of patients with a General Practitioner (GP) diagnosis of PMR had an alternative diagnosis, many being serious alternative inflammatory diseases requiring specialist management. Treatment of PMR in the community before referral to the clinic was varied and, in many cases, involved opiates and non-steroidal anti-inflammatories (NSAIDs), both of which are not ideal in an elderly population. The commencement of glucocorticoid therapy should be deferred until after specialist evaluation to enable an accurate clinical diagnosis. A delay in treatment can only realistically be avoided if GPs have access to a Fast-track PMR clinic. We believe that rheumatologists should consider establishing fast-track PMR clinics and this study provides a strong case for and a template to support this practice innovation.

3.2 Introduction

Fast-track clinics have been implemented for over 20 years with notable success in rheumatology for early inflammatory arthritis (Gärtner et al., 2012) with substantially better patient pain outcomes. The fast-track clinic model has since been replicated for GCA and has achieved an 88% reduction in permanent visual impairment compared to standard care (Diamantopoulos et al., 2016).

Accurate diagnosis and treatment of PMR is crucial to prevent long-term glucocorticoid-related complications and improve patient outcomes. Some studies have reported that up to 30% of patients referred for PMR assessment are initially misdiagnosed (Nielsen et al., 2023a) which may result in unnecessary long-term glucocorticoid treatment. To date, there is no standardised fast-track approach to PMR diagnosis, with the majority of PMR patients still being diagnosed and treated in the community in a heterogeneous manner. The often-non-specific presenting symptoms of PMR, and the lack of diagnostic criteria or a definitive test, mean this condition poses a significant challenge for primary care.

The lengthy waiting list for general rheumatology referrals to assess difficult-to-treat PMR or those with complex disease also contributes to problems in management. It has resulted in only a minority of cases of PMR currently being referred for specialist evaluation, with one study reporting 50% of patients already being on glucocorticoids before rheumatologist review (Donskov et al., 2023). Over the past decade, there has been increased awareness of the diagnostic challenge that PMR presents, and of the potential morbidity and disability associated with both the disease, and the immunosuppression required for its management. In 2010, the British Society of

Rheumatology recommendations for the management of PMR advised specialist review of PMR patients in certain instances such as those with atypical presentations and treatment-resistant disease/ glucocorticoid contraindications (Dasgupta et al., 2010). In 2023, an international task force also recognised this service failure and developed international consensus-based recommendations for early referral of individuals with suspected PMR. They advised that all patients with suspected or recently diagnosed PMR should be considered for specialist evaluation (Keller et al., 2023b). The task force also concluded primary care physicians should undertake a thorough history and clinical examination with basic laboratory investigations for patients with suspected PMR, and for those with severe symptoms to be seen by rheumatology in rapid access clinics, preferably with deferral of glucocorticoid therapy. For those patients with an initial good response to glucocorticoids and a low risk of adverse events, they deemed it reasonable to manage those cases in primary care.

Our objectives in establishing a fast-track PMR clinic were:

1. To examine the feasibility of establishing a novel fast-track PMR clinic.
2. To define both patient and disease characteristics in newly diagnosed PMR.
3. To define the alternative diagnoses in patients referred with suspected PMR.
4. To examine the clinical impact of a fast-track PMR clinic.
5. To establish the rate of treatment-related adverse events in an Irish PMR cohort.
6. To establish the rate of relapse in an Irish PMR cohort over the first 12 months of PMR treatment.
7. To inform future planning of rheumatology services.

3.3 Methods

3.3.1 Design and study population

This study was a multicentre prospective longitudinal cohort study. It was conducted at the departments of Rheumatology at both Tallaght University Hospital (TUH), Dublin and St James Hospital (SJH), Dublin. Initially, a planning meeting was held between the primary investigators at each site (Dr Sharon Cowley and Professor David Kane at TUH and Dr Patricia Harkins and Professor Richard Conway at SJH). Dr Sharon Cowley and Dr Patricia Harkins attended both sites to see and assess new suspected PMR patients with oversight from Professor Kane at TUH and Professor Conway at SJH. Primary care physicians in our catchment area with a population of 600,000 were invited to refer patients over 50 years with suspicion of new PMR to our fast-track clinic. Engagement with primary care included attending local GP meetings to promote the new service and sending an email-based flyer to GPs in the catchment area to capture those not at the meeting (see figure 3.1). Referral criteria included new onset bilateral shoulder or pelvic girdle pain and/or elevated inflammatory markers and/or early morning stiffness. Primary care physicians were advised that patients should ideally be steroid naïve, or at least on steroid therapy for less than 4 weeks. Referrals were accepted via email to a dedicated PMR clinic address, along with the patient's history, laboratory results, and contact details. The patients were contacted by telephone on the same working day with an appointment time arranged within 72 hours.

Figure 3.1 Fast track PMR clinic flyer distributed to primary care.



Fast-track PMR Clinic

Key messages

- 20% of newly diagnosed PMR patients have been reported to have underlying GCA on temporal ultrasound artery scanning.
- We are now taking PMR patient referrals to determine the prevalence of GCA in Irish patients with PMR.
- Untreated GCA can lead to complications such as blindness and stroke.

Who to refer:

Polymyalgia Rheumatica:

Patients **aged >50 years** with **new onset bilateral shoulder and/or hip pain** and **elevated inflammatory markers**.

Ideally patients should be steroid naive.

How to refer:

- o Email: sharon.cowley@tuh.ie with referral details.
- o Review within 48 hours from referral, Monday to Friday.

3.3.2 The Fast-track Clinic Development.

Inclusion criteria included:

1. Patients with new onset bilateral shoulder pain and/or hip pain and/or stiffness.
2. Patients over 50 years of age.
3. Patients on glucocorticoid treatment for < 4 weeks duration.

Exclusion criteria included:

1. Patients <50 years.
2. Patients on glucocorticoid treatment >4 weeks duration.
3. Patients on synthetic or biological disease-modifying treatment for any reason.
4. Patients with a diagnosis of another inflammatory rheumatic condition.
5. Patients who lacked the capacity to consent or refused to consent to treatment in the clinic.

All patients referred underwent a thorough history and clinical examination. An extensive laboratory evaluation was also conducted to include baseline ESR, CRP, full blood count, liver profile, renal function, fibrinogen, Hba1c, lipid profile, RF, ACPA, ANCA-related antibodies, and extended myositis panel. Plain film radiographs of the shoulders were also completed. All patients had a baseline vascular ultrasound of their cranial and axillary arteries. The diagnosis of PMR was a clinical one, made in agreement by two rheumatologists. All PMR patients had their co-morbidities recorded and the Elixhauser Score was calculated on each patient. This is a scoring tool validated for clinical prognosis by offering comorbidity weighting and adjustment (Austin et al., 2015). PMR patients had follow-up at 1-month, 3-month, 6-month, and 12-month timepoints. Each review undertook the same format of clinical review accompanied by US evaluation and laboratory marker analysis. The diagnosis of PMR was reviewed at each clinic appointment.

3.3.3 Ultrasound protocols

As outlined in detail in chapter 2 the temporal artery ultrasound validation, training, and protocols used in the GCA fast-track clinic were applied to a PMR cohort. US of all 6

branches of the superficial temporal arteries and both axillary arteries was performed using a GE P9 device. Sonographic abnormalities considered indicative of vasculitis in the temporal artery included the halo sign with a thickened, non-compressible intima-media complex. Cut-off values of ≥ 0.29 mm for the parietal branch, ≥ 0.34 mm for the frontal branch and ≥ 0.42 for the common temporal branch were used (Schäfer et al., 2017). In the axillary arteries, a halo sign, and an intima-media thickness of > 1.0 mm was considered positive. This has been shown to have 100% sensitivity and specificity in the common, frontal, and axillary branches, and 97.2% sensitivity and 98.8% specificity in the case of the parietal branch (Schäfer et al., 2017).

A subset of patients with a clinical diagnosis of PMR had an ultrasound of their bilateral shoulder joints. This was done to assess the contribution and feasibility of including musculoskeletal ultrasound in a fast-track PMR clinic. The patients who underwent bilateral shoulder ultrasound were randomly selected consecutive patients and included those with both isolated PMR and subclinical GCA in PMR.

3.3.4 Ethical Approval

Full ethical approval was obtained from the Joint Research Ethics Committee for Tallaght University Hospital and St James Hospital, Dublin, Ireland. All patients gave fully informed written consent to participate in the fast-track clinic study.

3.3.5 Statistical Analysis

Descriptive analysis of the data was performed using SPSS. Data were expressed as the mean $\pm$ standard deviation (SD) for normally distributed continuous variables, as median (interquartile range) for non-normally distributed variables, and as percentages and frequencies for categorical variables. Continuous variables were compared using the independent t-test. Categorical variables are summarised by frequency and percentage (%) and compared using the chi-square test or Fisher's exact test. P values <0.05 were considered statistically significant.

3.4 Results

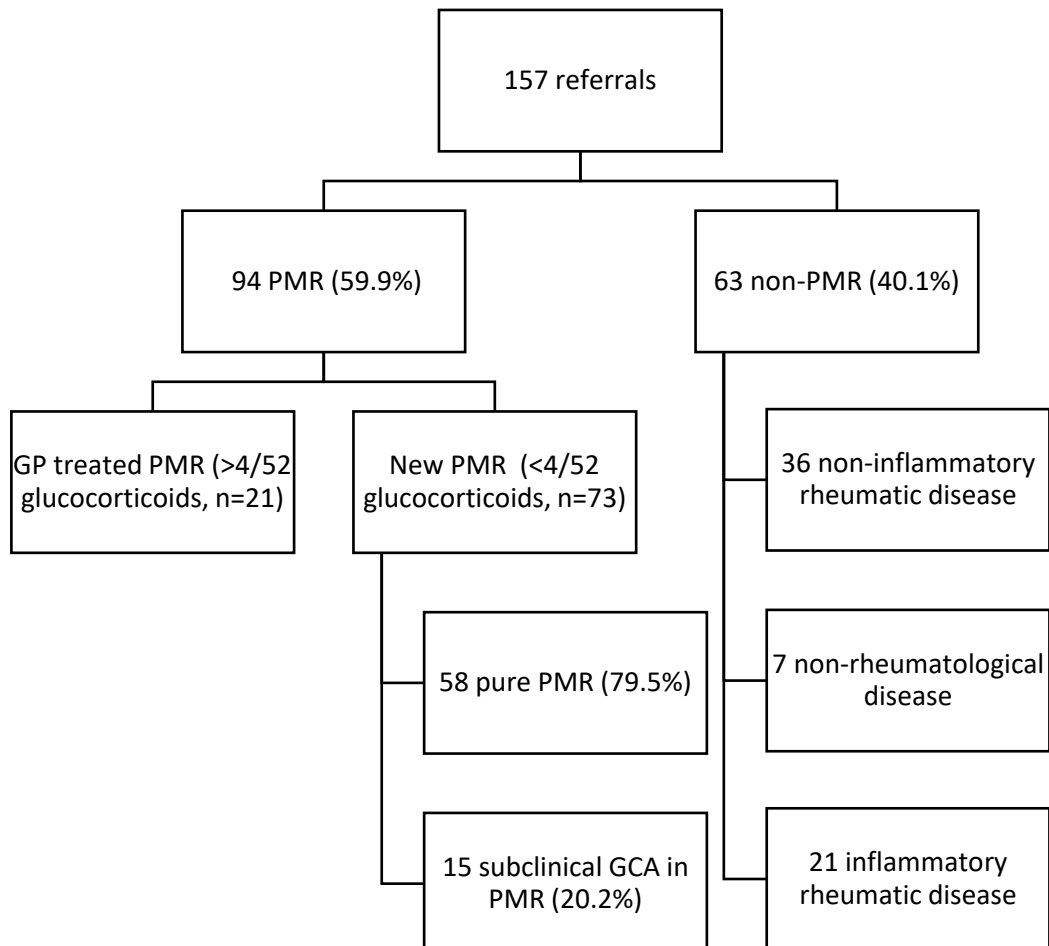
3.4.1 Patient Characteristics

Between July 2022 and July 2023, a total of 157 patients were referred from primary care with new suspected PMR. 76 (48.4%) patients met a clinical diagnosis of new PMR with agreement between two rheumatologists, while 21 (13.4%) had a diagnosis of 'treated PMR', already having received $>4/52$ weeks of glucocorticoid therapy in the setting of a characteristic clinical history and/or laboratory features of PMR with an adequate treatment response. 60 patients (38.2%) had an alternative diagnosis to PMR despite having a primary care suspicion of PMR. This is similar to figures previously reported for PMR misdiagnosis (Nielsen et al., 2023a). These numbers represented an average of 12 referrals a month or 2 referrals per 100,000 catchment population.

Age was normally distributed and the mean age of this PMR cohort at the time of diagnosis was 70.58 years [± 8.06]. The non-PMR patients had a mean age of 69.9 years [± 9.7]. There was no statistically significant difference in age between the PMR and non-PMR groups, $p=0.06$. The PMR cohort consisted of 39 males (51.3%) and 37 females

(48.7%). The non-PMR group was characterised by 41 females (68.3%) and 19 males (31.7%). This represented a statistically significant difference in gender between the PMR and non-PMR group, $p=0.02$. The PMR cohort had a median BMI of 27.3 [24.6-31.3] representing 2.7% of underweight patients, 24.7% normal weight, 38.4% overweight, and 34.2% with obesity.

Figure 3.2 Flow diagram of referrals to PMR clinic



3.4.2 Alternative diagnoses to PMR

60 patients had an alternative diagnosis to PMR at the initial assessment. The commonest alternative diagnosis was osteoarthritis (27). Other musculoskeletal diagnoses included fibromyalgia (5), rotator cuff disease (3), unilateral humeral fracture (1), HIV-related musculoskeletal pain (1), and sarcoidosis (1). There were several important inflammatory diagnoses including ANCA-associated vasculitis (3), myositis (3), seronegative inflammatory arthritis (SIA) (4), crystal arthropathy (3), and rheumatoid arthritis (2). Other serious diagnoses included carcinoma (5) including 2 ovarian cancers, 1 breast cancer, 1 colorectal cancer, and 1 prostate cancer. A further 3 were reclassified at 12 months with an alternative diagnosis to PMR (2 x SIA and 1 myositis). 38/63 (60.3%) of these patients required at least one further rheumatology consultation.

Table 3.1: Alternative diagnoses from Fast-track PMR clinic.

Alternative Diagnosis (Total 63)	Number (n)
Inflammatory Causes (20)	
Seropositive Inflammatory arthritis: - RF + only (1) - Anti-CCP + only (0) - RF and Anti-CCP + (1)	2
Seronegative Inflammatory Arthritis:	6
Inflammatory Myopathies: - PL7+ (1) - Ro52 + (1) - SRP + (1) - Anti-Hu (1)	4
Crystal Arthropathy - Gout (1) - CPPD (2)	3

Sarcoidosis (confirmed on BAL)	1
Polyarteritis Nodosa	1
ANCA vasculitis	3
- MPO + (2) - Atypical (1)	
Other (43)	
Osteoarthritis	27
Fibromyalgia Syndrome	5
Osteoporotic vertebral fracture	1
Carcinoma	5
Breast cancer (1)	
Ovarian cancer (2)	
Prostate cancer (1)	
Bowel cancer (1)	
Rotator cuff disease	3
Parkinson's Disease	1
HIV related musculoskeletal pain	1

3.4.3 Clinical features of PMR

Regarding presenting symptoms, 72/73 (98.6%) of patients with new PMR had bilateral shoulder pain, 64/73 (87.6%) had early morning stiffness, with the mean duration of stiffness lasting 96.2 minutes [± 76.9], 54/73 (73.9%) had hip involvement, 29/73 (39.7%) had neck pain on presentation, 14/73 (19.2%) had back pain, 12 patients (16.4%) had peripheral joint pain affecting at least one joint; with 9 reporting hand pain, 2 with wrist pain, 2 with knee pain and 1 with foot pain. 10/12 patients with peripheral joint pain had clinical evidence of joint swelling at the site of the painful joint. 12 patients (16.4%)

reported night sweats, 5 (6.8%) reported fevers, 18 (24.6%) reported anorexia, and 15 (20.5%) reported weight loss.

No patient reported clinical features of concomitant GCA on clinical assessment, including no cranial symptoms (headache, jaw claudication, scalp tenderness, or visual disturbance). 15 patients (20.5%) diagnosed with PMR had ultrasound features of subclinical giant cell arteritis at the time of diagnosis without any clinical features of GCA.

A further 21 patients were already on corticosteroid treatment >10mg for >4/52 weeks from primary care for suspected PMR without active features at the time of initial rheumatology review. These patients with a good initial response to glucocorticoids were discharged to primary care with a plan for a glucocorticoid taper over 6-8 months. These patients did not require re-referral to the service during their first year of treatment.

89.5% of those with a clinical diagnosis of new PMR made by two consultant rheumatologists met the 2012 ACR/EULAR PMR classification criteria (Dasgupta et al., 2012). 70.7% of patients with a non-PMR diagnosis also met the classification criteria ($p=0.010$) highlighting caution against use as a diagnostic criterion. The median (interquartile range) number of days from symptom onset until PMR diagnosis was 63.5 [30-95]. Certain clinical features helped to discriminate between PMR and non-PMR diagnosis. The presence of shoulder pain, hip pain, early morning stiffness, longer duration of early morning stiffness, and anorexia, were significantly more likely to be present in PMR patients. Peripheral joint pain was significantly higher in those with non-PMR diagnoses (see table 3.2).

Table 3.2 Clinical features of new PMR vs non-PMR

Patient characteristic	New PMR (n=73)	Non-PMR (n=63)	P value
Shoulder pain	99%, 95% CI [92.6%, 99.8%]	87%, 95% CI [76.9%, 93.4%]	.004
Hip pain	74%, 95% CI [62.9%, 82.7%]	37%, 95% CI [25.7%, 48.9%]	<.001
Early morning stiffness	88%, 95% CI [78.2%, 93.4%]	46%, 95% CI [34.3%, 58.2%]	<.001
Duration of EMS (mins, SD)	M = 96.2, SD = 76.9, 95% CI [78.6, 113.8]	M = 30.5, SD = 46.2, 95% CI [19.1, 41.9]	<.001
Neck pain	40%, 95% CI [29.3%, 51.2%]	27%, 95% CI [17.6%, 39.0%]	.07
Back pain	19%, 95% CI [11.8%, 29.7%]	13%, 95% CI [6.6%, 23.1%]	.32
Peripheral joint pain	16%, 95% CI [9.7%, 26.6%]	40%, 95% CI [28.5%, 52.0%]	.009
Peripheral joint swelling	14%, 95% CI [7.6%, 23.4%]	25%, 95% CI [16.3%, 37.3%]	.128
Night sweats	16%, 95% CI [9.7%, 26.6%]	8%, 95% CI [3.4%, 17.3%]	.05
Fevers	7%, 95% CI [3.0%, 15.1%]	5%, 95% CI [1.6%, 13.1%]	.48
Anorexia	25%, 95% CI [16.2%, 35.6%]	6%, 95% CI [2.5%, 15.2%]	<.001
Weight loss	21%, 95% CI [12.9%, 31.2%]	17%, 95% CI [10.0%, 28.6%]	.65

3.4.4 Laboratory features

3.4.4.1 Inflammatory markers

The mean baseline erythrocyte sedimentation rate (ESR) in those with new PMR was 44.8mm/hr [± 26.5] compared to 37.9mm/hr [± 25.7] in those with an alternative diagnosis to PMR ($p = 0.18$) (see Table 3.2). CRP was not normally distributed in both PMR and non-PMR cohorts. Baseline CRP levels helped discriminate between PMR and non-PMR with median baseline c-reactive protein (CRP) in new PMR of 8.5mg/L [3-21.5] compared to 7mg/L [2-18.6] in those with an alternative diagnosis, $p=0.03$. Several inflammatory laboratory features of PMR had significant differences between baseline and remission which may be helpful laboratory markers of relapse. Mean ESR at baseline was 44.2mm/hr ± 26.5 and reduced to 13.1mm/hr ± 11.8 for patients in remission, $p=0.007$. Mean CRP at baseline was 31.9mg/l ± 35.5 reducing to a mean of 3.3mg/l ± 4.1 in remission, $p=0.025$. Both ESR and CRP are well established as being elevated in the vast majority of patients at the time of PMR diagnosis (Manzo et al., 2019). Mean haptoglobins at baseline were 2.27g/l compared with 1.65g/l in remission, $p<0.001$. Haptoglobins are known to be elevated in inflammatory disease states and have previously been identified as a potential marker of disease activity in juvenile inflammatory arthritis (Berntson et al., 2022) however, this is a novel finding for PMR.

Table 3.3 Baseline vs remission inflammatory markers in PMR patients

Laboratory parameter	Baseline	Remission at 6 months	p-value
ESR (mm/hr)	44.2, SD = 26.5, 95% CI [38.1, 50.3]	13.1, SD = 11.8, 95% CI [10.4, 15.8]	.007
CRP (mg/l)	31.9, SD = 35.5, 95% CI [23.8, 40.0]	3.3, SD = 4.1, 95% CI [2.4, 4.2]	.025
Haptoglobins (g/l)	2.27, SD = 0.72, 95% CI [2.05, 2.49]	1.65, SD = 0.46, 95% CI [1.51, 1.79]	<.001

3.4.4.2 Haematological parameters

Haematological parameters did not help discriminate between PMR and non-PMR diagnoses. They had better utility in discriminating between active and non-active disease in PMR (see table 3.5). Haemoglobin (Hb) levels in PMR patients increased significantly between baseline and remission states, from 13.2g/dl $\pm$ 1.5 to 13.8g/dl $\pm$ 1.12 in remission, $p < 0.01$. The mean fibrinogen level was elevated at baseline in PMR, in the inflammatory state, compared to remission. The mean baseline fibrinogen was 4.02g/l $\pm$ 1.13 reducing to 3.3g/l $\pm$ 0.69 in PMR remission, $p < 0.001$. Elevated fibrinogen has also been identified in other cohorts as an accurate marker of disease activity in PMR (McCarthy et al., 2012). Additionally, the mean platelet count at baseline was $314.7 \times 10^9/l \pm 80.4$ compared with $267.2 \times 10^9/l \pm 84.6$ in remission, $p = 0.001$, reflecting a general reduction in the inflammatory response in remission. Neutrophils also exhibited a reduction between baseline and remission, going from a mean level of

7.6x 10⁹/l ± 3.38 to 6.1x 10⁹/l ± 2.06, p<0.01. The prior glucocorticoid exposure affecting over 60% (44/73) PMR patients before referral may have influenced this result. There were no significant differences between other white cell subtypes at baseline versus remission.

Table 3.4 Baseline vs remission haematological parameters in PMR patients

Laboratory parameter	Baseline (mean, SD, 95% CI)	6 months (mean, SD, 95% CI)	p-value
Haemoglobin (g/dl)	13.2 ± 1.15 (95% CI 12.93–13.47)	13.8 ± 1.12 (95% CI 13.54–14.06)	<0.01
Neutrophils (x10 ⁹ /l)	7.6 ± 3.38 (95% CI 6.82–8.38)	6.1 ± 2.06 (95% CI 5.62–6.58)	<0.01
Lymphocytes (x10 ⁹ /l)	2.5 ± 2.06 (95% CI 2.02–2.98)	2.1 ± 1.45 (95% CI 1.77–2.43)	0.180
Eosinophils (x10 ⁹ /l)	0.1 ± 0.12 (95% CI 0.07–0.13)	0.11 ± 0.11 (95% CI 0.08–0.14)	0.603
Mono (x10 ⁹ /l)	0.69 ± 0.29 (95% CI 0.62–0.76)	0.62 ± 0.27 (95% CI 0.56–0.68)	0.136
Platelets (x10 ⁹ /l)	314.7 ± 80.4 (95% CI 296.13–333.27)	267.2 ± 84.6 (95% CI 247.66–286.74)	0.001
Fibrinogen (g/l)	4.02 ± 1.13 (95% CI 3.76–4.28)	3.3 ± 0.69 (95% CI 3.14–3.46)	<0.001

3.4.4.3 Biochemical parameters

There were some interesting changes in biochemical parameters comparing baseline figures with remission in PMR patients, mainly representative of glucocorticoid treatment. Triglycerides (TGs) were significantly more elevated in those in remission at 6 months compared to baseline at 1.5 mmol/l ± 0.72 vs 2.99 mmol/l [± 1.94] respectively, $p=0.004$. This is likely because of the metabolic effects of glucocorticoid treatment. Similarly, there was an overall trend toward elevation in total cholesterol after 6 months of treatment, but this did not meet statistical significance. Sodium also exhibited a significant increase from baseline to remission from 138.9 [± 2.57] to 140.55 [± 2.21], $p<0.001$ again which is a known side effect of glucocorticoid therapy. Albumin significantly increased between baseline and remission from 42.88 [± 3.37] to 44.06 [± 2.86]; $p=0.03$, which is likely reflective of reduced albumin in the inflammatory state at baseline.

More significantly, there were reductions in blood levels of both alkaline phosphatase and gamma-glutamyl transferase (GGT) from the baseline to the remission state. Alkaline phosphatase reduced from 85.12 [± 22.63] to 65.94 [± 20.01]; $p<0.001$, and GGT reduced from 38.45 [± 29.6] to 28.74 [± 15.20]; $p=0.01$. This may be representative of higher inflammation levels at baseline compared to remission and has been seen in some older studies of liver enzymes in inflammatory rheumatic disease and PMR (Akeson et al., 1980, von Knorring and Wassatjerna, 1976).

Table 3.5 Baseline versus remission biochemical parameters in PMR patients

Laboratory parameter	Baseline (n=73)	Remission at 6 months (n=73)	P value
Total Cholesterol (mmol/l)	4.92, SD = 1.21, 95% CI [4.64, 5.20]	5.31, SD = 1.41, 95% CI [4.99, 5.63]	.28
HDL (mmol/l)	1.67, SD = 0.59, 95% CI [1.53, 1.81]	1.73, SD = 0.66, 95% CI [1.58, 1.88]	.17
LDL (mmol/l)	2.47, SD = 0.98, 95% CI [2.25, 2.69]	2.62, SD = 1.04, 95% CI [2.38, 2.86]	.32
Triglycerides (mmol/l)	1.52, SD = 0.72, 95% CI [1.35, 1.69]	2.99, SD = 1.94, 95% CI [2.54, 3.44]	.004
Creatinine (μmol/L)	78.17, SD = 19.1, 95% CI [73.79, 82.55]	81.1, SD = 16.04, 95% CI [77.42, 84.78]	.18
eGFR (ml/min/1.73m ²)	75.53, SD = 15.66, 95% CI [71.94, 79.12]	72.38, SD = 13.35, 95% CI [69.32, 75.44]	.09
Sodium (mmol/L)	138.9, SD = 2.57, 95% CI [138.31, 139.49]	140.55, SD = 2.21, 95% CI [140.04, 141.06]	<.001
Potassium (mmol/L)	4.28, SD = 0.5, 95% CI [4.17, 4.39]	4.48, SD = 0.53, 95% CI [4.36, 4.60]	.06
Corrected Calcium (mmol/L)	2.37, SD = 0.08, 95% CI [2.35, 2.39]	2.38, SD = 0.13, 95% CI [2.35, 2.41]	.38
Albumin (g/L)	42.88, SD = 3.37, 95% CI [42.11, 43.65]	44.06, SD = 2.86, 95% CI [43.40, 44.72]	.03
Bilirubin (μmol/L)	7.45, SD = 3.31, 95% CI [6.69, 8.21]	7.94, SD = 4.61, 95% CI [6.88, 9.00]	.19

Alkaline phosphatase (IU/L)	85.12, SD = 22.63, 95% CI [79.93, 90.31]	65.94, SD = 20.01, 95% CI [61.35, 70.53]	<.001
GGT (IU/L)	38.45, SD = 29.6, 95% CI [31.66, 45.24]	28.74, SD = 15.2, 95% CI [25.25, 32.23]	.01
AST (IU/L)	21.3, SD = 7.11, 95% CI [19.67, 22.93]	21.06, SD = 5.31, 95% CI [19.84, 22.28]	.48
ALT (IU/L)	20.39, SD = 10.41, 95% CI [18.00, 22.78]	21.06, SD = 9.04, 95% CI [18.99, 23.13]	.41
HbA1c (mmol/mol)	42.7, SD = 7.84, 95% CI [40.90, 44.50]	45.27, SD = 10.85, 95% CI [42.78, 47.76]	.12

3.4.4.4 Autoimmune antibodies

Autoimmune antibodies helped discriminate PMR from non-PMR diagnoses. In two patients diagnosed with seropositive rheumatoid arthritis, one was rheumatoid factor (RF) positive and the other was anti-cyclic citrullinated (anti-CCP) positive. Three patients were diagnosed with myositis at the baseline visit with positive anti-pL7, anti-Ro52, and anti-SRP antibodies in conjunction with clinical features.

There were a further two patients with weak positive extended myositis panel positivity at the outset (1 with anti-PM-Scl100 antibody and 1 with anti-Hu antibody). These patients were treated as PMR from the outset based on their characteristic PMR presentation and low levels of myositis antibodies. The patient with weak anti-PM-Scl100 antibody initially responded to glucocorticoid but relapsed twice and is now in remission on tocilizumab. He is still classified as PMR clinically. The patient with anti-Hu

never attained a reduction in ESR or CRP with PMR dose glucocorticoids and remained clinically active; her myositis panel was rechecked, and anti-Hu became more significantly positive after 6 months. She was reclassified as myositis based on suggestive imaging findings in addition to the clinical picture.

There were three patients diagnosed with ANCA vasculitis at the outset with the help of positive antibodies (2 x anti-MPO and 1 x atypical ANCA). These patients all had subtle interstitial lung involvement on computed tomography of the thorax without any other organ involvement and were treated as microscopic polyangiitis (MPA). There were a further 2 patients with atypical ANCA identified on their initial investigations, one thought related to cocaine use (which has remained positive at follow-up) and the other of unclear etiology (which subsequently normalised). Both patients were treated as PMR from the outset based on their clinical presentation and lack of other organ involvement. One is currently treated with glucocorticoids and the other is on glucocorticoid plus tocilizumab. Our numbers of ANCA vasculitis and antibody-positive myositis diagnoses were too small to complete further sub-analysis.

3.4.5 Comorbidity in PMR

The PMR cohort had a mean of 2.5 other comorbidities with a median Elixhauser Comorbidity Index score of 0. This score is a measure of overall severity of comorbidities, predicting hospital length of stay and in-hospital mortality. Despite on average having 2.5 other medical conditions, this model predicted our cohort had a low risk of hospitalisation or in-hospital mortality.

Figure 3.3 Elixhauser Index of in-hospital death

0	Hypertension, diabetes, hypothyroidism, peptic ulcer disease, AIDS/HIV, alcohol abuse, psychosis
2	Peripheral vascular disease
3	Chronic pulmonary disease, coagulopathy, rheumatoid arthritis
4	Pulmonary circulation disorder. solid tumour without metastasis
5	Fluid and electrolyte disorders, renal failure, cardiac arrhythmias
6	Weight loss, neurodegenerative disorders
7	Congestive heart failure, paralysis
9	Lymphoma
11	Liver disease
12	Metastatic cancer
-1	Valvular disease
-2	Blood loss anaemia, deficiency anaemia
-3	Depression
-4	Obesity
-7	Drug abuse

Legend: Weightings given to co-morbidities in the Elixhauser Index of in-hospital death

(van Walraven et al., 2009)

The most common comorbidities affecting >25% of PMR patients were hypertension (58%), hyperlipidaemia (51%), osteoarthritis (30%), and obesity (27%). Significantly 14% of patients had type 2 diabetes at the time of PMR diagnosis which was a big concern in exposing them to a significant duration of glucocorticoid exposure. The majority of the PMR cohort (54.6%) were either overweight (29.3%) or obese (25.3%) at the time of diagnosis. There was also a considerable smoking history with 7.8% being active smokers and 44.7% ex-smokers.

3.4.6 Primary care management of PMR before referral to the fast-track clinic

3.4.6.1. Glucocorticoids

Varying doses of glucocorticoid were commenced in primary care ranging from an initial dose of 12.5mg to 40mg. This choice of starting dose is not in keeping with the 2015 ACR/EULAR PMR treatment guidelines which recommend a starting dose of 12.5-25mg and strongly recommends against the use of initial doses >30 mg/day (Dejaco et al., 2015). The mean cumulative glucocorticoid exposure in these patients upon referral was also high at 457.73mg $\pm$ 293.6. At the time of referral, 60.3% of patients (44/73) had glucocorticoid treatment started in primary care, while 39.7% were glucocorticoid naïve.

3.4.6.2 Bone protection

Interestingly, of the 39 patients who were established on steroid therapy for <4/52 in primary care, only 8 (20%) were initiated on some form of bone protection by their

General Practitioner. 2 patients were initiated on a bisphosphonate, and 6 commenced on calcium and vitamin D supplementation.

3.4.6.3 Analgesics

Of those with a final diagnosis of PMR, 29% had been treated with a non-steroidal anti-inflammatory (NSAID) medication in primary care, while 15% were prescribed an opioid medication before referral. This practice is not in keeping with current PMR treatment guidelines. This elderly, comorbid population is at increased risk of side effects from both NSAIDs and opiates, including renal impairment, gastric ulceration, confusion, and falls to name a few.

3.4.6.4 Time to rheumatology referral

The mean time from symptom onset to referral to the fast-track clinic was 11.43 weeks ± 9.26 which represents a significant delay despite the fast-track clinic offering review within 48 hours of referral. The reasons for this delay were unclear. Possibilities include patient difficulty in accessing primary care, GPs being unaware of the new fast-track clinic service, or a lag-time in changing practice to refer suspected new PMR to rheumatology directly.

3.4.7 Treatment initiated in PMR clinic

Patients with PMR were treated in accordance with the 2015 ACR/EULAR guidelines (Dejaco et al., 2015). The starting glucocorticoid dose was between 12.5-25mg based on clinical judgement. The mean starting dose of all PMR patients at the fast-track clinic,

including both GP and FTC prescriptions was $18.48\text{mg} \pm 6.87$. 29 patients (39.7%) were glucocorticoid naïve on referral to the fast-track clinic. In cases where patients had already been initiated on doses of $>25\text{mg}$ in primary care, patients were tapered down from the initial starting dose.

All patients in the fast-track clinic had an assessment of osteoporosis risk and were initiated on bone protection in the form of a bisphosphonate and/or calcium and vitamin D replacement. All patients except 2 (3.3%) accepted bisphosphonate bone protection while on high-dose glucocorticoids. Continuation of bisphosphonate was based on their osteoporotic risk. All patients were also offered proton pump inhibitor cover to prevent gastric complications while on glucocorticoid doses $>7\text{mg}$.

Glucocorticoids were tapered to achieve a dose of 10mg or less by 8 weeks of treatment. The mean glucocorticoid treatment dose at 3 months was $8.4\text{mg} \pm 3.1$, $5.9\text{mg} \pm 2.8$ at 6 months, and $1.9\text{mg} \pm 4.1$ at 12 months of treatment. The percentage of patients in glucocorticoid-free remission at 3, 6, and 12 months was 2.6%, 5.3% and 57.8% respectively. Our data compares favourably with a recent meta-analysis reporting only 33% of PMR patients in glucocorticoid-free remission at one year (Floris et al., 2022). This may reflect their meticulous management in the fast-track clinic and careful tapering of glucocorticoids. Despite this, the mean cumulative glucocorticoid exposure at 3, 6, and 12 months was $1462.9\text{mg} \pm 591.5$, $2075.8\text{mg} \pm 656.7$, and $2687.4\text{mg} \pm 935.6$, which is still significant.

During the first 12 months of treatment, 2 patients were lost to the PMR cohort at 12 months (1 patient did not attend follow-up appointments despite multiple rescheduling attempts, 1 patient passed away from unrelated causes after 7 months of treatment).

Three others already accounted for had their diagnosis of PMR reclassified (1 was reclassified as myositis, and 2 reclassified as SIA). 57.8% of patients were in glucocorticoid-free remission at 12 months. The only clinical feature associated with glucocorticoid-free remission at 12 months was the lack of hip PMR symptoms at baseline, $p=0.02$. Previous studies have suggested an association between the presence of hip PMR and more severe disease (De Miguel et al., 2023b).

Table 3.6: Characteristics associated with glucocorticoid free remission at 12 months.

Characteristic	GC-free remission 12 months (n=41)	Not in GC-free remission 12 months (n=30)	P-value
Age	70.1, SD = 7.84, 95% CI [67.70, 72.50]	69.9, SD = 7.88, 95% CI [67.08, 72.72]	.97
BMI	27.6, SD = 4.08, 95% CI [26.35, 28.85]	28.17, SD = 5.1, 95% CI [26.34, 30.00]	.33
Baseline ESR	41.08, SD = 24.06, 95% CI [33.72, 48.44]	46.9, SD = 30.96, 95% CI [35.82, 57.98]	.49
Baseline CRP	33.15, SD = 30.93, 95% CI [23.68, 42.62]	30.3, SD = 38.59, 95% CI [16.49, 44.11]	.67

Table 3.7: Clinical features associated with glucocorticoid free remission at 12 months

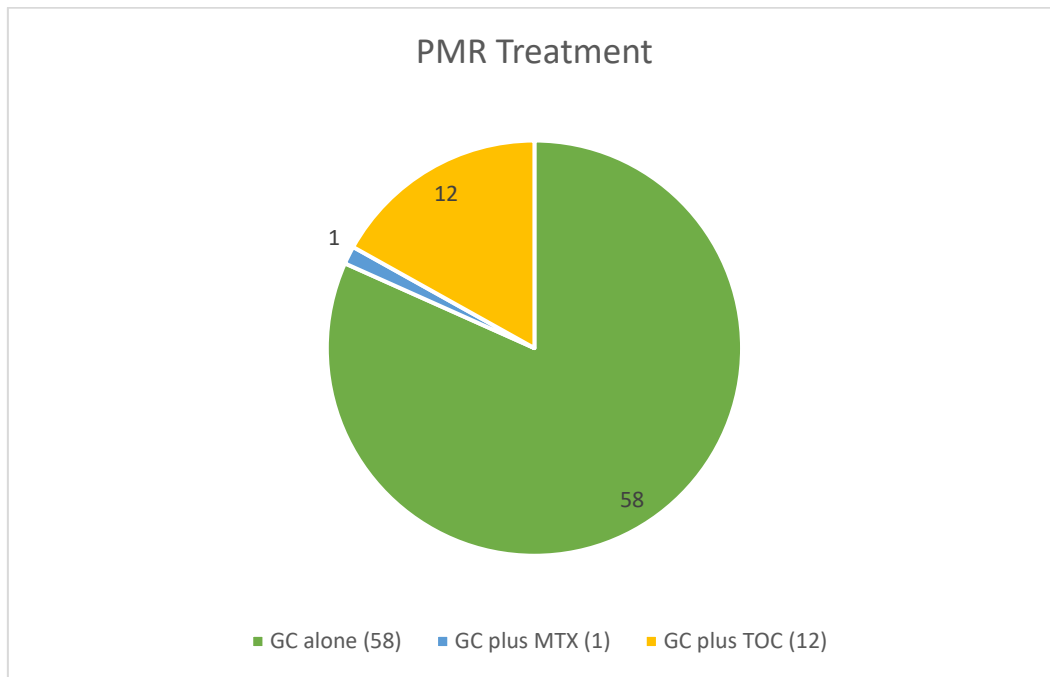
Characteristic	No. attaining GC free remission 12 months (n, %)	No. not attaining GC free remission 12 months (n, %)	P value
Shoulder PMR	30 (42.9%)	40 (57.1%)	0.57
No Hip PMR	14 (82.4%)	3 (17.6%)	0.02
Back pain	8 (61.5%)	5 (38.5%)	0.53
Neck pain	16 (59.3%)	11 (40.7%)	0.51
Early morning stiffness	37 (59.7%)	25 (40.3%)	0.30
Fever	4 (80%)	1 (20%)	0.29
Night sweats	9 (75%)	3 (25%)	0.16
Weight loss	9 (60%)	6 (40%)	0.51
Anorexia	13 (76.5%)	4 (23.5%)	0.06

3.4.7.2 Disease-modifying treatment

13/71 (18.3%) of PMR patients at 12 months were not adequately treated with standard glucocorticoid therapy alone. One PMR patient was initiated on methotrexate in addition to glucocorticoids for severe PMR with symptoms with difficulty weaning glucocorticoids from the starting dose, along with peripheral joint pain. 12 patients were commenced on tocilizumab (anti-il-6R antagonist) during the first 12 months for various reasons – 1 for brittle diabetes (started month 1), 3 for severe disease not responding to high dose glucocorticoids >20mg (started month 1), and 7 for either a relapse occurring on ≥ 10 mg treatment dose or at least 2 relapses and unable to taper

glucocorticoid to <5mg during the first 12 months of treatment (started month 4 (1), month 5 (2), month 6 (1), month 8 (1), month 9 (1) month 12 (2)).

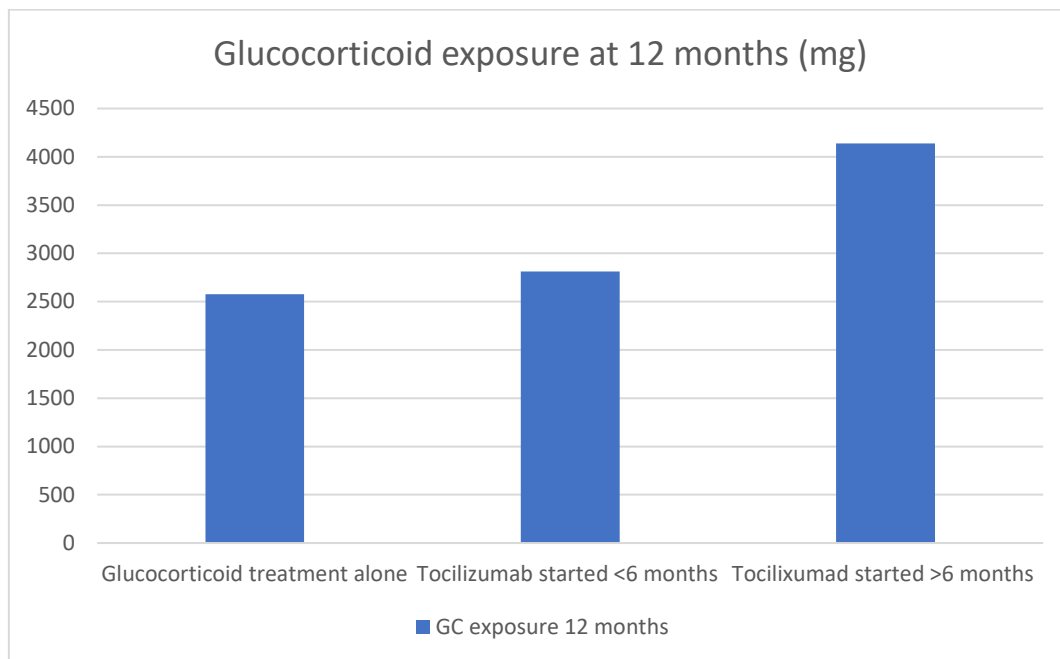
Figure 3.4 PMR treatment



3.4.7.3 Glucocorticoid exposure

Patients requiring tocilizumab for more severe disease had higher overall glucocorticoid burden, reflective of the failure to treat them with glucocorticoid alone. The mean glucocorticoid exposure for patients at 12 months treated with glucocorticoid alone was 2576.2mg $\pm$ 772.9, compared to 2811.9mg $\pm$ 1095.7 for those initiated on tocilizumab $\leq$ 6 months, and 4138.8mg $\pm$ 2129.7 for those initiated on tocilizumab $\geq$ 6 months. There was a significant difference in the cumulative glucocorticoid exposure of patients initiated on tocilizumab early ($\leq$ 6 months) compared with later ($\geq$ 6 months), at 1326.9mg less, $p=0.04$.

Figure 3.5: Glucocorticoid exposure



3.4.7.4 Infections and hospitalisations

Regarding infections and hospitalisations, there were 2 infections (16.7%) in the tocilizumab plus glucocorticoid treated group (1 SARS-coV-1 infection and 1 respiratory infection both treated in the community), and no hospitalisations. 11/71 (15.5%) patients were treated in the community with antibiotics for various infections in the glucocorticoid group, and an additional 2 treated for shingles, but no hospitalisations for infection. There were 3 hospitalisations for other reasons (1 transient ischaemic attack, 1 non-ST elevation myocardial infarction, 1 relapse of PMR where patient stopped taking glucocorticoid of their own accord). Overall tocilizumab treatment in PMR proved to be both safe and efficacious with no increased infections/hospitalisations compared to those treated with glucocorticoid alone, a reduction in cumulative glucocorticoid burden, and fewer relapses.

Table 3.8: Infections and hospitalisations

Outcome	GC alone (n=58)	Tocilizumab + GC (n=12)	p-value
Infection treated in community	13 (22%)	2 (16%)	1.00
Hospitalisation for infection	0	0	—
Hospitalisation for any reason	3 (5%)	0	1.00

3.4.8 Relapse of PMR in the first 12 months

Overall, 29 PMR patients with 12 months follow-up (40.8%), relapsed during the first 12 months after diagnosis. The median time to relapse was 5 months. All relapses were minor, except for 1 patient with subclinical GCA who was classified as having a major relapse (new headache with ischaemic symptom of jaw claudication). 2/12 (16.7%) patients on tocilizumab plus glucocorticoid relapsed over 12 months compared to 32/71 (45%) on glucocorticoid alone. Higher CRP levels at baseline were statistically associated with relapse in PMR symptoms over the following 12 months ($p=0.006$). Higher ESR levels at baseline were also statistically significant in predicting a relapse ($p=0.018$). The only clinical symptom predictive of relapse was the presence of hip girdle PMR symptoms at baseline.

Table 3.9: Demographics and inflammatory markers of PMR patients with and without relapse

Characteristic	No relapse (n=44)	Relapse (n=29)	p
Age	70.9, SD = 7.88, 95% CI [68.57, 73.23]	69.8, SD = 8.05, 95% CI [66.87, 72.73]	.53
BMI	28.4, SD = 4.1, 95% CI [27.19, 29.61]	27.5, SD = 5.1, 95% CI [25.64, 29.36]	.64
Baseline ESR	36.5, SD = 23.6, 95% CI [29.53, 43.47]	51.2, SD = 27.9, 95% CI [41.05, 61.35]	.018
Baseline CRP	20.8, SD = 20.4, 95% CI [14.77, 26.83]	42.2, SD = 40.7, 95% CI [27.39, 57.01]	.006
Baseline platelets	308.28, SD=91.85 CI [275.17, 341.40]	320.26 SD=76.67 CI [295.49, 345.11]	.56

Table 3.10: Clinical characteristics of patients with and without relapse of PMR

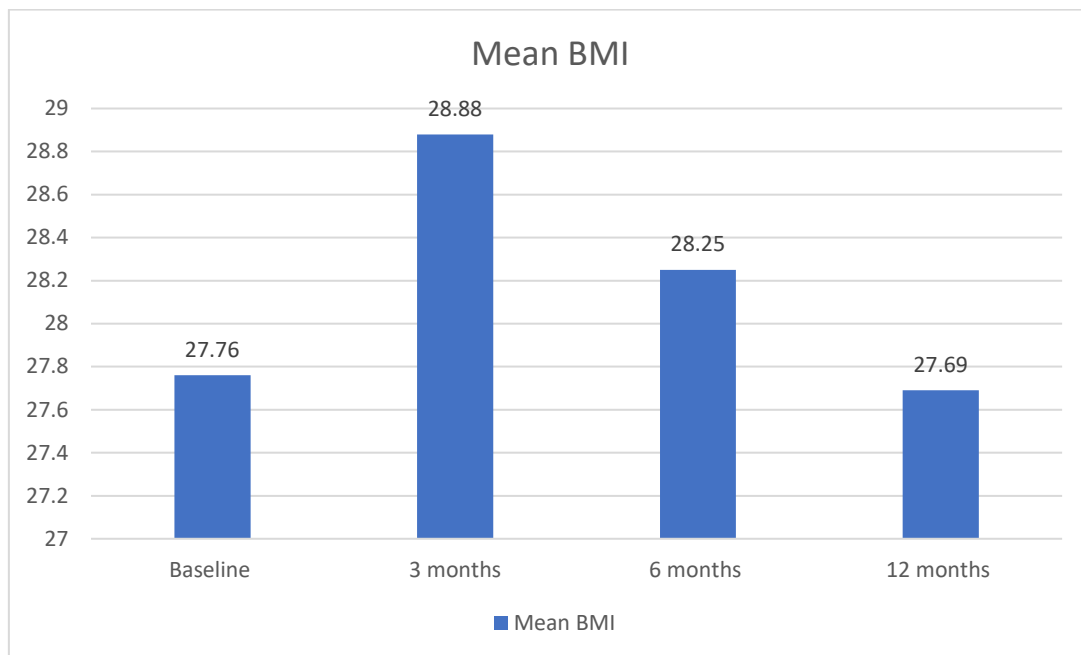
Characteristic	No relapse by 12 months (n, %)	Relapsed before 12 months (n, %)	P value
Shoulder symptoms	35 (50%)	35 (50%)	0.51
Hip symptoms	31 (57.4%)	23 (42.6%)	<i>0.014</i>
Back pain	6 (46.2%)	7 (53.8%)	0.50
Neck pain	12 (44.4%)	15 (66.6%)	0.28
Early morning stiffness	33 (53.2%)	29 (46.7%)	0.23
Fever	2 (40%)	3 (50%)	0.48
Night sweats	5 (41.7%)	7 (58.3%)	0.36

Anorexia	8 (47.1%)	9 (58.9%)	0.47
Weight loss	6 (40%)	9 (60%)	0.26

3.4.9 Treatment related adverse events.

Regarding glucocorticoid-related adverse events, almost two-thirds of patients experienced sleep disturbance secondary to steroid therapy. 3 patients received a new diagnosis of type 2 diabetes mellitus ($\text{hba1c} \geq 48\text{mmol/mol}$), and all the new diabetes cases had a hba1c in the pre-diabetes range ($42\text{-}47\text{mmol/mol}$) at the time of PMR diagnosis. 5 patients with normal hba1c at baseline developed pre-diabetes over 12 months glucocorticoid therapy for PMR. 4% reported mood disturbance during treatment. 11 (15%) received antibiotics for infection, 2 (3%) had an episode of shingles during their treatment course, 5 (6%) suffered an osteoporotic wedge compression fracture, and 1 patient had a low-impact humeral shaft fracture. Mean BMI increased from baseline to 3 months (27.76 ± 4.67 to 28.88 ± 5.30), followed by a return to baseline by 12 months (27.69 ± 5.26). Overall, there was no statistically significant change in BMI with PMR treatment over 12 months of treatment.

Table 3.11: Changes in BMI from baseline to 12 months



3.4.10 Other adverse events

Additionally, 1 patient had a non-ST elevation myocardial infarction (NSTEMI), and 1 patient had a transient ischaemic attack (TIA). During glucocorticoid therapy for PMR, 5 patients (7%) were diagnosed with malignancy identified in the fast-track PMR clinic (2 colorectal cancers, 1 prostate cancer, 1 lung cancer, and 1 neuroendocrine tumour) indicating a possible paraneoplastic cause for their PMR. 1 other patient passed away during follow up from natural causes.

3.4.11 Ultrasound features of PMR

3.4.11.1 Vascular Ultrasound

Vascular ultrasound was completed on all PMR patients. 1/5 had ultrasound features of subclinical GCA at the time of diagnosis. The patients with subclinical GCA had a

significant male predominance at 80% compared to 44.8% males in the PMR with normal vascular US group, $p=0.04$. The mean age of subjects with subclinical GCA in PMR was 70 years. Those with subclinical GCA in PMR had slightly more glucocorticoid exposure at $470.7\text{mg} \pm 649.1$ compared to those with isolated PMR at 457.7 ± 293.6 ; $p=0.941$, at the time of initial rheumatology review despite both groups having a similar time from symptom onset to rheumatology review at 11.43 weeks [± 9.26] and 11.24 weeks [± 11.91] for PMR and subclinical GCA in PMR respectively. This may be reflective of more difficult-to-treat disease. ESR was higher at baseline in those with subclinical GCA in PMR compared to their pure PMR counterparts at 54.9mm/hr and 44.4mm/hr respectively but this was not statistically significant; $p=0.20$. There was no difference in baseline CRP levels between the two groups; $p=0.98$. Detailed analysis of the subclinical GCA in PMR group is reported in chapter 5.

3.4.11.2 Musculoskeletal Ultrasound

A subset of 22 patients underwent bilateral shoulder ultrasound. These patients were selected randomly, and the cohort included both patients with isolated PMR (19) and subclinical GCA in PMR (3). 59% had findings of bilateral subacromial subdeltoid (SASD) bursitis, 31.8% had unilateral US-identified SASD bursitis, and bilateral biceps tendon pathology was present in 22.7%. Those with bilateral SASD bursitis had a higher mean baseline ESR of 58mm/hr than those without this finding at baseline (ESR 40mm/hr; $p=0.169$). This is in keeping with previous magnetic resonance imaging (MRI) and US studies which have shown PMR patients with normal or high ESRs have similar inflammatory shoulder lesions (Cantini et al., 2001). Glucocorticoid exposure before the

time of US was almost identical between those with and without US-identified SASD bursitis at 172.9mg and 178.5mg respectively. The duration of time from symptom onset to ultrasound did not predict the presence of SASD bursitis (94.2 vs 111.8 days, $p=0.50$).

Subacromial-subdeltoid bursitis was the most frequent musculoskeletal ultrasound finding in our PMR cohort. This has also been shown in previous studies (Mackie et al., 2015a) and this finding has also been identified in positron emission tomography (PET) studies (Owen et al., 2024b).

3.5 Discussion

To our knowledge, this is the first report of a fast-track PMR clinic in Ireland or the UK. It is reasonable that rheumatology services provide this service on a widespread level. Using the referral criteria described in the methods and with a catchment population of 600,000 we received 12 referrals a month and diagnosed 6 cases of PMR a month giving an annual PMR incidence of 0.12/1000 population. This is at the lower end of the reported incidence and may represent an underestimate with less severe cases of PMR continuing to be managed in primary care. Given recent recommendations for early referral of cases of PMR for rheumatological assessment, this data is useful for planning these services. Based on our figures, it is estimated that a rapid access PMR clinic would require 0.5 new patient slots per week per 100,000 catchment population and 0.97 review slots per week per 100,000. As most PMR patients can then be discharged back to primary care with a management plan the rapid access clinic can be sustained with

this level of capacity. This assumes that PMR patients continue to be treated according to current practice with steroid therapy only. If biologic therapy is instituted in future PMR management then a greater capacity for review appointments would need to be provided.

There was significant heterogeneity in the clinical presentations and final diagnosis of patients referred to the PMR clinic. Over a third of patients (38%) had an alternative diagnosis to PMR. Osteoarthritis and seronegative inflammatory arthritis were the commonest alternative diagnoses to PMR but there were several patients with serious pathology including ANCA vasculitis, polyarteritis nodosa, myositis, and malignancy. These conditions are more challenging to diagnose in primary care with more limited consultation time for patient assessment and more limited access to diagnostics. There were also 3 patients reclassified as alternative diagnoses to PMR over 12 months of follow-up, despite initial specialist review at baseline, which again highlights diagnostic difficulty. In addition, 3 patients with PMR had normal ESR and CRP at baseline (2 on glucocorticoid therapy from primary care and 1 glucocorticoid naïve). Although such cases have been reported (Manzo et al., 2019) this may have caused diagnostic uncertainty for primary care. It also highlights the importance of assessing the patient before glucocorticoid treatment, as they may mask clinical and laboratory features. The reported risk of misdiagnosis may be as high as 30% for PMR patients diagnosed by a rheumatologist, and potentially higher by primary care providers (Pease et al., 2005, Gonzalez-Gay et al., 2000, Paltta et al., 2023). This substantiates the calls for specialist-led rapid access PMR clinics.

5 patients with PMR (7%) were diagnosed with a malignancy during their first year of treatment including 2 colorectal cancers, 1 prostate cancer, 1 lung cancer, and 1 neuroendocrine tumour. This may indicate a paraneoplastic presentation of PMR which has some evidence of association with PMR in the first 6-12 months after diagnosis (Muller et al., 2018). There is a paucity of evidence in the literature to classify PMR as a true paraneoplastic disease however clinicians should be observant for new malignancies. There were a further 5 patients who presented with PMR-like symptoms but were diagnosed with a new malignancy at the outset (1 breast cancer, 2 ovarian cancer, 1 prostate cancer, and 1 bowel cancer). It could be argued that rheumatologists are better positioned to diagnose new malignancies in PMR, with more access to diagnostics than their primary care colleagues.

There is a known association of PMR with GCA. GCA may present in patients diagnosed with PMR at any time from 4.5 months to beyond 24 months the initial PMR presentation (Nielsen et al., 2022). Only one patient in this cohort developed GCA in the first 12 months of treatment. Rapid access strategies are already implemented globally for GCA. Given the association between PMR and GCA, similar protocols carried out by the same experts may have value. Rheumatology services already have experience of running fast-track services for GCA which may lend itself to being extended to PMR given the common disease spectrum. However, more studies are required to identify patients most likely to benefit from PMR rapid access clinics with GCA screening.

The standard recommended workup consists of RF, anti-CCP, CRP, ESR, full blood count, renal function, liver function, bone profile (Dejaco et al., 2015). We performed a more extended panel of laboratory blood markers, including anti-neutrophil cytoplasmic antibodies (ANCA) and an extended myositis panel. Our experience is that ANCA testing at baseline had utility. All 3 patients diagnosed with ANCA vasculitis (4%) presented clinically as textbook PMR without overt extra-musculoskeletal features. This diagnosis would likely have been delayed without knowledge of the antibody status. It prompted further investigations and confirmed the diagnosis of ANCA vasculitis. The extended myositis panel was less useful as there were some low-level positive results of unclear significance. However, 4 patients (5.5%) had a final diagnosis of antibody-positive myositis with an initial clinical presentation of classic PMR in 1 and lower extremity stiffness myalgia in the other 3. It may be useful in patients presenting atypically with isolated back/pelvic girdle symptoms. This would warrant study in larger cohorts.

It was clear from this study that primary care was not adherent to the PMR treatment guidelines regarding starting doses of glucocorticoids. Patients were started on significantly less glucocorticoids when commenced by rheumatology. Patients treated initially in primary care also did not have adequate bone protection or gastric ulcer protection add-on therapy. Partnership between primary care and rheumatology is vital for the management of patients with PMR. Patients reviewed by rheumatology should have a clear plan of instruction upon discharge to primary care. Clear guidance should also be provided on when to refer back to specialist clinics.

40% of patients with suspected PMR in primary care had an alternative diagnosis to PMR. This is a significant cohort of patients potentially exposed to inappropriate treatment with glucocorticoids. While some of the alternative inflammatory disease may respond to PMR dose glucocorticoids, this is not standard practice. Alternative glucocorticoid treatment regimens and approved glucocorticoid-sparing agents are preferable. This inappropriate PMR treatment for non-PMR diagnosis may also delay diagnosis and inadequately treat potentially serious inflammatory rheumatic disease.

Glucocorticoids were responsible for adverse events in our patient cohort including sleep disturbance, mood disturbance, new diabetes mellitus and pre-diabetes, and fractures. There is potentially serious morbidity and mortality associated with such side effects. Treatment should aim to taper the patient to the minimum dose required to limit these effects. There is a need for more studies on alternative agents for PMR treatment. Rheumatology lead clinics may provide an opportunity to study this patient cohort and involve more centres in clinical trials.

Glucocorticoids also failed to adequately treat every PMR patient in our cohort, with almost a fifth of this cohort requiring a glucocorticoid-sparing agent. Biological therapies are emerging in PMR with evidence for anti-IL6-R agents. This armamentarium may continue to grow with several other biological treatment prospects currently in trial. These are best initiated by specialist rheumatology clinics with experience in newer targeted therapies, and further define the need for fast-track PMR clinics.

We believe that rheumatologists should consider establishing fast-track PMR clinics and this study provides a strong case for and a template to support this practice innovation. A streamlined clinic will ensure all patients have the correct diagnosis, get the correct steroid dose, may be evaluated for GCA and subclinical GCA, have closer follow-up if required, and provide an opportunity for further research of PMR, compared with current practice.

Chapter 4:

An Evaluation of Subclinical Giant

Cell Arteritis in an Inception

Polymyalgia Rheumatica Cohort.

4.1 Abstract

Introduction

GCA and PMR are closely related conditions, presenting on a spectrum of disease (GPSD). Many PMR patients develop GCA months to years after the initial presentation of PMR. Recent advances in imaging have led to the identification of a subset of PMR patients without any initial presenting symptoms of GCA, but with features of GCA on imaging, which has been termed 'subclinical GCA in PMR'. The natural history of this finding remains unclear as does whether all PMR patients require screening for GCA and subclinical GCA at the time of PMR diagnosis, and ultimately what treatment protocols should be applied to these patients.

Methods

Primary care physicians were invited to refer patients with newly suspected PMR to the first Irish fast-track PMR clinic. Referral criteria included new onset shoulder or pelvic girdle pain and/or stiffness with elevated inflammatory markers. All patients were seen within 72 hours of referral. All patients had an extensive clinical review and assessment of laboratory parameters. Any patient who presented with symptoms suggestive of GCA (headache, visual disturbances, jaw or tongue claudication, scalp tenderness, or limb claudication) were excluded from the PMR cohort. Patients with a rheumatology diagnosis of PMR had an ultrasound (US) of both their temporal and axillary arteries.

Results

20.5% of PMR patients had ultrasound-confirmed subclinical GCA in PMR. These patients were significantly more likely to be male. There were no other clinical or laboratory features of statistical significance to discriminate them from pure PMR. Patients with subclinical GCA in PMR were more likely to relapse earlier than patients with either PMR or GCA and require higher overall glucocorticoid doses compared with pure PMR patients.

Conclusions

Subclinical GCA in PMR represents a significant subgroup of the GPSD spectrum of disease. Ultrasound appears more sensitive for diagnosis compared to clinical or laboratory features. These patients relapse earlier and have an overall higher glucocorticoid exposure and greater need for glucocorticoid-sparing agents.

4.2 Introduction

PMR and GCA are two frequently overlapping diseases. In clinical practice, GCA and PMR can present in association or as separate entities. It is reported that patients with GCA have manifestations of PMR in almost half of cases, and up to 20% of untreated PMR patients may develop GCA symptoms (Dejaco, 2011). Evidence from a recent meta-analysis has shown that inflammatory vascular involvement may be identified in PMR patients without any clinical symptoms of GCA, so-called 'subclinical GCA in PMR' (Hemmig et al., 2022). The lack of any specific clinical features of GCA in subclinical GCA in PMR is challenging in the clinical setting, with a high reported pooled prevalence of 23%, and 29% in studies incorporating the use of PET/CT imaging into their protocol (Hemmig et al., 2022). Older studies of pure PMR have shown that one in ten PMR patients go on to develop GCA along with severe ischaemic complications of visual loss, stroke and/or limb claudication in up to 50% of these (Narváez et al., 2015), highlighting the importance of identifying subclinical GCA in PMR from the outset. More studies are required to identify the phenotypic and laboratory features associated with PMR patients with subclinical vascular involvement at diagnosis. This may aid the appropriate risk stratification of PMR patients and contribute to a greater understanding of the GPSD spectrum.

As previously outlined in chapter 2, vascular ultrasound has high diagnostic accuracy, may be performed at the bedside during the initial clinical review, and is non-invasive. For these reasons, it is recommended as a first-line diagnostic tool in patients with suspected GCA (Dejaco et al., 2018). The quality and resolution of US images are

constantly improving. Very high-resolution US (frequency 55mHz) has shown improved assessment of vascular territories involved in GCA with superior distinction of the intima, media, and adventitial layers and allows exploration of early subclinical structural intimal changes in the arterial wall (Sundholm et al., 2019). US imaging of musculoskeletal structures in PMR has also greatly contributed to understanding the peri-tendinous and bursal pathology involved. It is also helpful to exclude confounding diseases such as tendinopathies, osteoarthritis, and crystal deposition diseases.

Despite improvements in GCA and PMR diagnosis associated with US, several unmet needs call for prospective observational and long-term follow-up studies in real-world settings. The benefit of routine vascular screening for subclinical GCA in PMR would depend on its true prevalence, associated costs, and benefit to patient care. It is still not known which PMR patients should be screened for GCA at the time of diagnosis, and how to optimally treat these patients to balance the risk of ischaemic symptoms with glucocorticoid side effects including diabetes mellitus and osteoporosis.

The emergence of the GPSD spectrum as a concept and the identification of 'subclinical GCA in PMR' bring a new research agenda to the conditions of GCA and PMR. The entire spectrum and course of GPSD should be prospectively examined, with particular attention to the anatomical distribution of inflammation in the varying disease subsets. Ideally, prospective multicentre studies with clinical, imaging, laboratory, and pathological characteristics should be recorded at baseline, at pre-defined follow-up intervals, with additional visits for relapses or adverse events. Associations between the

outcome measures and baseline characteristics should be analysed. In this way, a unified stratification and management strategy for GPSD, with early identification of high-risk patients to enable targeted treatment protocols, can be formulated. Such an approach should reduce the inappropriate use of glucocorticoids and lead to a better use of health economic resources (Tomelleri et al., 2023b). Establishing the first Irish Polymyalgia Fast-Track Clinic (PMR FTC) will help further this agenda. In chapters 2 and 3, we have shown a high estimated incidence of both PMR and GCA in Ireland. In addition, the experience of setting up and validating the first Irish GCA FTC in 2020 has paved the way for the first Irish PMR FTC to complete the assessment of the entire GPSD spectrum in a standardised, uniform manner in this study.

4.3 Review of US-identified subclinical GCA in PMR

Review of the literature to date on US identification of subclinical GCA in PMR has identified a paucity of studies, particularly in those in whom any meaningful conclusions can be drawn on the clinical phenotype of subclinical GCA in PMR. There are several problems with some of the older studies, including being carried out on US machines of poorer quality and resolution, compared to modern-day technology (Kraft et al., 1996, Schmidt and Gromnica-Ihle, 2002). In addition, many of the older studies did not report at all on the clinical features of PMR patients in whom subclinical GCA in PMR was identified (Lauwerys et al., 1997, Stammli et al., 2000). Two recent studies have contributed towards an understanding of the clinical phenotype of patients with PMR and subclinical GCA. They have characterised the clinical features and laboratory parameters (ESR and CRP) associated with this PMR subgroup (De Miguel et al., 2023b,

Burg et al., 2023). One further looked at subclinical GCA in PMR only in the context of one clinical feature - early morning stiffness (Manzo et al., 2023) (see table 4.1).

The most robust study, which was an international multicentre prospective study of almost 350 patients, identified that older patients with a shorter early morning stiffness and more hip girdle symptoms had a higher incidence of subclinical GCA in PMR (De Miguel et al., 2023b). These findings have only been replicated in one other single-centre study to date, which in addition identified a male predominance for subclinical GCA in PMR, albeit with smaller study numbers (n=60) (Burg et al., 2023). Further studies detailing clinical characteristics, a more robust laboratory marker analysis, and identification of the impact of cardiovascular risk factors on vascular ultrasound results would offer a much more vigorous exploration of this subgroup in the GSPD spectrum of disease.

Table 4.1 Studies assessing vascular ultrasound in PMR patients without any clinical feature of GCA.

Study	Country	PMR patients screened for GCA (n)	PMR with US finding of GCA (n, %)	Vessels Examined	Mean Age (yrs.)
Kraft, 1996	<i>Germany</i>	8	0 (0%)	TA	70
Lauwerys, 1997	<i>Belgium</i>	21	1 (4.7%)	TA	
Stammeler, 2000	<i>Germany</i>	22	7/22 (31.8%)	TA	67
Schmidt, 2002	Germany	102	8 (7.8%)	TA	69
Burg, 2023	Germany	60	13 (21.6%)	TA, Occ, Car, Ax, CRA, Vert	74
De Miguel, 2023	Spain, Italy, Bulgaria, Portugal, Slovenia	346	79 (22.8%)	TA, Ax	77
Manzo, 2023	Italy	143	23 (16%)	TA, Ax, Car, SC	71.5
Total		702	131 (18.6%)		

Legend: TA, temporal artery; Occ, occipital artery; Car, carotid artery; Ax, Axillary Artery; CRA, central retinal artery; Vert, vertebral artery, SC, subclavian artery

The objectives of this study were:

1. To assess the prevalence of subclinical GCA with temporal and axillary ultrasound in patients with newly diagnosed PMR.

2. To describe the clinical features in an inception cohort of subclinical GCA patients and compare them with cohorts of PMR and GCA patients.
3. To describe the laboratory features of subclinical GCA patients and compare them with cohorts of PMR and GCA patients.
4. To assess the cardiovascular risk comorbidities in subclinical GCA in PMR and evaluate their impact on the diagnostic accuracy of temporal and axillary ultrasound.
5. To define the natural history of subclinical GCA in PMR including relapse, progression to GCA, and adverse events over 1 year follow-up.
6. To compare cumulative glucocorticoid doses of patients with pure PMR compared to PMR with subclinical GCA.

4.4 Methods

As outlined in chapter 2 and 3, fast-track GCA and PMR clinics were established at TUH and SJH to establish a multicentre prospective longitudinal study. Patients with a new suspected diagnosis of PMR in primary care were recruited to the PMR FTC between July 2022 and July 2023. Patients were required to be over 50 years of age, have a new onset of bilateral shoulder pain and/or stiffness, and not be on glucocorticoid treatment exceeding 4 weeks in duration. All patients were reviewed in the fast-track PMR clinic within 72 hours. In addition, any patients with cranial or ischaemic symptoms of GCA at the outset were excluded from the PMR cohort and assessed in the GCA clinic.

Inclusion criteria for PMR patients included:

1. Patients with new onset bilateral shoulder or hip pain and/or new early morning stiffness.
2. Patients over 50 years of age.
3. Patients on glucocorticoid treatment for < 4 weeks duration.

Exclusion criteria included:

1. Patients <50 years.
2. Patients on glucocorticoid treatment >4 weeks duration.
3. Patients on synthetic or biological disease-modifying treatment for any reason.
4. Patients with a diagnosis of another inflammatory rheumatic condition.
5. Patients who lacked the capacity to consent or refused to consent to treatment in the clinic.

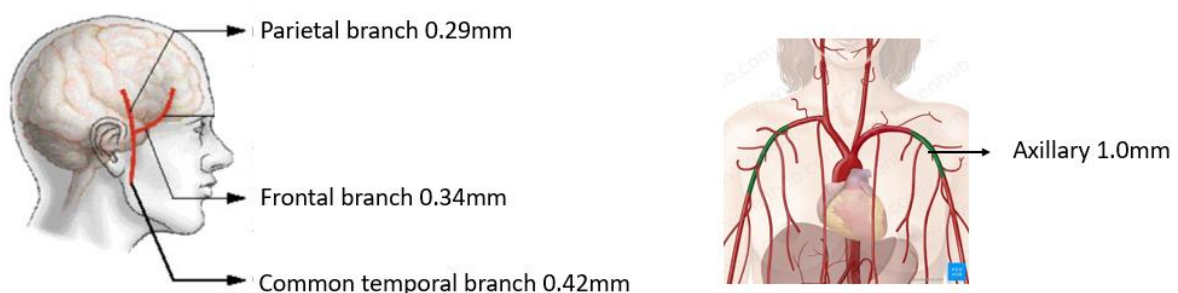
All patients referred underwent a thorough history and clinical examination. An extensive laboratory evaluation was also conducted including baseline ESR, CRP, full blood count, liver profile, renal function, fibrinogen, Hba1c, lipid profile, RF, ACPA, ANCA-related antibodies, and extended myositis panel. Plain film radiographs of the shoulders were also completed. All patients had a baseline vascular ultrasound of their cranial and axillary arteries. The diagnosis of PMR was a clinical one, made in agreement by two rheumatologists. PMR patients' cardiovascular comorbidities were recorded, as was the American College of Cardiology / American Heart Association Atherosclerotic Cardiovascular disease risk estimate ASCVD score in patients <75 years for whom the tool is validated. This is a standardised tool to predict 10-year risk of stroke and cardiovascular disease in patients <75 years and recommend management strategies for

those at risk (Goff et al., 2014). PMR patients had follow-up at 1-month, 3-month, 6-month, and 12-month time points. Each review undertook the same format of clinical review accompanied by US evaluation and laboratory marker analysis.

4.4.2 Ultrasound protocols

As outlined in detail in chapter 2, the temporal artery ultrasound validation, training, and protocols used in the GCA fast-track clinic were applied to a PMR cohort. US of all 6 branches of the superficial temporal arteries and both axillary arteries was performed using a GE P9 device. Sonographic abnormalities considered indicative of vasculitis in the temporal arteritis included the halo sign characterised by a thickened, non-compressible intima-media complex. Cut-off values of $\geq 0.29\text{mm}$ for the parietal branch, $\geq 0.34\text{mm}$ for the frontal branch and ≥ 0.42 for the common temporal branch were used (Schäfer et al., 2017). In the axillary arteries, a halo sign, and an intima-media thickness of $>1.0\text{mm}$ was considered positive. This has been shown to have 100% sensitivity and specificity in the common, frontal, and axillary branches, and 97.2% sensitivity and 98.8% specificity in the case of the parietal branch (Schäfer et al., 2017).

Figure 4.1 Cut-off values for temporal and axillary artery positivity



4.4.3 Ethical Approval

Full ethical approval was obtained from the Joint Research Ethics Committee for Tallaght University Hospital and St James Hospital, Dublin, Ireland. All patients gave fully informed written consent to participate in the fast-track clinic study.

4.4.4 Statistical Analysis

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 have been performed in SPSS.

4.5 Results

4.5.1 Patient characteristics

Between July 2022 and July 2023, a total of 157 patients with new suspected PMR were referred from primary care to the FTC with 73 having a confirmed diagnosis of PMR after 12 months follow-up. In the GCA FTC, 80 patients were assessed with 24 new GCA patients diagnosed. 15/73 PMR patients (20.5%), had subclinical GCA in PMR identified with vascular ultrasound, in the absence of any clinical features of GCA.

Age was not normally distributed in the pure PMR group. The median age of patients in the pure PMR group was 71 years [64-76], while those in the subclinical GCA in PMR group had a median age of 72 years [67-77], $p=0.95$. The median age in the GCA group was 71 years [67.5-76] with no significant difference in age between GCA and subclinical GCA in the PMR groups, $p=0.65$. Pure PMR patients were more likely to be female (55% females vs 45% males), compared with a male predominance observed in the subclinical GCA in PMR group, at 80%, $p=0.01$. This finding of a male tendency towards subclinical GCA in PMR was also observed in a previous study (Burg et al., 2023). The GCA group consisted of 54.2% males. There was no statistically significant difference in gender between the GCA and subclinical GCA groups, $p=0.10$. The mean BMI in the subclinical GCA in PMR group was 26.7 kg/m^2 . Further breakdown revealed that no patients were underweight, 46.7% of patients were normal weight, 20% were overweight, and 33.3% were obese. This was similar in both pure PMR and GCA groups with the majority of patients being either overweight or obese.

Table 4.2 Demographics comparing pure PMR, subclinical GCA in PMR, and GCA subgroups.

Clinical Characteristic	Pure PMR (58) (median [IQR] or mean [SD] or n, %)	Subclinical GCA in PMR (15) (median [IQR] or mean [SD] or n, %)	GCA (24) (median [IQR] or mean [SD] or n, %)	P-value
Age (years)	71[64-76]	72[67-77]	71[67.5-76]	0.79
Female Gender	32 (55.2%)	3 (20%)	11 (45.8%)	0.05 (<i>P</i> =0.01 PMR and subclinical GCA)
Male gender	26 (44.8%)	12 (80%)	13 (54.2%)	0.05 (<i>P</i> =0.01 PMR and subclinical GCA)
BMI <18.4 kg/m ²	2 (3.4%) *	0*	0*	*Numbers too small to calculate p value
BMI 18.5-24.9 kg/m ²	11 (18.9%)	7 (46.7%)	9 (37%)	0.29
BMI 25-29.9 kg/m ²	25 (43.1%)	3 (20%) *	7 (29%)	*Numbers too small to calculate p value
BMI >30 kg/m ²	20 (34.5%)	5 (33.3%)	8 (33%)	0.61

4.5.2 Clinical Characteristics of patients with subclinical GCA in PMR

Regarding presenting symptoms, all patients (n=15, 100%) with subclinical GCA in PMR had bilateral shoulder pain, 13 patients (86.7%) had early morning stiffness, with the mean duration of stiffness lasting 85 minutes [± 72.7]. 12 (80%) patients had hip girdle pain/stiffness, 6 (40%) had neck pain on presentation, 1 (6.7%) had back pain, 3 (20%)

patients had peripheral joint pain affecting at least one joint; with 2 reporting hand pain, and 1 with ankle pain. 2 patients with peripheral joint pain had clinical evidence of joint swelling at the site of the painful joint. 4 patients (26.7%) reported night sweats, 2 (13.3%) reported fevers, 2 (13.3%) reported anorexia, and 4 (26.7%) reported weight loss. Compared to their pure PMR counterparts there was no differentiating clinical feature that met statistical significance with the presence of subclinical GCA in PMR. However, subclinical GCA in PMR patients did tend to have a shorter duration of early morning stiffness, $p=0.09$, along with more constitutional symptoms, especially fever, $p=0.05$, and night sweats, $p=0.06$, compared with their pure PMR counterparts. The De Miguel study also observed that patients with subclinical GCA in PMR had a shorter duration of early morning stiffness than their pure PMR counterparts (De Miguel et al., 2023b). Table 4.3 shows the main clinical differences between the patients with pure PMR and the patients with PMR with subclinical GCA.

Table 4.3 Clinical characteristics of pure PMR patients compared with subclinical GCA in PMR patients.

Clinical Characteristic	Pure PMR (n=58)	Subclinical GCA in PMR (n=15)	P-value
Shoulder PMR	57 (98.3%)	15 (100%)	0.79
Hip PMR	42 (72.4%)	12 (80%)	0.41
Neck pain	23 (39.7%)	6 (40%)	0.37
Back pain	13 (22.4%)	1 (6.7%)	0.39
Presence of early morning stiffness (EMS)	51 (87.9%)	13 (86.7%)	0.41
Duration of EMS (mean, SD)	99.1 [± 88.9]	85 [± 72.7]	0.09
Peripheral joint pain	9 (15.5%)	3 (20%)	0.20
Swollen peripheral joints	8 (13.8%)	3 (13.3%)	0.62
Fever	3 (5.2%)	3 (13.3%)	0.05
Night sweats	8 (13.8%)	4 (26.7%)	0.06
Anorexia	16 (27.6%)	2 (13.3%)	0.46
Weight loss	11 (19%)	4 (26.7%)	0.15

4.5.3 Laboratory features of subclinical GCA in PMR

4.5.3.1 Inflammatory markers

The mean baseline ESR in patients with subclinical GCA in PMR was numerically higher at 53.6mm/h ± 33.6 , compared with 41.6mm/h ± 23.9 in the pure PMR group, but this was not statistically significant; $p=0.25$. CRP did not have a normal distribution and the median baseline CRP in subclinical GCA in PMR was 25mg/l [16-49], compared with 16mg/l [6-48.5] in pure PMR patients, $p=0.36$. A pilot analysis of IL-6, il-8, TNF-alpha,

and IL-1 was completed on a subset of patients at the baseline visit. The median baseline IL-6 level in subclinical GCA in PMR patients was 13.7pg/ml [3.13-41.8], compared with 8.43pg/ml [5.33-18.64] in PMR, $p=0.41$. Patients with subclinical GCA in PMR had a median baseline IL-8 level of 15.6pg/ml [11.2-20.8], compared with pure PMR patients with levels of 31.7pg/ml [16.85-99.65], $p=0.06$. The median baseline TNF- α levels in patients with subclinical GCA in PMR were 11.45pg/ml [9.38-12.95], compared to 14.9pg/ml [11.77 – 16.82] in those with pure PMR, $p=0.04$. Finally, the median baseline IL-1 level in patients with subclinical GCA in PMR was 0.36pg/ml [0.24-0.43], compared with 0.35pg/ml [0.23-1.06], $p=0.66$ (see table 4.4). There was no significant correlation between age and ESR ($r=0.05$, $p=0.85$) or age and CRP ($r=0.22$, $p=0.41$).

The only result of statistical significance between subclinical GCA in PMR and pure PMR was TNF- α . This result is of unclear clinical significance. In keeping with De Miguel's multicentre prospective European cohort, we did not appreciate any difference in ESR or CRP comparing subclinical GCA in PMR to pure PMR. The referrals to our PMR FTC had significant glucocorticoid exposure before referral, with a mean cumulative glucocorticoid exposure in these patients upon referral of 457.73mg $\pm$ 293.6. Only 38% of the whole group were steroid naïve at the time of initial assessment for baseline blood tests, which is a limiting factor in this analysis. Numbers are too small to offer any meaningful conclusions from a sub-analysis comparing steroid-naïve and steroid-exposed patients.

Table 4.4 Inflammatory markers in pure PMR and subclinical GCA in PMR.

Laboratory parameter	Pure PMR (mean, [SD] or median, [IQR])	Subclinical GCA in PMR (mean, [SD] or median, [IQR])	P-value
ESR (mm/h)	41.6 [$\pm$ 23.9] (n=58)	53.6 [$\pm$ 33.6] (n=15)	0.25
CRP (mg/l)	16 [6-48.5] (n=58)	25 [16-49] (n=15)	0.36
IL-6 (pg/ml)	13.7 [3.13-41.8] (n=37)	8.43 [5.33-18.64] (n=9)	0.41
IL-8 (pg/ml)	31.7 [16.85-99.65] (n=25)	15.6 [11.2-20.8] (n=7)	0.06
TNF α (pg/ml)	14.9[1.77 – 16.82] (n=30)	11.45 [9.38-12.95] (n=8)	0.04
IL-1 (pg/ml)	0.35 [0.23-1.06] (n=30)	0.36 [0.24-0.43] (n=8)	0.66

ESR and CRP were numerically higher in GCA than in subclinical GCA, but this did not reach statistical significance. Overall, those with subclinical GCA had ESR and CRP levels between the ranges observed in both PMR and GCA. Subclinical GCA tended to have median IL-6, IL-8, and TNF-alpha levels closer to the figures observed in GCA patients, while IL-1 levels were closer to those in the pure PMR group (see table 4.5). None of these reached statistical significance.

Table 4.5 Inflammatory markers in GCA and subclinical GCA in PMR.

Laboratory parameter	GCA (mean [SD] or median [IQR])	Subclinical GCA in PMR (mean, [SD] or median, IQR])	P-value
ESR (mm/h)	64.7 [$\pm$ 30.86] (n=24)	53.6 [$\pm$ 33.6] (n=15)	0.24
CRP (mg/l)	55.5 [11.75-91.5] (n=24)	25 [16-49] (n=15)	0.28
IL-6 (pg/ml)	8.7 [3.13-27.5] (n=10)	8.43 [5.33-18.64] (n=9)	0.9
IL-8 (pg/ml)	16.3 [11.3-22.2] (n=7)	15.6 [11.2-20.8] (n=7)	0.9
TNFα (pg/ml)	12.95 [9.47-15.85] (n=8)	11.45 [9.38-12.95] (n=8)	0.59
IL-1 (pg/ml)	0.27 [0.27-0.39] (n=7)	0.36 [0.24-0.43] (n=8)	0.42

4.5.3.2 Haematological markers

Haematological blood markers were not particularly useful for differentiating subclinical GCA in PMR from pure PMR (see table 4.6). While there was a statistical difference in monocyte counts between pure PMR and subclinical GCA in PMR, this should be interpreted in the context of significant glucocorticoid exposure in both PMR subgroups. 26.7% of subclinical GCA in PMR patients were glucocorticoid-naïve at baseline, compared with 43% of the pure PMR group. This may represent a more severe clinical

presentation of the subclinical GCA group before PMR FTC referral, necessitating glucocorticoids from primary care.

Monocytes, platelets, and fibrinogen were all numerically increased in the total PMR group (including both pure PMR and subclinical GCA in PMR) in glucocorticoid -naïve patients compared to those with previous glucocorticoid exposure, but this was not statistically significant. This may be the reason for the increased monocytes in the pure PMR group, a reflection of the increased numbers of glucocorticoid-naïve patients in this group.

GCA patients had statistically more elevated platelet counts than their subclinical GCA counterparts, $p=0.02$. Fibrinogen was numerically higher in GCA compared with both subclinical GCA in PMR and pure PMR, perhaps reflective of a higher inflammatory state (see table 4.7).

Table 4.6 Haematological parameters in subclinical GCA in PMR and pure PMR

Laboratory parameter	Pure PMR (n=58)	Subclinical GCA in PMR (n=15)	P-value
Haemoglobin (g/dl)	13.1, SD = 1.17, 95% CI [12.80, 13.40]	13.2, SD = 1.53, 95% CI [12.43, 13.97]	.78
Neutrophils ($\times 10^9/l$)	7.37, SD = 3.18, 95% CI [6.55, 8.19]	8.73, SD = 3.59, 95% CI [6.91, 10.55]	.17
Lymphocytes ($\times 10^9/l$)	1.89, SD = 0.73, 95% CI [1.70, 2.08]	2.65, SD = 4.06, 95% CI [0.60, 4.70]	.18
Mono ($\times 10^9/l$)	0.72, SD = 0.29, 95% CI [0.65, 0.79]	0.65, SD = 0.8, 95% CI [0.25, 1.05]	<.001
Platelets ($\times 10^9/l$)	313.3, SD = 182.0, 95% CI [266.46, 360.14]	325.1, SD = 91.4, 95% CI [278.85, 371.35]	.61
Fibrinogen (g/l)	4.07, SD = 1.07, 95% CI [3.79, 4.35]	4.03, SD = 1.44, 95% CI [3.30, 4.76]	.91

Table 4.7 Haematological parameters in GCA and subclinical GCA in PMR

Laboratory parameter	GCA (n=24)	Subclinical GCA in PMR (n=15)	p-value
Neutrophils ($\times 10^9/l$)	9.03, SD = 3.66, 95% CI [7.57, 10.49]	8.73, SD = 3.59, 95% CI [6.91, 10.55]	.45
Lymphocytes ($\times 10^9/l$)	1.92, SD = 1.05, 95% CI [1.50, 2.34]	2.65, SD = 4.06, 95% CI [0.60, 4.70]	.40
Mono ($\times 10^9/l$)	0.68, SD = 0.28, 95% CI [0.57, 0.79]	0.65, SD = 0.8, 95% CI [0.25, 1.05]	.38
Platelets ($\times 10^9/l$)	402.18, SD = 222.6, 95% CI [313.12, 491.24]	325.1, SD = 91.4, 95% CI [278.85, 371.35]	.02

Fibrinogen (g/l)	4.33, SD = 1.61, 95% CI [3.69, 4.97]	4.03, SD = 1.44, 95% CI [3.30, 4.76]	.14

4.5.3.3 Biochemical markers

Biochemical markers were also not informative in differentiating pure PMR from subclinical GCA in PMR. LDL was seen to be more elevated in those with subclinical GCA in PMR, perhaps indicating an increased risk of cardiovascular disease but pure PMR patients had higher levels of lipid-lowering agents prescribed, so the significance of this finding is uncertain.

Table 4.8 Biochemical markers in subclinical GCA in PMR

Laboratory parameter	Pure PMR (n=58)	Subclinical GCA in PMR (n=15)	p-value
Total Cholesterol (mmol/L)	4.04, SD = 1.22, 95% CI [3.73, 4.35]	5.2, SD = 1.24, 95% CI [4.57, 5.83]	.52
HDL (mmol/L)	1.65, SD = 0.63, 95% CI [1.49, 1.81]	1.72, SD = 0.81, 95% CI [1.31, 2.13]	.80
LDL (mmol/L)	2.38, SD = 0.95, 95% CI [2.14, 2.62]	2.75, SD = 1.11, 95% CI [2.19, 3.31]	<.001
TG (mmol/L)	1.51, SD = 0.61, 95% CI [1.35, 1.67]	1.56, SD = 1.08, 95% CI [1.01, 2.11]	.88
Creatinine (μmol/L)	78.0, SD = 20.14, 95% CI [72.82, 83.18]	77.6, SD = 14.9, 95% CI [70.06, 85.14]	.94
eGFR (ml/min/1.73m ²)	74.5, SD = 16.54, 95% CI [70.24, 78.76]	80.9, SD = 10.5, 95% CI [75.59, 86.21]	.25
Sodium (mmol/L)	138.8, SD = 2.5, 95% CI [138.16, 139.44]	139.1, SD = 3.1, 95% CI [137.53, 140.67]	.76
Potassium (mmol/L)	4.3, SD = 0.53, 95% CI [4.16, 4.44]	4.43, SD = 0.3, 95% CI [4.28, 4.58]	.43
Corrected Calcium (mmol/L)	2.54, SD = 2.36, 95% CI [1.93, 3.15]	2.24, SD = 0.05, 95% CI [2.21, 2.27]	.57

Albumin (g/L)	42.56, SD = 3.45, 95% CI [41.67, 43.45]	44.33, SD = 2.73, 95% CI [42.95, 45.71]	.22
Bilirubin (μmol/L)	6.96, SD = 2.78, 95% CI [6.24, 7.68]	9.67, SD = 4.8, 95% CI [7.24, 12.10]	.07
Alkaline phosphatase (U/L)	84.52, SD = 22.97, 95% CI [78.61, 90.43]	87.83, SD = 22.89, 95% CI [76.25, 99.41]	.75
GGT (IU/L)	39.56, SD = 32.09, 95% CI [31.30, 47.82]	33.5, SD = 14.77, 95% CI [26.03, 40.97]	.65
AST (IU/L)	21.37, SD = 7.55, 95% CI [19.43, 23.31]	21.0, SD = 5.25, 95% CI [18.34, 23.66]	.91
ALT (IU/L)	19.26, SD = 9.44, 95% CI [16.83, 21.69]	25.5, SD = 13.83, 95% CI [18.50, 32.50]	.18
Hba1c (mmol/mol)	42.71, SD = 8.15, 95% CI [40.61, 44.81]	43.07, SD = 6.62, 95% CI [39.72, 46.42]	.92

4.6 Cardiovascular Risk Factors in Subclinical GCA in PMR

There is some concern that cardiovascular risk may influence the findings of vascular US in patients undergoing temporal and axillary artery ultrasound assessment for suspected vasculitis. A previous study has shown that those with very high cardiovascular risk factors have a higher IMT compared with patients with moderate or low cardiovascular risk (Martire et al., 2021).

In this cohort, we compared the cardiovascular risk factors of patients with pure PMR and subclinical GCA in PMR.

1. Hypertension

28/58 of patients (47.5%) of patients with pure PMR had a diagnosis of hypertension and were on anti-hypertensive medications compared with 11/15 (73%) of those with subclinical GCA, $p=0.11$.

2. Smoking

30/58 (51%) of patients with pure PMR never smoked, while 2/58 (3%) were active smokers and 26/58 (45%) were ex-smokers. This compared with 5/15 (33%) of patients having never smoked in the subclinical GCA in PMR group, 2/15 (13%) being active smokers, and 8/15 (53%) being ex-smokers, $p=0.24$.

3. Hyperlipidaemia

21/58 (36%) of patients with pure PMR were on treatment with a lipid-lowering medication for hyperlipidaemia. This is compared with 4/11 (26.7%) of the subclinical GCA in PMR group having a diagnosis of hyperlipidaemia for which a lipid-lowering drug was prescribed, $p=0.11$. The mean total cholesterol for those with subclinical GCA was $5.2\text{mmol/L} \pm 1.24$, compared with $4.04\text{mmol/L} \pm 1.22$ in the pure PMR group, $p=0.52$. The mean HDL for patients with subclinical GCA was $1.72\text{mmol/L} \pm 0.81$ compared with $1.65\text{mmol/L} \pm 0.63$ in the pure PMR group, $p=0.8$. LDL did show a statistically significant difference between the groups, with levels of $2.75\text{mmol/L} \pm 1.11$ in subclinical GCA and $2.38\text{mmol/L} \pm 0.95$ in pure PMR, $P<0.001$, perhaps reflective of the slightly higher percentage of pure PMR patients on a lipid-lowering agent. Triglyceride levels were almost identical between both groups, $p=0.88$.

4. Diabetes Mellitus

17% of patients with pure PMR had a diagnosis of diabetes mellitus compared with 20% of those with subclinical GCA in PMR, $p=0.11$. There was no difference in the mean hba1c between pure PMR and subclinical GCA in PMR (42.7mmol/mol and 43.07 mmol/mol), $p=0.92$.

Overall cardiovascular risk was calculated in the total PMR cohort with the American College of Cardiology / American Heart Association Atherosclerotic Cardiovascular disease risk estimate ASCVD score. This is a standardised tool to predict the 10-year risk of stroke and cardiovascular disease in patients <75 years and recommend management strategies for those at risk (Goff et al., 2014). Only patients in our cohort under the age of 75 years were included as per the validation of the tool. Overall, 32.2% of patients with pure PMR had an intermediate cardiovascular risk score, and 16.9% were at high risk. This is compared with 40% of those with subclinical GCA having an intermediate risk, and 20% having high risk (see figure 4.6). No statistically elevated cardiovascular risk overall was identified for those with subclinical GCA in PMR, compared with those with pure PMR, $p=0.27$, with the caveat that not all patients could have this risk calculated (validated only for patients <75 years). There was no significant correlation between ASCVD and halo count; $r=0.268$, $p=0.45$, ASCVD and halo score; $r=-0.254$, $p=0.48$, or ASCVD and OGUS; $r=-0.155$, $p=0.66$. There was a significant positive correlation between cardiovascular risk score and increasing age, $r=0.825$, $p=0.003$.

To explore whether conventional cardiovascular risk might account for the presence of subclinical GCA on vascular ultrasound, logistic regression analyses were performed with subclinical GCA in PMR as the dependent variable. Univariable models showed no

significant association between subclinical GCA and LDL cholesterol (OR 0.80, 95% CI 0.34–1.90), total cholesterol (OR 0.87, 95% CI 0.43–1.74), HDL cholesterol (OR 2.21, 95% CI 0.53–9.31), diabetes (OR 0.82, 95% CI 0.16–4.28) or BMI (OR 0.92, 95% CI 0.81–1.04). Hypertension (OR 2.79, 95% CI 0.78–9.98, $p = 0.11$) and ever-smoking (OR 2.50, 95% CI 0.70–8.92, $p = 0.16$) tended to be more common in the subclinical GCA group, but did not reach statistical significance.

In an exploratory multivariable model including LDL, hypertension, smoking status and diabetes, none of these variables was independently associated with subclinical GCA status; all adjusted odds ratios were close to unity with wide confidence intervals crossing 1. Overall, these analyses suggest that conventional ASCVD-type cardiovascular risk factors do not explain the presence of subclinical GCA in this cohort.

Figure 4.2 Correlation between ASCVD and baseline Halo count in subclinical GCA in

PMR

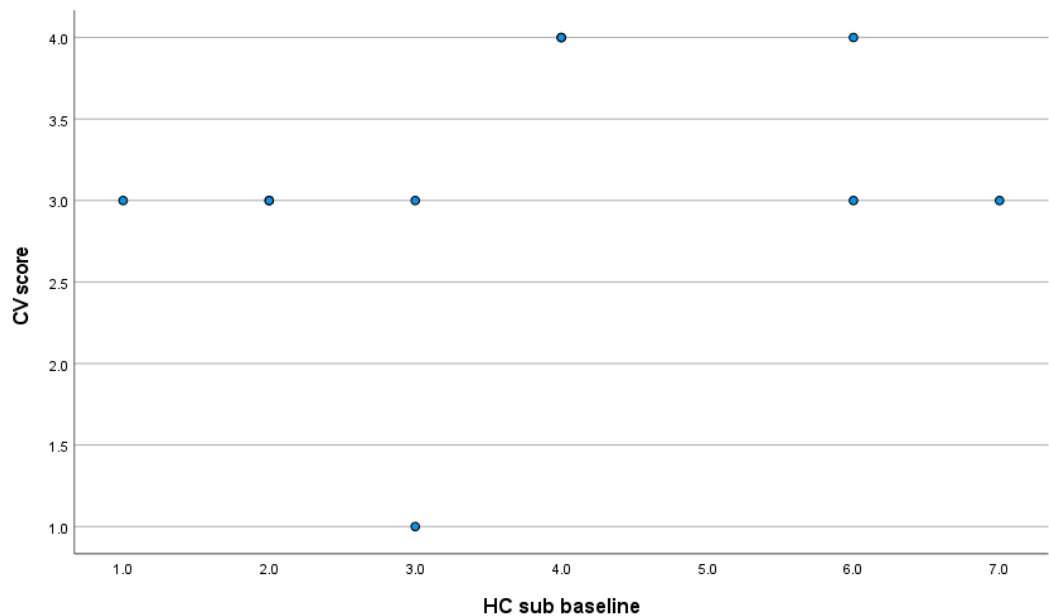


Figure 4.3 Correlation between ASCVD and baseline Halo score in subclinical GCA in

PMR

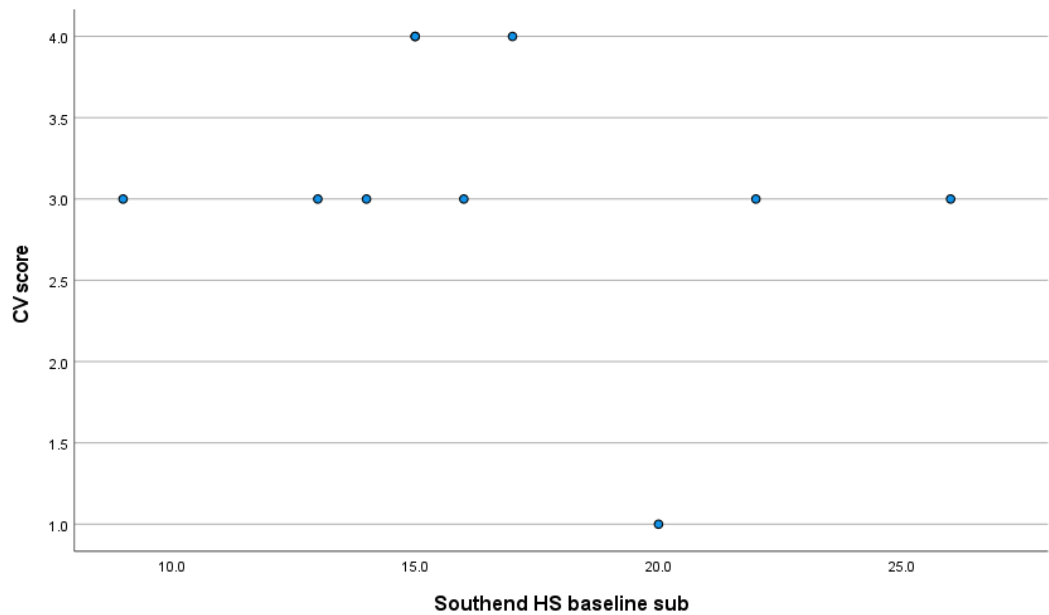


Figure 4.4 Correlation between ASCVD and baseline OGUS in subclinical GCA in PMR

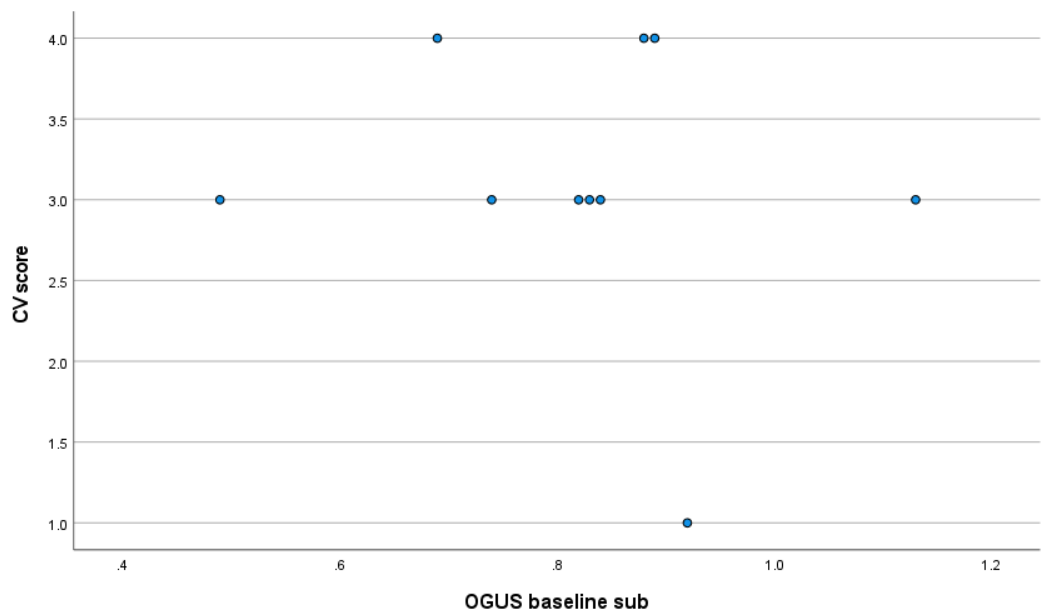


Figure 4.5 Cardiovascular risk factors in pure PMR and subclinical GCA in PMR.

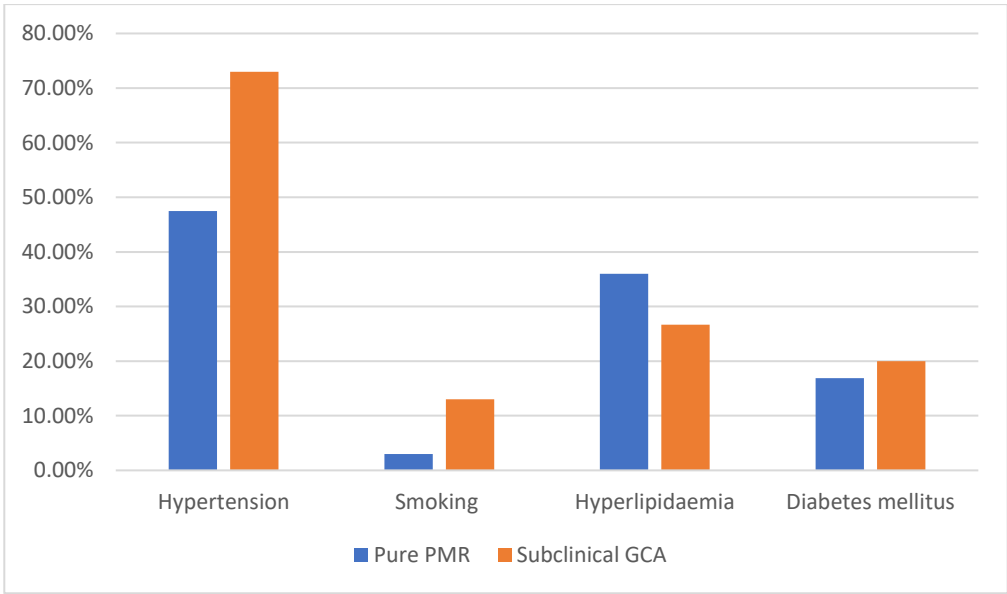


Figure 4.6 Distribution of cardiovascular risk in pure PMR and subclinical GCA in PMR

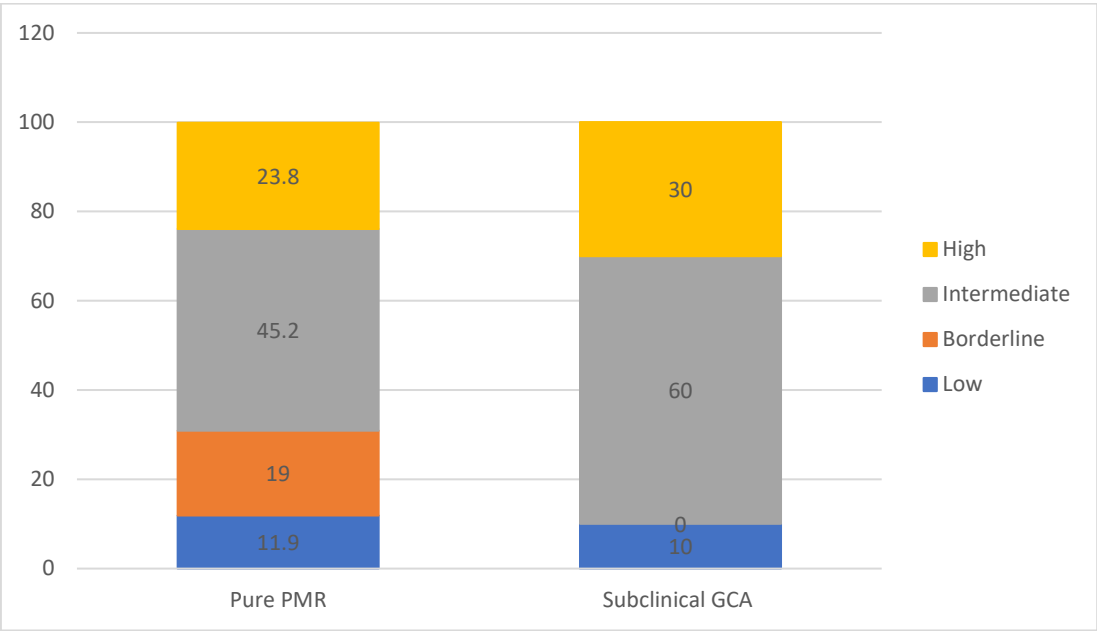
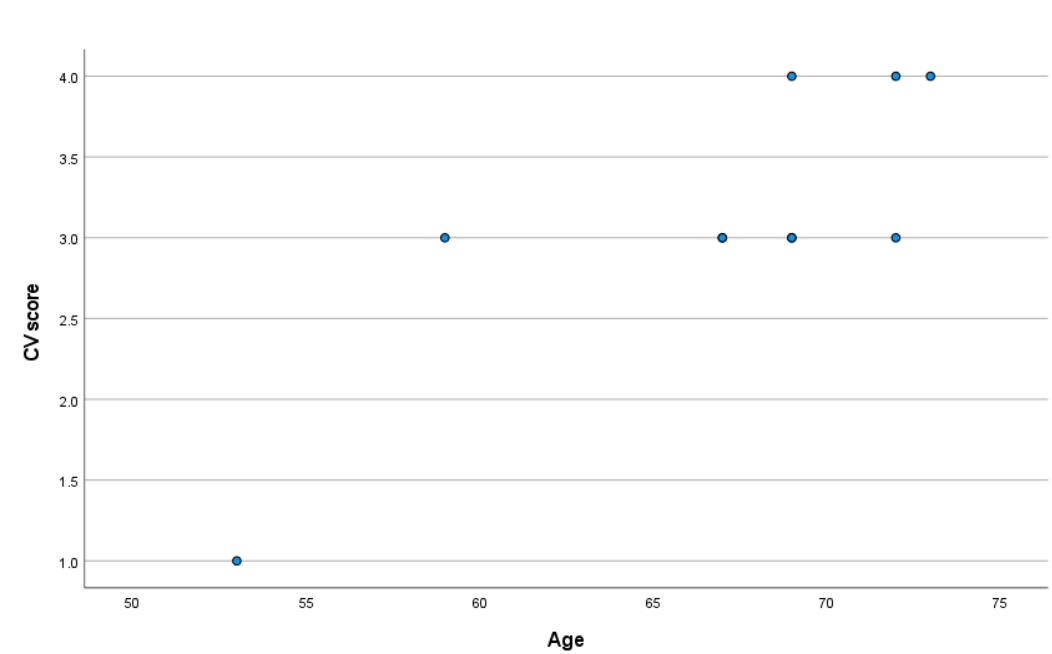


Figure 4.7 Correlation between ASCVD and age



4.7 Treatment of subclinical GCA in PMR patients

4.7.1 Glucocorticoid Treatment

Patients with PMR were treated in accordance with the 2015 ACR/EULAR guidelines (Dejaco et al., 2015). The starting glucocorticoid dose was 12.5-25mg based on clinical judgment. Factors considered to decide the starting dose included BMI, duration, and severity of symptoms, and inflammatory markers. This treatment was initiated for patients with pure PMR and subclinical GCA in PMR alike to understand the natural history of the disease and appreciate if any differences were observed in the outcomes of the subclinical GCA group. The mean starting glucocorticoid dose of all patients attending the FTC was 18.48mg $\pm$ 6.87. The median starting dose of glucocorticoid for pure PMR was 15mg [15-20], and 20mg [15-25] for subclinical GCA in PMR, $p < 0.001$. The median cumulative glucocorticoid exposure prescribed by primary care for pure PMR patients on referral to the FTC was 105mg [0-375], and for subclinical GCA in PMR, this figure was 280mg [0-770].

39% of the total PMR FTC patients were glucocorticoid naïve on referral to the fast-track clinic. This represented 27% of subclinical GCA in PMR patients and 43% of the pure PMR group. There were 4 patients (33%) with subclinical GCA initiated on glucocorticoid doses of more than 25mg in primary care before referral to the FTC. This compares with 5 patients (8.6%) of the pure PMR group having exposure to >25mg glucocorticoid in primary care before referral, $p = 0.02$. This may represent a more severe clinical presentation of the subclinical GCA group before PMR FTC referral, necessitating high-dose glucocorticoids from primary care. In cases where patients had already been

initiated on doses of >25mg in primary care, patients were tapered down from that initial starting dose.

All patients in the fast-track clinic had an assessment of osteoporosis risk and were initiated on bone protection in the form of a bisphosphonate and/or calcium and vitamin D replacement. All patients in the subclinical GCA group and 96% of the pure PMR group accepted bisphosphonate bone protection while on high-dose glucocorticoids. Continuation of bisphosphonate was based on their osteoporotic risk. All patients were also offered proton pump inhibitor cover to prevent gastric complications while on glucocorticoid doses >7mg.

Glucocorticoids were tapered to achieve a dose of 10mg or less by 8 weeks of treatment. The mean glucocorticoid treatment dose at 1 month for pure PMR was 12.3mg $\pm$ 4.9, and 22.3mg $\pm$ 9.04 for subclinical GCA in PMR. At 3 months, the pure PMR group was on a mean dose of 8.2mg $\pm$ 2.75, and those with subclinical GCA on 8.8mg $\pm$ 4.31. By 6 months, this had reduced to a mean dose of 5.95mg $\pm$ 2.34 in the pure PMR group and 5.46mg $\pm$ 4.23 in the subclinical GCA group. At the 12-month timepoint, patients with pure PMR were treated with a mean glucocorticoid dose of 1.05mg $\pm$ 2.04, while those with subclinical GCA in PMR were on 3.4mg $\pm$ 7.6.

The cumulative glucocorticoid exposure for those with pure PMR at 1-month, 3-month, 6-month, and 12-month timepoints was 734mg $\pm$ 404.1, 1,247.1mg $\pm$ 391.3, 1,932.2mg $\pm$

491.3, and 2,486mg $\pm$ 630.3 respectively. This is compared with mean cumulative doses in the subclinical GCA in PMR group which were 1,328mg $\pm$ 774.7, 2,036mg $\pm$ 808.1, 2,575.5mg $\pm$ 918.1, and 3,449.9mg $\pm$ 1399.5 at 1-, 3-, 6-, and 12-month timepoints respectively. This represented significantly higher cumulative steroid doses at all timepoints for those with subclinical GCA in PMR compared with pure PMR (see table 4.9). In the GCA cohort, the total glucocorticoid exposure was 1,470mg $\pm$ 384.88 at 1 month 2,603.14mg $\pm$ 440.84 at 3 months, 3,235.74mg $\pm$ 869.15 at 6 months, and 3,844.31mg $\pm$ 1,420.89 at 12 months. While GCA patients had higher cumulative glucocorticoid doses than subclinical GCA in PMR at 3- and 6-month timepoints, by 12 months this was not statistically higher (see table 4.10)

Table 4.9 Cumulative glucocorticoid exposure in pure PMR and subclinical GCA in PMR.

Timepoint	Pure PMR (n=58)	Subclinical GCA in PMR (n=15)	p-value
1 month	734 mg, SD = 404.1, 95% CI [630.0, 838.0]	1328 mg, SD = 74.7, 95% CI [1290.2, 1365.8]	.003
3 months	1247.1 mg, SD = 391.3, 95% CI [1146.4, 1347.8]	2036 mg, SD = 808.1, 95% CI [1627.0, 2445.0]	<.001
6 months	1932.2 mg, SD = 491.3, 95% CI [1805.8, 2058.6]	2575.5 mg, SD = 918.1, 95% CI [2110.9, 3040.1]	.007
12 months	2575.5 mg, SD = 918.1, 95% CI [2339.2, 2811.8]	3449.9 mg, SD = 1399.5, 95% CI [2741.7, 4158.1]	.02

Table 4.10 Cumulative glucocorticoid exposure in GCA and subclinical GCA in PMR.

Timepoint	GCA (n=24)	Subclinical GCA in PMR (n=15)	p-value
1 month	1470 mg, SD = 384.88, 95% CI [1316.0, 1624.0]	1328 mg, SD = 774.7, 95% CI [935.9, 1720.1]	.44
3 months	2603.14 mg, SD = 440.84, 95% CI [2426.8, 2779.5]	2036 mg, SD = 808.1, 95% CI [1627.0, 2445.0]	.007
6 months	3235.74 mg, SD = 869.15, 95% CI [2888.0, 3583.5]	2575.5 mg, SD = 918.1, 95% CI [2110.9, 3040.1]	.03
12 months	3844.31 mg, SD = 1420.89, 95% CI [3275.8, 4412.8]	3449.9 mg, SD = 1399.5, 95% CI [2741.7, 4158.1]	.40

4.7.2 Glucocorticoid sparing treatment

A significant number of total PMR patients were not adequately treated with standard glucocorticoid treatment alone (18.3%). 1 patient was initiated on methotrexate (pure PMR), with a further 12 patients initiated on tocilizumab (5 subclinical GCA and 7 pure PMR) (see table 4.11). Overall, 33.3% of subclinical GCA in PMR patients required a glucocorticoid-sparing agent, compared to only 13.7% of those with pure PMR, $p=0.07$.

Table 4.11 Glucocorticoid sparing treatment commenced in pure PMR and subclinical GCA in PMR.

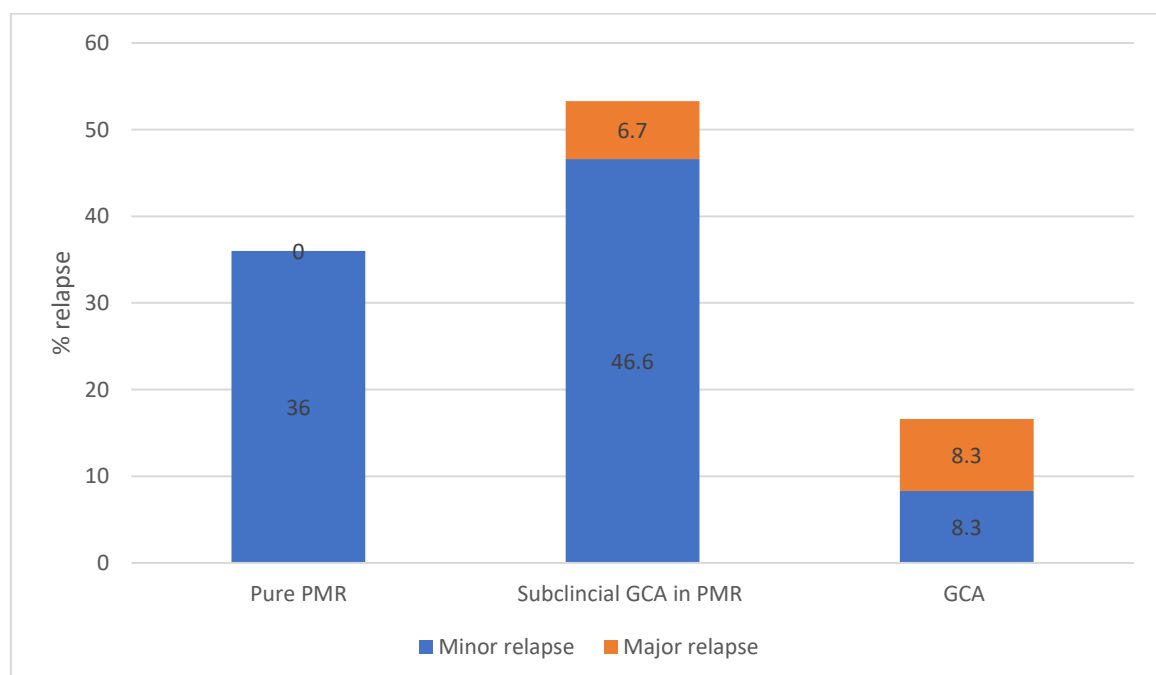
Patient	Drug	Reason for starting	Time started
Pure PMR			
Patient 1	Methotrexate	Brittle diabetes mellitus	Month 1
Patient 2	Tocilizumab	Difficulty weaning steroid and peripheral joint pain	Month 2
Patient 3	Tocilizumab	Relapse x 2	Month 4
Patient 4	Tocilizumab	Relapse	Month 5
Patient 5	Tocilizumab	Relapse	Month 5
Patient 6	Tocilizumab	Relapse x 2	Month 6
Patient 7	Tocilizumab	Relapse	Month 8
Patient 8	Tocilizumab	Relapse	Month 12
Subclinical GCA in PMR			
Patient 1	Tocilizumab	Unable to taper glucocorticoid <20mg.	Month 1
Patient 2	Tocilizumab	Unable to taper glucocorticoid <20mg.	Month 1
Patient 3	Tocilizumab	Unable to taper glucocorticoid <20mg.	Month 1
Patient 4	Tocilizumab	Relapse x 2	Month 9
Patient 5	Tocilizumab	Relapse x 2	Month 12

4.8 Relapse of subclinical GCA in PMR patients

There was an overall high relapse rate for all PMR patients. Throughout 12 months of follow-up, 8/15 (53%) with subclinical GCA in PMR suffered a relapse, with 7 being minor relapses and 1 being a major relapse (new ischaemic symptoms of jaw claudication with associated headache). 21/58 patients (36%) with pure PMR relapsed in the first 12 months of follow-up, $p=0.22$. All relapses in the pure PMR group were with purely PMR symptoms, and none relapsing as GCA. The relapse rate in GCA was lower than that of PMR, likely due to initiation of glucocorticoid sparing medication from the outset in most patients. 4/24 (16.7%) patients diagnosed with GCA relapsed over 12 months, with 2 major relapses and 2 minor relapses (see figure 4.8).

The median time to relapse in subclinical GCA in PMR was earlier than both pure PMR or GCA, at 4 months [IQR 1-9]. Those with pure PMR had a median time to relapse of 6 months [3-6]. GCA patients relapsed at a median time of 6.5 months [3-11].

Figure 4.8 Relapses in pure PMR, subclinical GCA in PMR and GCA.



4.9 Discussion

Multiple studies have identified subclinical GCA in PMR using vascular US as part of the GPSD spectrum (Schmidt and Gromnica-Ihle, 2002, Kraft et al., 1996, De Miguel et al., 2023b, Burg et al., 2023). However, many of these studies were performed in an era before the validation of US cut-off points to identify vasculitis on imaging, which was published in 2017 (Schäfer et al., 2017). There has also been significant improvement in US technology in recent years. Our study applied the Schäfer et al cut-off points for arterial wall thickness in GCA to identify vasculitis in the temporal and axillary arteries. This confirmed a prevalence of 20.5% of subclinical GCA on vascular US in an Irish PMR cohort. This finding is consistent with a recent meta-analysis reporting a pooled prevalence across all imaging modalities of 23% (Hemmig et al., 2022). This represents a significant proportion of PMR patients. Detecting vasculitis in the absence of specific vasculitic symptoms is challenging without ultrasound. Another major challenge for rheumatologists is whether performing vascular US in PMR is justified to improve patient care and outcomes. This consideration is important to inform service planning and training of rheumatologists in vascular ultrasound.

It is important to acknowledge that this study had a number of limitations. Our sample size of PMR patients was modest with 73 patients out of 157 initial referrals having a diagnosis of PMR after 1 year. It was also a single-country cohort. Detection of vasculitic changes was operator dependant and 1 clinician sonographer was not blinded to the clinical history of the case although this was mitigated for by having a second blinded sonographer review the images.

All patients were reviewed within 72 hours of GP referral. This was feasible in this study with a dedicated clinician to run the clinic and a second clinician available to cover leave. In the real world, offering review of all query PMR patients would be a significant volume of work, especially as less than half of the referrals had a final diagnosis of PMR. It would require investment in rheumatologists and clinic space to achieve this on a national level. Based on our referral rates of 157 referrals for our catchment population over one year, this would require 3 new patient slots per week needing 1 hour each, approximately 7 PMR review slots and 1.5 non-PMR review slots weekly 20 minutes each. This equates to 7 hours clinical time (roughly 2 x 3.5-hour clinics), not including results follow up. This mode; would be the ideal best practice, and is supported by international guidelines. Ideally all patients are reviewed by rheumatology at the outset, before any management has begun, stratified according to risk, and either reviewed by primary care with a clear management plan or continue with specialist services if appropriate.

Studies of longitudinal cohorts of PMR patients with subclinical GCA are critical if we are to address this question. We set out to analyse our prospective longitudinal cohort to elucidate these questions. In this study, males were significantly more likely to have subclinical GCA than females. Males also had a higher frequency of subclinical GCA in the Burg study (Burg et al., 2023). Some literature has reported differences in the inflammatory responses of males and females. One study looking at the influence of the X chromosome on inflammation, studied cytokine production and protein phosphorylation following Toll-like receptor activation and found higher levels of

inflammatory cytokines in men compared with women (Lefèvre et al., 2019). Perhaps this is a potential explanation for this finding.

There was no significant difference in the age of patients with subclinical GCA in PMR compared to pure PMR. This suggests that subclinical GCA in PMR is not just a component of 'inflamm-aging', and that other factors contribute to the etiology. There was no significant correlation between age and ESR or age and CRP in our cohort. A combination of genetics and environmental triggers may contribute to the etiology.

No other clinical feature reached statistical significance in differentiating subclinical GCA in PMR from pure PMR, however, the patients with subclinical GCA had a slightly higher frequency of hip girdle symptoms, and constitutional symptoms. In the largest study to date on subclinical GCA, hip girdle symptoms were a significant clinical discriminator (De Miguel et al., 2023b). We observed that patients with subclinical GCA in PMR tend to have a shorter early morning stiffness duration than pure PMR patients, which was a finding that reached significance in the De Miguel study. Our study and the De Miguel study confirm that in routine clinical practice, clinical features (except hip girdle symptoms) do not allow accurate identification of subclinical GCA patients.

Glucocorticoid resistance was observed frequently in our patients with subclinical GCA in PMR. This may be a sign to alert the clinician to possible subclinical GCA. This has also been observed in other studies examining glucocorticoid-resistant PMR. One such study

found features of large vessel GCA on PET/CT in almost 40% of PMR patients with glucocorticoid resistance to PMR dose treatment (Cimmino et al., 2008). In centres without access to vascular US imaging at the time of PMR diagnosis, a failure to respond to initial dose PMR glucocorticoids should prompt careful evaluation for subclinical GCA. Given this, a significant proportion of patients were commenced on glucocorticoid sparing treatment with tocilizumab. Despite showing promising results in recent clinical trials and this study, this treatment has not made in into the EULAR or ACR guidelines for treatment yet, but this is on the horizon.

Laboratory inflammatory markers are not a reliable differentiator between subclinical GCA in PMR and pure PMR. While there were numerical trends towards subclinical GCA in PMR having slightly higher ESR and CRP compared to pure PMR, and slightly lower ESR and CRP compared to GCA, this was not statistically significant. Again, this echoes the results from De Miguel's study. Our study was limited by a significant proportion of patients already commenced on glucocorticoids from primary care at the time of our initial laboratory workup. ESR and CRP are certainly useful when elevated in the GPSD spectrum for diagnosis of GCA or PMR but did not differentiate between PMR, subclinical GCA, and GCA.

Blood markers including monocytes have also generated interest in GCA, with high circulating monocytes and macrophages forming giant cells. One study showed a cut-off of $\geq 0.9 \times 10^6/\text{l}$ had a specificity of 95% in suspected GCA (Mulhearn et al., 2022). The mean monocyte counts in our GCA and subclinical GCA cohorts were below this cut-off

but likely hampered by glucocorticoid exposure. Nonetheless, this is a thought-provoking avenue for future diagnostics. IL-6 levels are also of interest with the successful treatment of GCA and PMR with IL-6R blocking agents. In this chapter we have reported on a pilot of IL-6 level measurement analysed in a subset of PMR, GCA, and subclinical GCA patients at the time of diagnosis. We found widely varying ranges of IL-6 in all 3 patient cohorts at the time of diagnosis. Perhaps it has greater utility in differentiating disease remission and relapse. We have also completed an analysis of the entire cohort on our saved serum which we will further discuss in chapter 7.

The presence of high cardiovascular risk is of concern amongst older populations regarding a higher false-positive diagnosis due to atherosclerosis of arteries. We have examined this and found no statistical difference in the prevalence of hypertension, hyperlipidaemia, diabetes mellitus, smoking, or the overall 10-year cardiovascular risk between PMR and subclinical GCA in PMR cohorts. This substantiates that US-identified subclinical GCA in PMR is a distinct cohort in the GPSD spectrum. Cardiovascular risk factors may have more significance in other vascular territories, such as the carotids and vertebrae. Future studies with normal controls that are age-matched and cardiovascular risk-matched to PMR patients may definitively identify if there are higher rates of false positive US findings associated with cardiovascular risk factors.

This study has examined the natural history of subclinical GCA in PMR. Patients with it, tend to relapse earlier than their pure PMR or GCA counterparts, require significantly higher glucocorticoid doses than those with pure PMR, and are thus exposed to a high

cumulative glucocorticoid burden. Subclinical GCA in PMR also exhibited a higher frequency of progression to GCA than those with pure PMR over 12 months of follow-up. We are limited in assessing the statistical significance of this due to the small overall numbers of GCA development in PMR. Our subclinical GCA in PMR cohort also required glucocorticoid-sparing agents more frequently than those with pure PMR for more treatment-resistant disease. There were several patients with subclinical GCA in PMR initiated on high-dose glucocorticoids at the time of FTC referral. Many of these patients had difficulty weaning glucocorticoid in the first month of treatment and required an additional disease-modifying agent, benefitting from its initiation. None of the patients in the subclinical GCA cohort experienced blindness or stroke. However, we followed these patients closely and were proactive in escalating treatment. If vascular US assessment is carried out at baseline assessment of PMR patients, we recommend that those with a positive scan should be followed closely for relapse in the rheumatology clinic. Despite aiming to treat all patients with identified subclinical GCA in PMR as PMR to observe the natural history, many were already commenced on clinical grounds on glucocorticoid doses over 25mg in primary care. We also closely followed these patients and were proactive in treating patients who relapsed. This may likely have influenced the rate of progression to GCA in this cohort.

In contrast, it appears reasonable that PMR patients with a negative scan (pure PMR) may be discharged back to primary care with a treatment plan. None of our pure PMR patients developed GCA in 1 year of follow-up. Our experience is that in the absence of access to vascular US at the time of PMR diagnosis, all PMR patients should be started

on recommended doses of glucocorticoids as per the 2015 ACR/EULAR PMR management guidelines. Those who fail to respond to standard doses require careful clinical evaluation for mimics and consideration of vascular ultrasound to assess for vasculitis. This is especially true if prominent constitutional features are present.

Subclinical GCA in PMR is part of the GCA-PMR spectrum of disease. The findings of this study show that subclinical GCA in PMR patients were clinically very similar to pure PMR patients, however, US changes were in keeping with GCA findings. Interestingly, was no significant progression to overt GCA found over 1 year of follow up only 1 patient (6.7%) developed GCA. Overall, it behaved a distinct, predominantly large-vessel phenotype that does not evolve into classic GCA but had more frequent and earlier PMR disease flares than pure PMR. This pattern aligns more with a stable large-vessel phenotype with minimal cranial involvement, not necessarily a prodrome.

In summary, subclinical GCA in PMR represents a significant subgroup of the GPSD spectrum of disease. Ultrasound is more sensitive and specific for diagnosis compared to any clinical or laboratory feature alone or in combination. Once identified, subclinical GCA patients tended to relapse earlier than pure PMR and require higher glucocorticoid doses, resulting in more glucocorticoid-sparing agents prescribed. While male gender, a tendency towards more constitutional and hip girdle symptoms, and less early morning stiffness, were observed in slightly higher frequency in subclinical GCA in PMR, these findings failed to reliably differentiate subclinical GCA from pure PMR. Ultrasound

scanning of every PMR patient with vascular ultrasound is not currently recommended in the management guidelines. However, this study shows it should be strongly considered to identify subclinical GCA at the time of PMR diagnosis, as these patients are at higher risk of relapse, require higher doses of glucocorticoid and immunosuppressives, and were more likely to develop GCA than their pure PMR counterparts, and would benefit from close rheumatology follow-up. It would allow for more personalised medicine and benefit intelligent and reactive patient centred clinics.

Chapter 5:

The role of ultrasound in PMR and

GCA diagnosis, monitoring and

predicting outcomes.

5.1 Abstract

Introduction

Ultrasound (US) is a well-validated imaging modality for the diagnosis of GCA. The US findings in subclinical GCA have been reported to follow an extra-cranial predominant pattern, however time to resolution, association with relapse, longer-term monitoring of disease, and the role of ultrasound in guiding therapy have yet to be described.

Methods

Patients were recruited via the GCA and PMR fast-track clinics at TUH and SJH. Patients with GCA and PMR patients with ultrasound-identified subclinical GCA were included. All patients had clinical follow-up at 1-month, 3-month, 6-month, and 12-month time points with vascular US performed.

An extension study was conducted on GCA patients recruited from the TUH fast-track clinic during 2020-2022, to extend their follow-up to two years. Patients treated with weekly tocilizumab were spaced to two-weekly dosing at one year. A retrospective analysis of the OMERACT GCA Ultrasound Score (OGUS) at baseline and 12 months was performed and compared with patient clinical outcomes.

Results

Patients with subclinical GCA in PMR have more axillary vessel involvement than their GCA counterparts (46.7% vs 33.3). Halo count, halo score, and OGUS steadily decreased over the first 6 months in GCA patients. There was an initial decrease in US scores in subclinical GCA in PMR over the first 3 months, followed by an increase at 6 months. GCA patients exhibited a steady decrease in HC, HS, and OGUS over the first six months.

This difference may be reflective of the significantly lower glucocorticoid doses used to treat subclinical GCA in PMR. The median time to relapse in subclinical GCA in PMR was 4 months, earlier than either PMR or GCA relapse. A significant positive correlation was observed between baseline HC and HS and loss of vision in the GCA cohort. Having an OGUS >1 at 12 months was associated with more relapses when tocilizumab was dosed fortnightly (33% vs 14%), without reaching statistical significance.

Conclusions

US has a confirmed role in the diagnosis of both GCA and PMR. The use of scores in monitoring patients and treatment decisions is promising. Scores in subclinical GCA in PMR initially improved, but a subsequent rise was observed. This is a novel finding. In contrast, GCA scores steadily decreased over the first 12 months of treatment. These changes may reflect the earlier time to relapse in subclinical GCA in PMR and raise questions regarding the optimal treatment of subclinical GCA in PMR. This cohort had significantly higher glucocorticoid requirement compared with pure PMR patients, and perhaps this endorses a treatment protocol more in keeping with GCA. Longer follow-up of these patients, monitoring for development of ischaemic symptoms, and calculation of the overall glucocorticoid burden after 2-3 years of treatment will determine the significance of increasing OGUS score.

5.2 Introduction

Ultrasound of the temporal and axillary arteries is recommended as the first-line imaging modality in patients with suspected GCA (Dejaco et al., 2018). The use of ultrasound to diagnose GCA was first reported in 1995 (Schmidt et al., 1995). The pathognomonic 'halo sign' characterised by a dark hypoechoic area around the vessel lumen, was described shortly after (Schmidt et al., 1997). The compression sign was later described in 2012 as the persistent visibility of the temporal artery despite transducer-imposed arterial compression (Aschwanden et al., 2013). Since then, the Outcome Measures in Rheumatology (OMERACT) large vessel vasculitis working group has validated the halo and compression signs as the most significant US abnormalities in GCA with 91-99% inter-rater agreement. Recent developments in ultrasound, such as improved image resolution, the introduction of standardised scanning techniques, and validated US findings in the presence of vasculitis have all contributed to the move away from temporal artery biopsy (TAB) for diagnosis. While historically TAB was used as the primary diagnostic test in suspected GCA, the EULAR large vessel imaging guideline and the informative TABUL trial have impacted clinical practice. The TABUL trial showed the sensitivity of TAB to be much less than previously reported and inferior to US with a sensitivity of 39% versus 54% in US (Luqmani et al., 2016). EULAR recommends ultrasound as the first-line investigation for suspected large vessel vasculitis. The use of ultrasound in diagnosis has steadily grown in Europe in recent years, with the Spanish ARTESER register showing growth in temporal artery US-diagnosed GCA from 25.8% to 52.9% from 2013 to 2019 (De Miguel et al., 2022).

More recently, computation of US findings has greatly contributed to increasing the diagnostic performance of vascular US. There has been a shift from dichotomously classifying US findings as positive or negative based on the presence or absence of a single halo sign to a more robust measurement comprising composite scoring of intima-media thickness in multiple vessel branches. The halo count, halo score, and OMERACT GCA Ultrasonography Score (OGUS) have all been recently described. The halo count (HC) gives one point for the presence of each halo identified in 8 arterial areas (bilateral common temporal artery, bilateral frontal temporal artery, bilateral parietal temporal artery, and bilateral axillary arteries) to a maximum score of 8. The halo score (HS) is a composite measurement formulated from a score of 0-4 at each branch of the common temporal, parietal, and frontal arteries (maximum score 24), as well as a weighted score for the axillary arteries (0-4 x 3, maximum score 24) to give them equal significance with the temporal artery branches, adding to a total maximum score of 48 (see figure 5.1). The halo count and halo score have been shown to correlate with laboratory markers of systemic inflammation in real-world cohorts (Molina Collada et al., 2022).

The OGUS is a score formulated from a Delphi exercise of experts that attained 93% agreement. It is calculated based on the sums of the intima-media thickness measured in each of 8 arterial segments (2 x axillary and 2 x 3 temporal artery segments) divided by the rounded cut-off values of IMTs in each segment (Dejaco et al., 2023a) i.e. [Common trunk of superficial temporal arteries: 0.4 mm; parietal and frontal branches: 0.3 mm; axillary arteries: 1.0 mm]] /divided by the number of segments available]. OGUS correlates moderately with ESR, CRP, and the Birmingham Vasculitis Activity Score

(Dejaco et al., 2023a). Even though the OGUS score was developed for disease monitoring it may also offer diagnostic and prognostic information (Conticini et al., 2024).

While US is a useful tool for diagnosing GCA, the possible application of US as a monitoring tool has only been recently studied. In the 'GUSTO' trial, rapid reduction in intima-media thickness was observed in US findings after pulses of glucocorticoid treatment, followed by a return to near baseline after one month of tocilizumab treatment, with subsequent slow reduction in intima-media thickness (Christ et al., 2021). Similarly, in the 'Prognosis of Temporal Arteritis PROTEA' study it was demonstrated that the halo sign and intima-media thickness rapidly reduced in the temporal artery after standard glucocorticoid treatment, and had a more protracted reduction in the axillary arteries (Ponte et al., 2021). However, the value of US for relapse detection is yet to be established from prospective cohorts. Fast-track clinics (FTCs) provide invaluable access to GCA patients to establish prospective cohorts. They may help to establish if there is any additional value of US imaging in follow-up over clinical and laboratory assessment alone.

Ultrasound of PMR patients identifies subclinical GCA in PMR which has an estimated prevalence of 22% (De Miguel et al., 2023b). Ultrasound features including the pattern of involvement, and the degree of intima-media involvement are incompletely studied. In addition, the relationship between ultrasound features and the patient's clinical

course has not been extensively studied. It is unclear if ultrasound in subclinical GCA in PMR offers any insight into disease prognosis. There are no published studies documenting follow-up ultrasound scores in this cohort and comparing them to GCA patients. This study aimed to assess the use of follow-up ultrasound in these cohorts. The De Miguel subclinical GCA in PMR paper was published during the completion of this study (De Miguel et al., 2023b). We approached the De Miguel group to collaborate on this research. To improve sample size and power from this study, we combined our patients with the European cohort of subclinical GCA in PMR patients. They were also compared with a larger GCA cohort, which added GCA patients from the TUH GCA fast-track clinic from 2020-2022 to the cohort described in chapter 2 and recruited in 2022-2023.

In 2018, NICE and NHS England approved one year of weekly subcutaneous tocilizumab for use in relapsing or refractory GCA, following the GiACTA trial publication (Stone et al., 2017b). In the Republic of Ireland, the Health Products Regulation Authority (HPRA) has not restricted tocilizumab to relapsing or refractory GCA. There is leniency of use after 12 months of treatment as per clinical need. There remains uncertainty regarding the optimal treatment duration and approach to tapering and discontinuation. The open-label extension phase of the GiACTA trial did not help to mitigate this uncertainty, since only 42% of patients treated with a 12-month course of weekly tocilizumab remained in remission at 2 years following therapy suspension at 1 year (Stone et al., 2021). Laboratory markers are rendered of little clinical use after initiation of tocilizumab due to the blockade of IL-6 signalling, inhibition of the hepatic production

of C-reactive protein (CRP), and other acute phase proteins like the erythrocyte sedimentation rate (ESR). It is unknown if serial US monitoring may inform the dose spacing and discontinuation of tocilizumab. This study aimed to continue the GCA FTC format of patient assessment up to 2 years after diagnosis with clinical assessment and vascular US and examine the utility of an extended approach on tocilizumab dose spacing after 1 year of treatment.

5.2.2 Objectives

The objectives of this study were:

1. To describe the temporal and axillary artery ultrasound pattern in patients with subclinical GCA in PMR and compare it to GCA.
2. To compare the Halo count, Halo score, and OGUS in patients with subclinical GCA in PMR and GCA.
3. To identify if any ultrasound features may predict relapse in subclinical GCA in PMR or GCA.
4. To combine our data with a European cohort of subclinical GCA in PMR patients and compare ultrasound findings with our total cohort of GCA patients since initiating the TUH GCA fast-track clinic in 2022.
5. To examine the role of US monitoring in GCA follow-up to inform dose spacing of tocilizumab.

5.3 Methods

5.3.1 Study design and population

Subclinical GCA in PMR patients were identified from our previously described PMR fast-track clinic (Chapter 2). GCA patients were identified from the fast-track GCA clinic. All patients had a clinical diagnosis of either PMR or GCA confirmed by two rheumatologists and were on glucocorticoid treatment for <4 weeks at the time of entry to the study. Both GCA and subclinical GCA in PMR patients had clinical follow-up at 1-month, 3-month, 6-month, and 12-month time points. Vascular ultrasound of the temporal and axillary arteries was completed at all time points, as were laboratory markers. Patients were advised to contact the department in the event of a relapse, so this could also be captured.

5.3.2 Larger cohort of GCA and subclinical GCA in PMR

As part of a larger analysis, additional patients (n=25) with subclinical GCA in PMR from a prospective European study with a similar methodology were added to our cohort (n=15). All patients had a similar corticosteroid tapering in keeping with the ACR/ EULAR PMR guidelines. All the additional patients had a prospective collection of clinical and ultrasound data. Additional GCA patients were also added to the analysis. These were patients recruited from our Irish GCA fast-track clinic from 2020-2022. These patients had the same methods of diagnosis, treatment, and follow-up as those recruited from the fast-track clinic from 2022 to 2023.

5.3.3 Tocilizumab spacing study

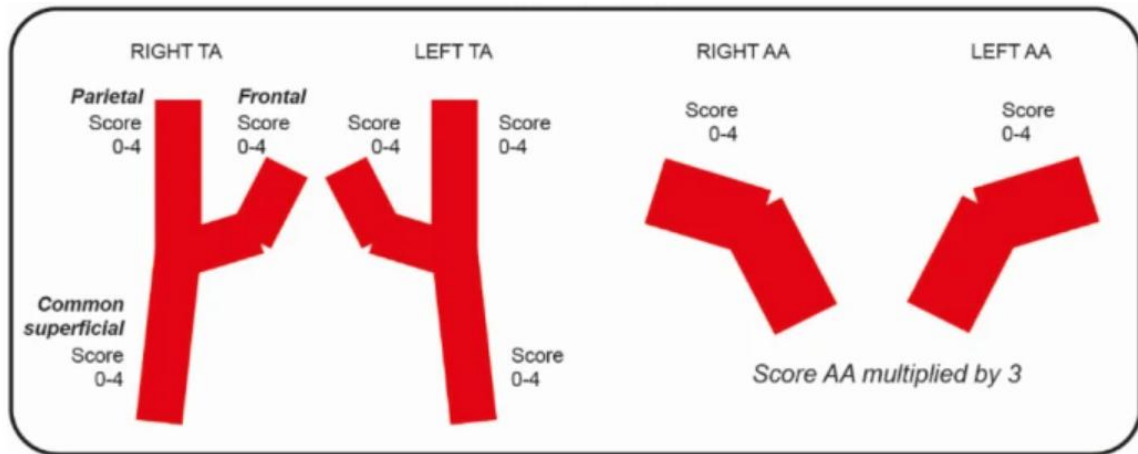
An extension study was conducted on GCA patients recruited from the TUH fast-track clinic during 2020-2022, to extend their follow-up to two years. GCA patients from our FTC recruited from 2020-2022, with a clinical diagnosis of GCA confirmed by two rheumatologists were enrolled. As per ACR/ Vasculitis Foundation guidelines, all GCA patients with a new diagnosis of GCA were started on tocilizumab if there were no contraindications. All patients had corticosteroid 26-week taper as per the GiACTA protocol. Tocilizumab was administered weekly for the first 12 months, and then every-other-week for an additional 12 months. An analysis of OGUS score at baseline and 12 months was performed and correlated with outcomes. Relapse of disease on tocilizumab was managed with temporary increases in systemic glucocorticoids.

5.3.4 Ultrasound protocol

Ultrasound protocols implemented are described in detail in chapter 2. Halo count, halo score, and OGUS were calculated on all patients with subclinical GCA in PMR and GCA at each time point.

Figure 5.1 Halo score thickness cut-off and Halo grading (0-4).

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



(van der Geest et al., 2020a)

Figure 5.2: OMERACT GCA Ultrasonography Score

Artery Segment	Measurement (mm)	Rounded Cut-off (mm)
Common superficial temporal artery	Right: ____ Left: ____	0.4
Frontal branch of temporal artery	Right: ____ Left: ____	0.3
Parietal branch of temporal artery	Right: ____ Left: ____	0.3
Axillary artery	Right: ____ Left: ____	1.0

Legend: To calculate OGUS:1. Measure IMT (intima-media thickness) in every available segment.2. Divide each IMT value by the rounded cut-off for that segment 3. Add all these ratios together 4. Divide the sum by the number of available segments (maximum 8). Interpretation: 0–<1: Mean IMT below cut-off >1: Mean IMT above cut-off Note: A value of 1 does NOT represent a diagnostic cut-off for GCA. (table is adapted from information in Dejaco et al.) (Dejaco et al., 2023a)

5.3.5 Ethical Approval

Full ethical approval for patients recruited from TUH and SJH was obtained from the Joint Research Ethics Committee (JREC) for Tallaght University Hospital and St James Hospital, Dublin, Ireland. All patients gave fully informed written consent to participate in the fast-track clinic study. The additional extended European cohort had ethical approval from the University Hospital 'La Paz', Spain and all patients provided written informed consent. The older GCA cohort from 2020-2022 from TUH and Cork University Hospital had ethical approval from both the JREC and Cork University Hospital Ethics Committee.

5.3.6 Statistical Analysis

Descriptive analysis of the data was performed using SPSS. Data were expressed as the mean $\pm$ standard deviation (SD) for normally distributed continuous variables, as median (interquartile range) for non-normally distributed variables, and as percentages and frequencies for categorical variables. Continuous variables were compared using the independent t-test. Categorical variables are summarised by frequency and percentage (%) and compared using the chi-square test or Fisher's exact test. Continuous variables with a linear relationship were examined with Pearson's or Spearman's correlation coefficient. P values <0.05 were considered statistically significant.

5.4 Results

5.4.1 Ultrasound features of Subclinical GCA in PMR

15/73 (20.5%) patients in our PMR cohort recruited from July 2022 – July 2023 had US-identified subclinical GCA in PMR. The distribution of disease in subclinical GCA in PMR was as follows:

- Purely cranial disease 8/15 (53.3%)
- Purely axillary disease 2/15 (13.3%)
- Mixed vessel involvement 5/15 (33.3%)

24 patients were diagnosed with GCA from our FTC, of which 21/24 were US positive and 3 were biopsy positive. The distribution of disease on US in GCA was as follows:

- Purely cranial involvement 14/21 (66.7%)
- Purely axillary involvement 1/21 (4.7%)
- Mixed vessel involvement 6/21 (28.5%)

The total number of patients with axillary involvement in the subclinical GCA in PMR group was 7/15 (46.7%), compared with a total of 7/21 (33.3%) in the GCA group, $p=0.48$.

Figure 5.3 Distribution of vascular findings in subclinical GCA in PMR

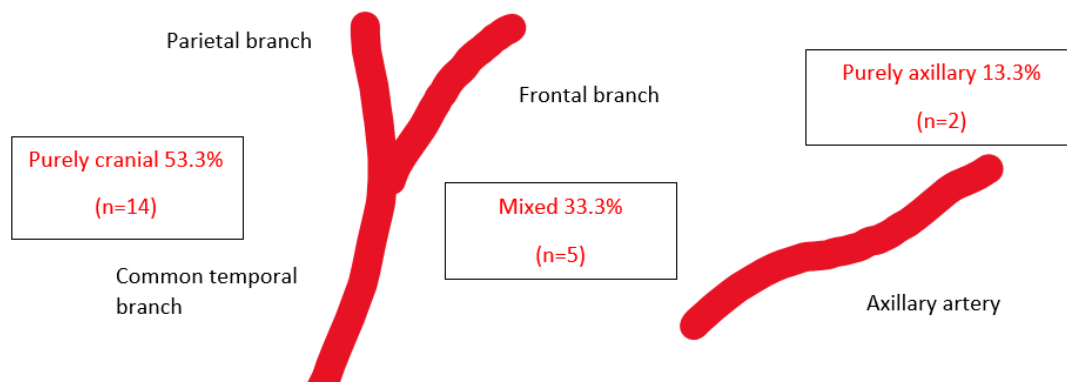


Figure 5.4 Distribution of vascular findings in GCA

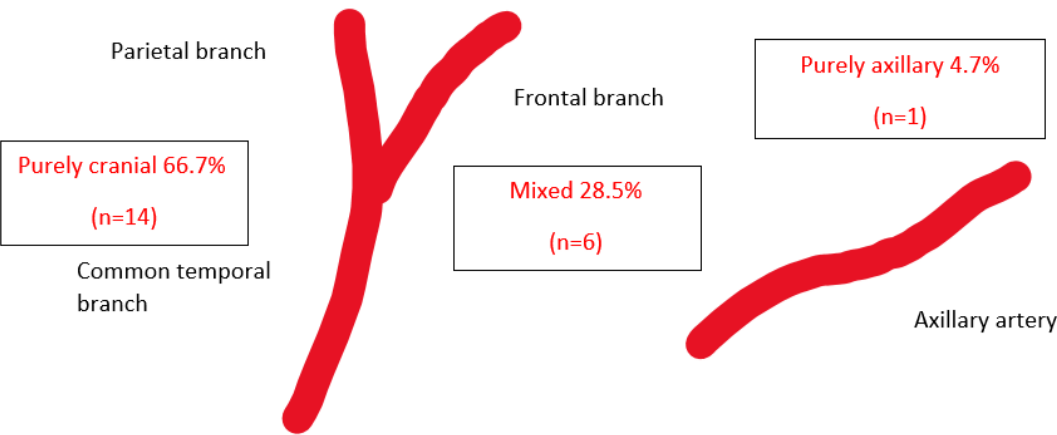
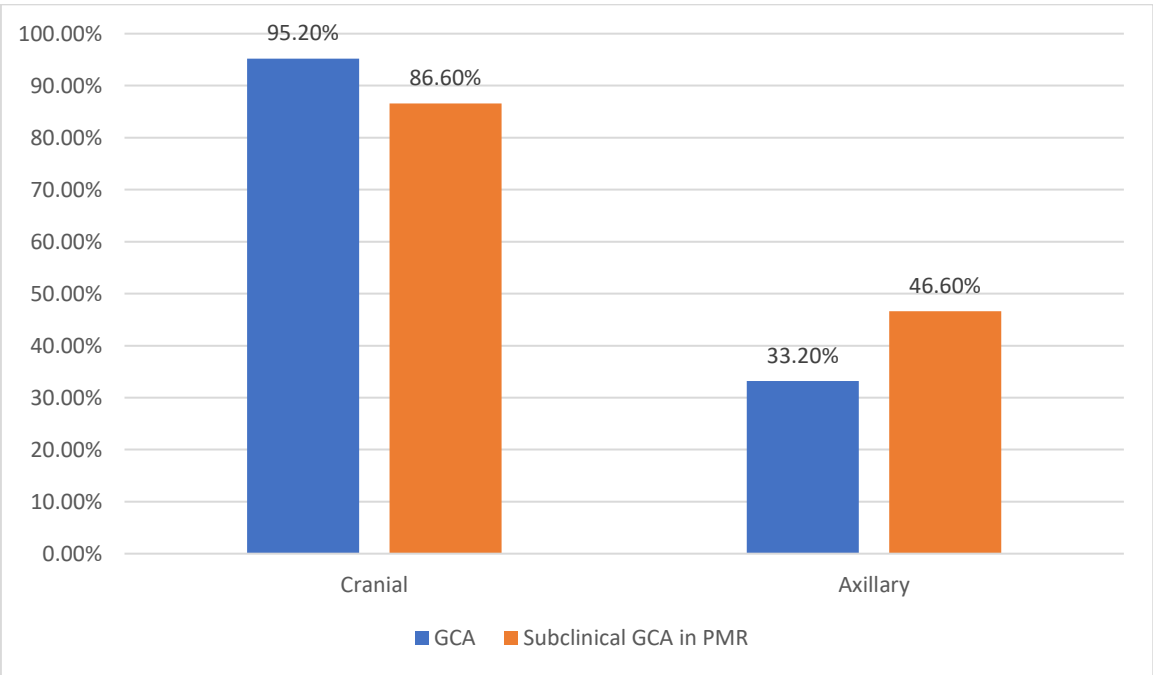


Figure 5.5: Distribution of disease in subclinical GCA in PMR and US-positive GCA patients.



5.4.2 Ultrasound Scores in subclinical GCA in PMR and GCA

The mean baseline HC in patients with subclinical GCA in PMR (n=15) was 3.86 ± 1.8 , while the mean baseline HS was 16.12 ± 5.57 , and the mean baseline OGUS was 0.81 ± 0.17 . For the GCA cohort, 21/24 GCA patients had a positive US. The mean baseline HC was 4.28 ± 1.87 , the mean baseline HS was 17.66 ± 6.91 , and the mean baseline OGUS was 0.96 ± 0.21 . The halo count was not statistically different between subclinical GCA in PMR and GCA patients, $p=0.5$; indicating that the number of abnormal vessels was similar between the two groups. However, the OGUS in GCA were significantly higher than in patients with subclinical GCA in PMR, indicating that the degree of vessel vasculitic involvement was more profound in GCA, $p=0.02$. The greater degree of vascular inflammation in the involved arteries may explain why those with subclinical GCA in PMR were not symptomatic with cranial symptoms.

Table 5.1 Baseline HC, HS, and OGUS

Score at baseline	Subclinical GCA in PMR (n=15)	GCA (n=21)	p-value
Halo Count	3.86, SD = 1.8, 95% CI [2.95, 4.77]	4.28, SD = 1.87, 95% CI [3.48, 5.08]	.5
Halo Score	16.12, SD = 5.57, 95% CI [13.30, 18.94]	17.66, SD = 6.91, 95% CI [14.70, 20.62]	.47
OGUS	0.81, SD = 0.17, 95% CI [0.72, 0.90]	0.96, SD = 0.21, 95% CI [0.87, 1.05]	.02

5.4.3 Relationship of US scores with inflammatory markers

HC, HS, or OGUS did not correlate with baseline ESR or CRP in subclinical GCA in PMR. Similarly, we did not observe a significant correlation between HC, HS, and OGUS in GCA with baseline ESR or CRP. OGUS has shown a moderate correlation with ESR and CRP in other studies (n=52) (Dejaco et al., 2023a). Our cohort may have been underpowered to illustrate this association.

Table 5.2 Correlations between HS, HC, OGUS, and ESR/ CRP

	Baseline ESR R value	Baseline ESR P value	Baseline CRP R value	Baseline CRP P value
HC Subclinical GCA in PMR	-0.11	0.69	-0.21	0.44
HS in Subclinical GCA in PMR	-0.12	0.66	-0.43	0.88
OGUS Subclinical GCA in PMR	-0.006	0.98	-0.23	0.39
HC GCA	-0.19	0.41	-0.06	0.78
HS GCA	-0.07	0.75	-0.02	0.91
OGUS GCA	-0.18	0.43	0.03	0.87

5.4.4 Time-to-normalisation of HC, HS, and OGUS

Time-to-normalisation for each vascular ultrasound outcome score was evaluated. In GCA patients, 95% had an OGUS score of <1 by 3 months of treatment. For HC and HS, a reduction was seen between baseline and 3 months (HC with 100% abnormal at

baseline to 38% abnormal at 3 months; and HS with 94% abnormal at baseline reduced to 38% abnormal at 3 months). There was no significant association between time to normalisation and future events, but a limitation was the cohort numbers.

Interestingly, in the subclinical GCA in PMR cohort the HC, HS, and OGUS all reduced from baseline over the first 3 months, but then a rise was noted (see figures 5.6, 5.7, 5.8). There was a statistically significant increase in HS from 3 to 12 months, $p=0.02$. A significant increase in the OGUS from 3 to 6 months, $p<0.001$, was also observed. HC increase from 3 to 6 months was not significant, $p=0.15$ reflecting the greater accuracy of HS and OGUS which employ accurate measurements of the intima-media thickness. The median time to relapse in subclinical GCA in PMR was earlier than either pure PMR or GCA, at 4 months [1-9], compared with 6 months [3-6] in pure PMR and 8.5 months [6.5-10.5] in GCA which may explain the rise in HC, HS, and OGUS after the 3-month time point.

There was a mean relapse-free survival time of 8.2 months in subclinical GCA in PMR, 9.2 months in PMR, and 11.4 months in GCA, $p=0.03$ (see figure 5.12). Comparing only subclinical GCA with pure PMR, this did not meet significance, $p=0.34$.

Figure 5.6 Halo count in Subclinical GCA in PMR, baseline to 12 months

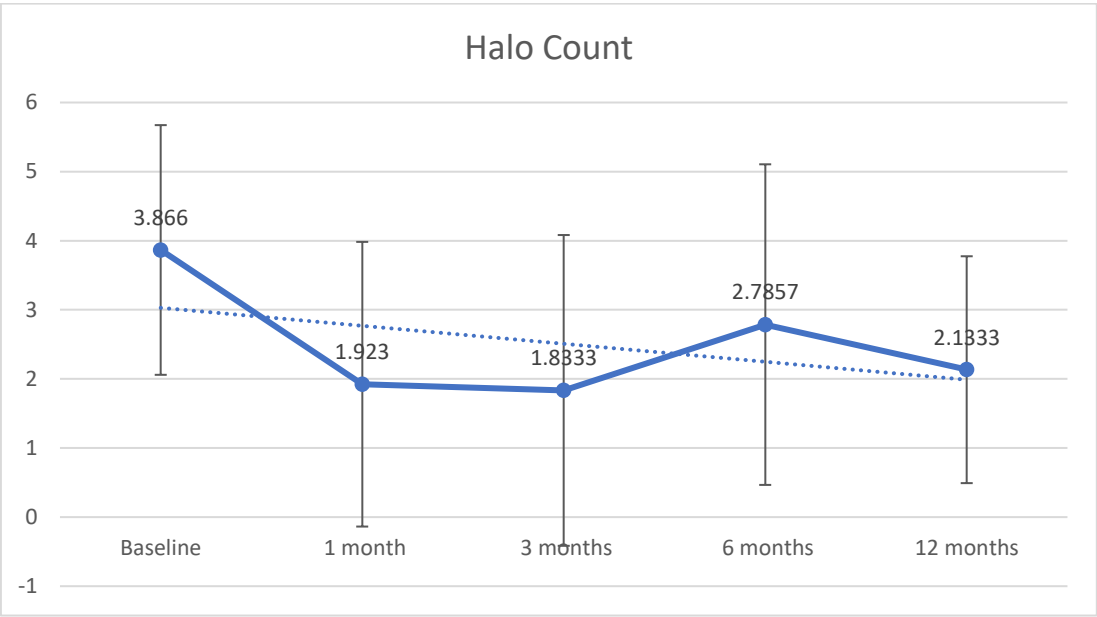


Figure 5.7 Halo Score in Subclinical GCA in PMR, baseline to 12 months

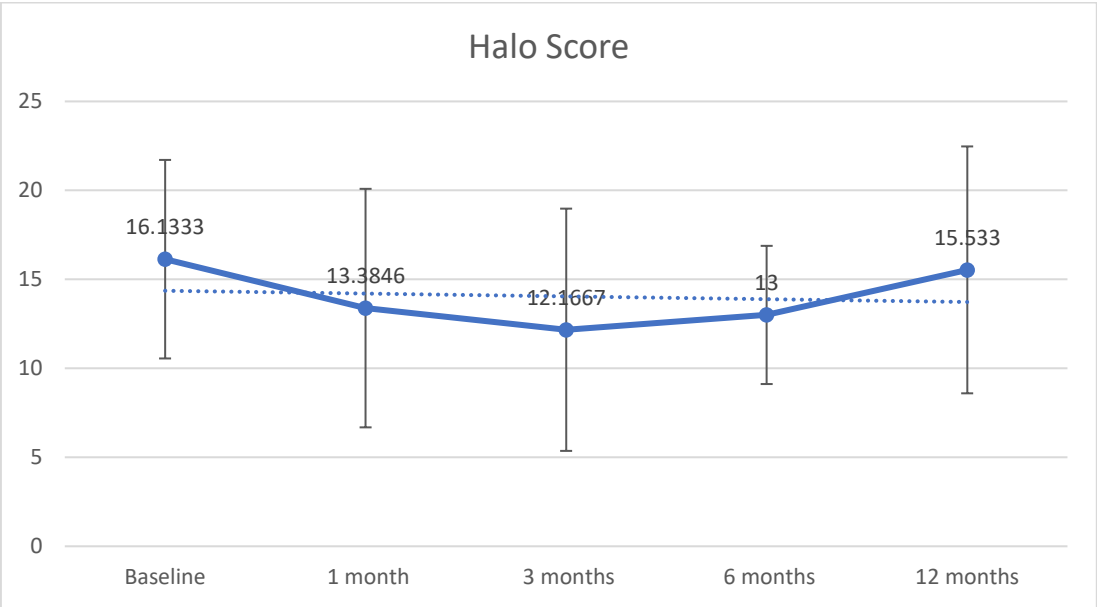


Figure 5.8 OGUS Score in Subclinical GCA in PMR, baseline to 12 months

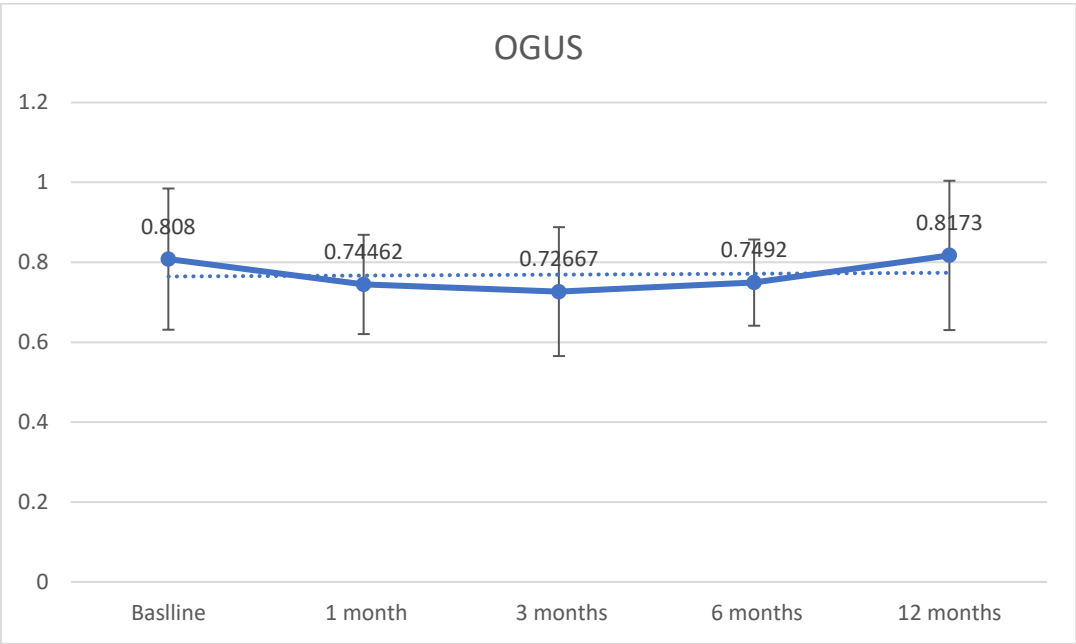


Figure 5.9 Halo Count in GCA, baseline to 12 months

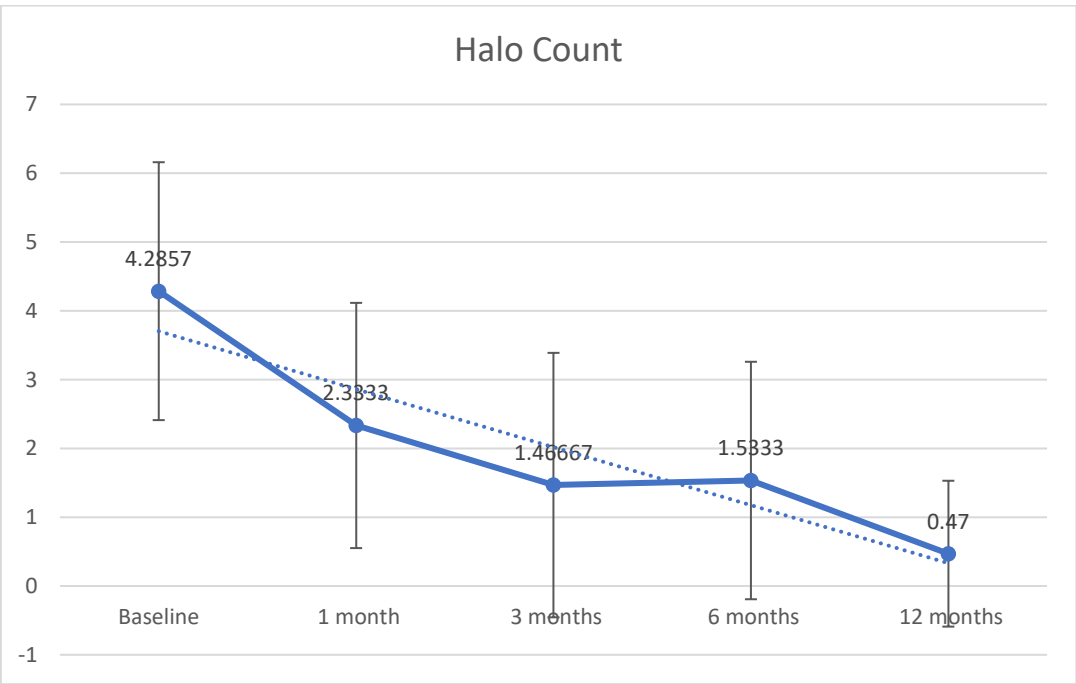


Figure 5.10 Halo Score in GCA, baseline to 12 months

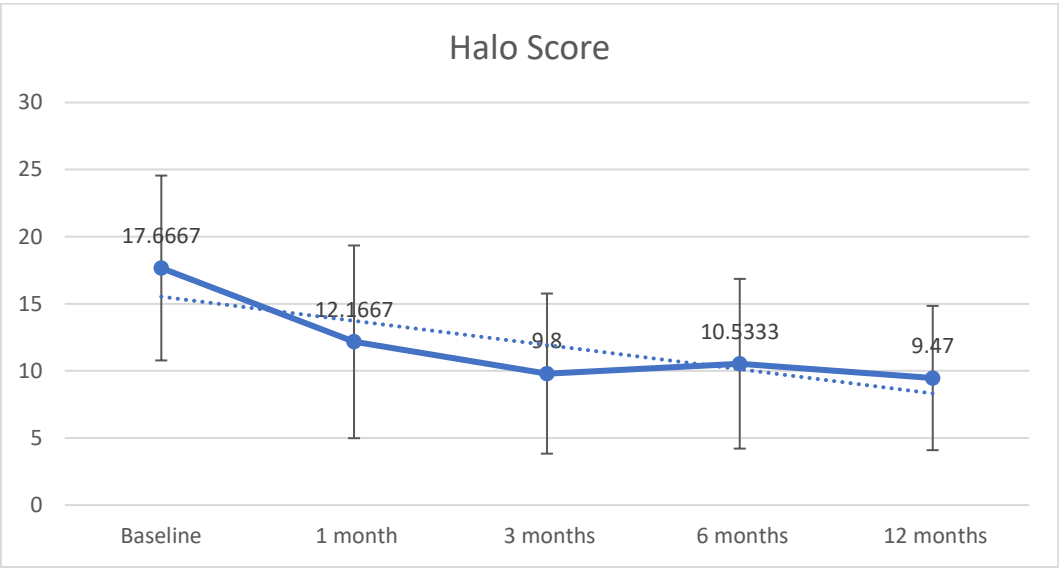


Figure 5.11 OGUS in GCA, baseline to 12 months

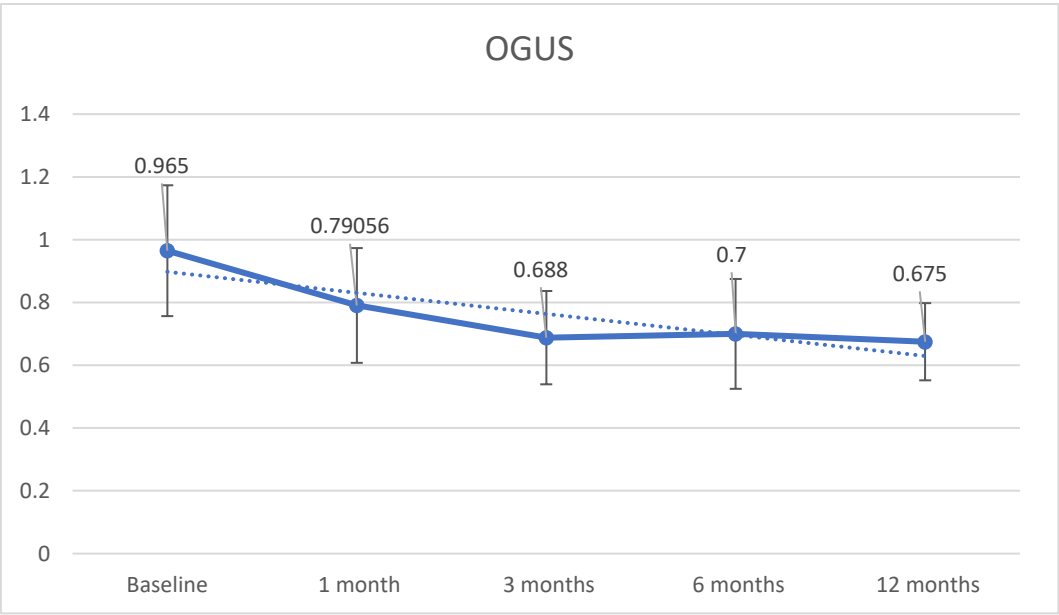
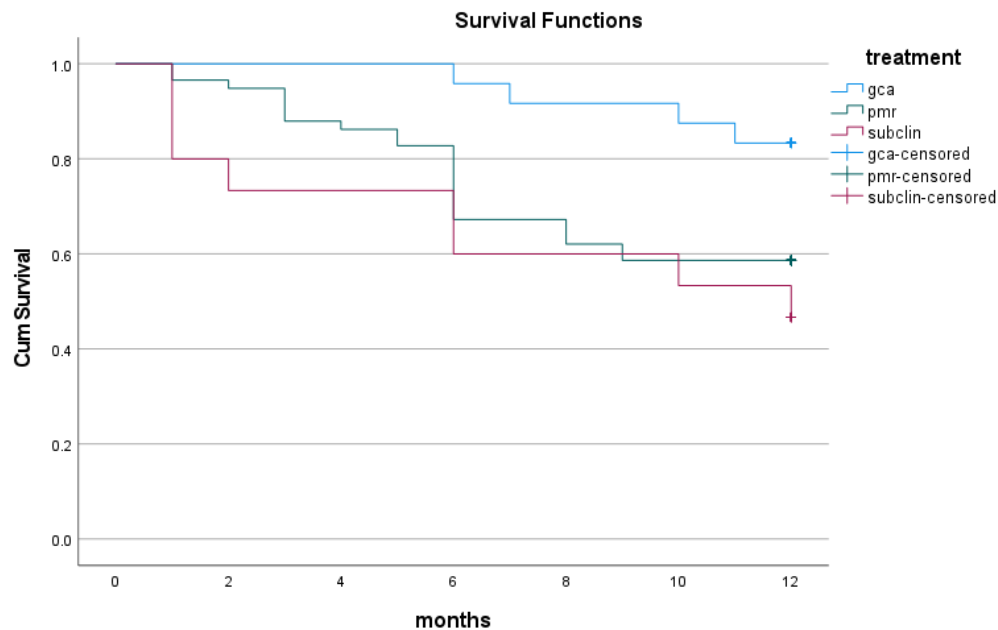


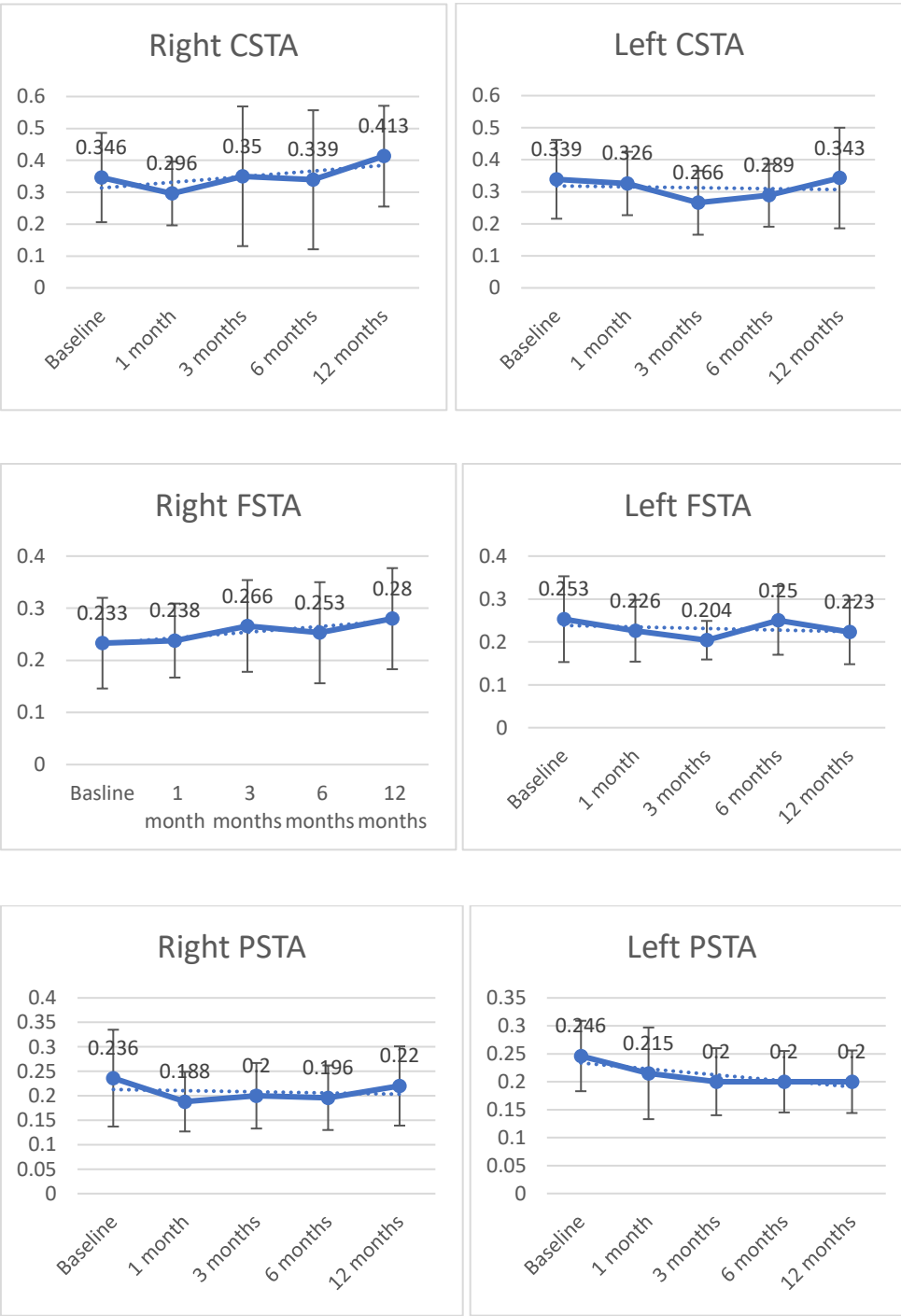
Figure 5.12 Time to relapse in PMR, subclinical GCA in PMR and GCA



5.4.5 Time to normalisation of cranial and axillary vessels

An overall downward trend with treatment was observed in the IMT of all branches of the superficial temporal arteries and axillary arteries in GCA. Opposing trends were observed in the right common superficial temporal artery, left common superficial temporal artery, right frontal superficial temporal artery, and both axillary arteries in patients with subclinical GCA in PMR, where an overall upward trajectory was observed at the 12-month point (see figure 5.13, 5.14). This may be due to lower doses of glucocorticoids used to treat subclinical GCA in PMR. There was a statistical difference in the mean change of IMT in all 8 branches combined when comparing GCA and subclinical GCA in PMR, $p < 0.001$.

Figure 5.13 Changes in IMT in subclinical GCA in PMR patients from 0 to 12 months



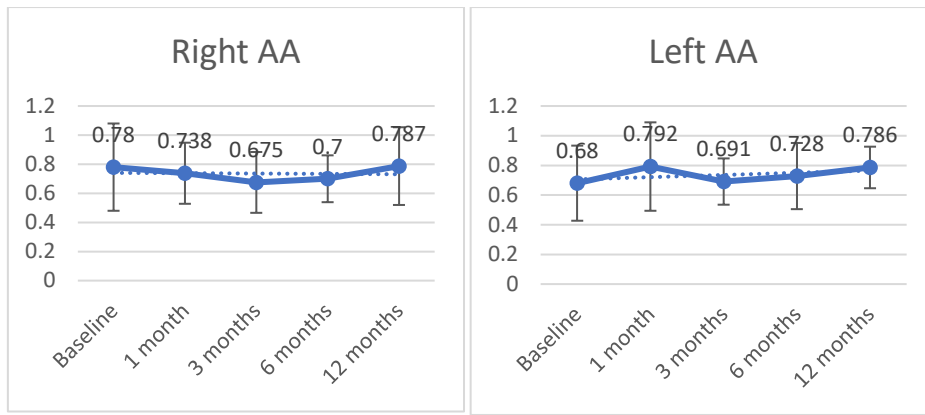
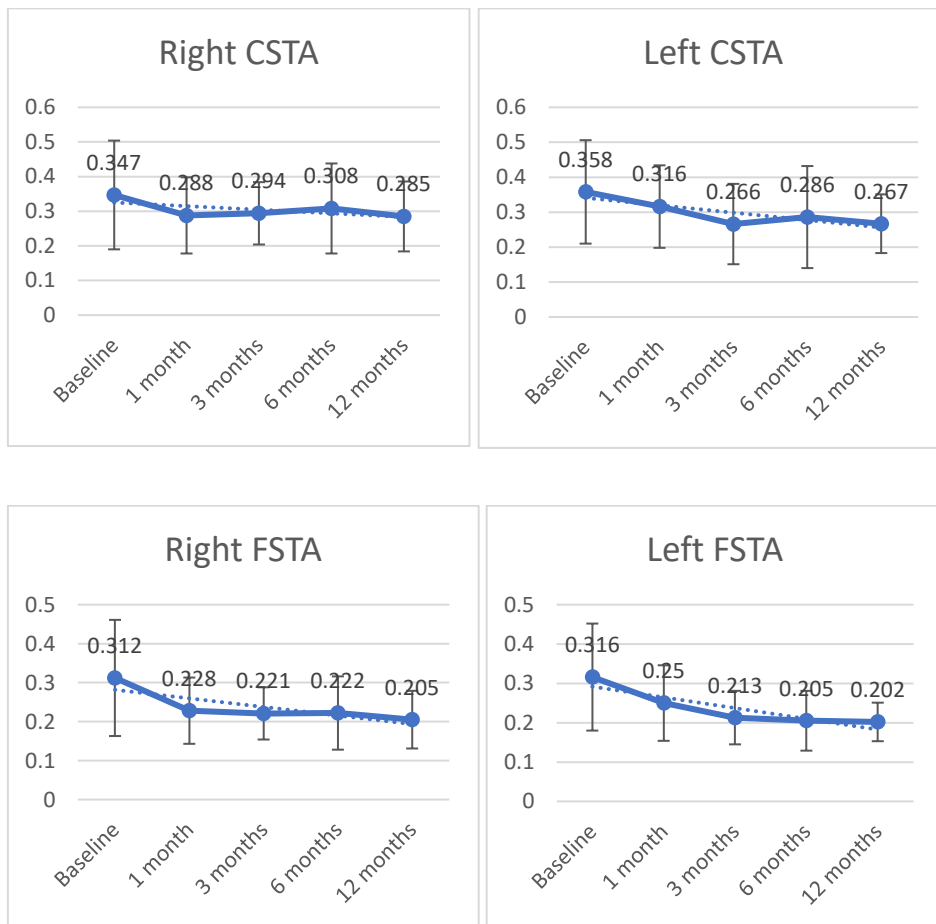
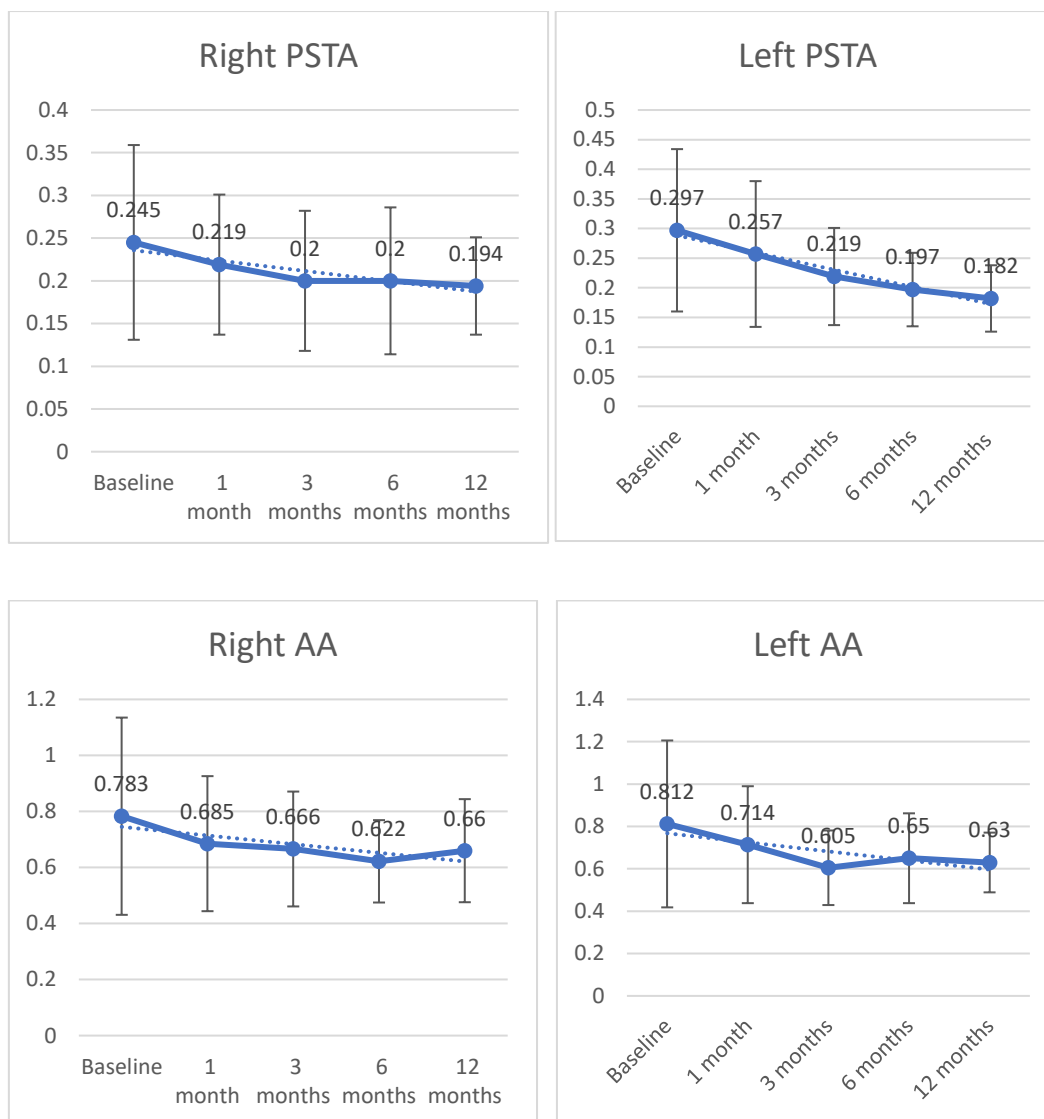


Figure 5.14 Changes in IMT in GCA patients from baseline to 12 months





5.4.6 US scoring in disease relapse and glucocorticoid exposure

There was a negative correlation between baseline HC, HS, and OGUS in subclinical GCA in PMR and relapse over the first 12 months. However, 11/15 (73%) of subclinical GCA patients had glucocorticoid exposure at diagnosis, with a median cumulative glucocorticoid exposure of 280mg [0-770] limiting the analysis. The mean starting glucocorticoid dose of all patients attending the FTC was 18.48mg [± 6.87]. 33% of patients with subclinical GCA were initiated on glucocorticoid doses >25mg in primary care before referral to the fast-track clinic. This compares with 5 patients (8.6%) of the

pure PMR group having exposure to >25mg glucocorticoid in primary care before referral, $p=0.02$.

In the GCA cohort ($n=21$), we did not observe a statistically significant correlation between relapse and baseline HC ($p=0.13$), HS ($p=0.06$), or OGUS, ($p=0.18$) (see table 5.4). Of note, 14/21, 66.7% of GCA patients had glucocorticoid exposure on referral to the GCA FTC, with a median cumulative glucocorticoid dose on referral of 180mg [50-465].

The change in OGUS may be a better measurement for this cohort with significant glucocorticoid exposure at baseline. The mean 0 to 6-month change in OGUS in patients who relapsed was $+0.098 [\pm 0.141]$, while the mean 0 to 6 month change in OGUS in those without relapse was $-0.062 [\pm 0.208]$, $p=0.09$. Other studies in GCA have concluded that the absence of OGUS improvement during follow-up may be used to assess the probability of relapse and the absence of remission at 6 months (Molina-Collada et al., 2024b).

There was a negative correlation between baseline HC and cumulative glucocorticoid exposure at 12 months in subclinical GCA in PMR; $r= -0.56$, $p=0.02$. This was also observed for baseline OGUS and cumulative glucocorticoid exposure at 12 months; $r= -0.63$, $p=0.01$. This may be due to those patients with higher HC and OGUS at baseline having more severe disease requiring treatment with tocilizumab earlier, and thus

having a lower overall glucocorticoid exposure at 12 months. In the GCA cohort, there was no correlation between HC, HS, and OGUS and cumulative glucocorticoid exposure or glucocorticoid-free remission at 12 months.

Table 5.3 Correlation between HC, HS, and OGUS and treatment outcomes

	Relapse	Cumulative GC dose at 12 months	GC-free remission at 12 months	Tocilizumab treatment
HC subclinical GCA in PMR	R=-0.607, p=0.01	R=-0.568, p=0.02	R=-0.005, p=0.98	R=-0.027, p=0.82
HS subclinical GCA in PMR	R=-0.423, p=0.11	R=-0.326, p=0.23	R=0.150, p=0.59	R=0.324, p=0.23
OGUS subclinical GCA in PMR	R=-0.426, p=0.11	R=-0.630, p=0.12	R=-0.286, p=0.30	R=0.257, p=0.35
HC GCA	R=-0.341, p=0.13	R= -0.194, p=0.42	R=0.078, p=0.75	R=0.361, p=0.10
HS GCA	R=-0.409, p=0.06	R=-0.027, p=0.91	R=0.131, p=0.59	R=0.289, p=0.28
OGUS GCA	R=-0.300, p=0.18	R=0.033, p=0.89	R=0.088, p=0.71	R=0.172, p=0.45

5.4.7 Clinical features associated with HC, HS, and OGUS

In the cohort of subclinical GCA in PMR patients, there was no significant correlation between any clinical features and baseline vascular US scores. In contrast, in the GCA cohort, there was a significant correlation between HC and HS and loss of vision; $r = 0.45$, $p = 0.03$ and $r = 0.44$, $p = 0.04$ respectively. Higher HC and HS were associated with an increased prevalence of visual loss in GCA. Another recent study has previously illustrated an association between HS and ocular ischaemia in GCA (van der Geest et al., 2020b). No patient in the subclinical GCA in PMR group suffered visual loss in 12 months of follow-up. There was also a negative correlation in the GCA cohort with HC, HS, and BMI; $r = -0.481$, $p = 0.03$ and $r = -0.498$, $p = 0.02$ respectively. Patients with a reduced BMI, which may be disease activity related, had higher HC and HS in GCA.

This raises the question regarding the significance of baseline HC and HS in guiding treatment in GCA. Perhaps patients with higher ultrasound scores warrant closer follow-up and consideration for higher glucocorticoid doses to prevent visual loss. This would need to be assessed with larger prospective studies.

5.4.8 Extended cohort of subclinical GCA in PMR and GCA

A larger cohort of subclinical GCA in PMR patients ($n = 40$) was formed by combining the patients from our PMR FTC ($n = 15$) with those from a prospective European cohort ($n = 25$). HS, HC, and OGUS were calculated on patients with US-identified subclinical GCA in PMR. All patients had a similar glucocorticoid tapering in keeping with the ACR/ EULAR PMR guidelines (Dejaco et al., 2015). These were compared with a larger cohort of GCA

patients from our GCA FTC from 2020-2022 and those from 2022-2023 which have already been described in this chapter 2, (total n=81).

There was a significant difference in the mean HC in the subclinical GCA in PMR cohort and the GCA cohort at 3.28 ± 1.92 and 4.34 ± 2.12 , $p=0.004$. This indicates that GCA patients had more vessels with vasculitic change in the larger cohort. The mean baseline HS in the subclinical GCA in PMR cohort was 17.5 ± 6.48 , while that of GCA patients was 24.3 ± 8.85 , $p<0.001$. This shows that vessels involved in GCA had higher intima-media thickness than their subclinical GCA in PMR counterparts, indicating more severe vessel oedema. Similarly, the mean baseline OGUS for patients with subclinical GCA in PMR was 0.9 ± 0.24 , while the OGUS in GCA was 1.14 ± 0.29 , $p<0.001$ (see table 5.4). HC, HS, or OGUS did not correlate with relapse in either the GCA or subclinical GCA in PMR extended groups. We did not have access to follow-up US scores in the extended European cohort to assess if a change in OGUS was predictive of relapse in a larger subclinical GCA in PMR cohort.

Table 5.4 HS, HC, and OGUS in larger subclinical GCA in PMR and GCA cohorts

Score at baseline	Subclinical GCA in PMR (n=40)	GCA (n=81)	p-value
Halo Count	3.28, SD = 1.92, 95% CI [2.68, 3.88]	4.34, SD = 2.12, 95% CI [3.88, 4.80]	.004
Halo Score	17.5, SD = 6.48, 95% CI [15.49, 19.51]	24.3, SD = 8.85, 95% CI [22.37, 26.23]	.001
OGUS	0.9, SD = 0.24, 95% CI [0.83, 0.97]	1.14, SD = 0.29, 95% CI [1.08, 1.20]	.001

5.5 The role of US in Tocilizumab spacing in GCA

Ultrasound has a fundamental role in the diagnosis of GCA in recent years, particularly in the FTC setting. The role of US in monitoring patients with GCA, and guiding treatment escalation and de-escalation is not defined. In particular, the finding of residual arterial wall thickening indicative of vasculitis in patients deemed in clinical remission has been a stumbling block. Nevertheless, new evidence is accumulating to support a potential role for imaging, especially US, as a monitoring tool to assess response to treatment and detect relapses in patients with GCA (Ponte et al., 2021).

This extension study from the original FTC GCA cohort at TUH aimed to examine the role of US monitoring in GCA to guide dose spacing of tocilizumab and assess the efficacy and safety of dose spacing in tocilizumab. NICE and NHS England have approved one year of weekly subcutaneous tocilizumab for use in relapsing or refractory GCA, following the GiACTA trial publication (Stone et al., 2017b). In other European jurisdictions and the US, tocilizumab is not limited to relapsing or refractory GCA and allows for leniency of use after 12 months of treatment in accordance with clinical need.

There remains uncertainty regarding the optimal treatment duration and approach to tapering and discontinuation. The open-label extension phase of the GiACTA trial did not help to mitigate this uncertainty, since only 42% of patients treated with a 12-month course of weekly tocilizumab remained in remission at 2 years following therapy suspension at 1 year (Stone et al., 2021). It is unknown if serial US monitoring may inform

the dose spacing of tocilizumab. This study aimed to continue the GCA FTC format of patient assessment up to 2 years after diagnosis with clinical assessment and vascular US and examine the utility of an extended approach on tocilizumab dose spacing after 1 year of treatment.

GCA patients from our FTC recruited from 2020-2022, with a clinical diagnosis of GCA were prospectively enrolled. As per ACR/ Vasculitis Foundation guidelines, all GCA patients with a new diagnosis of GCA were started on tocilizumab if there were no contraindications. All patients had corticosteroid 26-week taper as per the GiACTA protocol. Tocilizumab was administered weekly for the first 12 months, and then every-other-week for an additional 12 months. A retrospective analysis of OGUS score at baseline and 12 months was performed and correlated with relapse. Relapse of disease on tocilizumab was managed with temporary increases in systemic glucocorticoids.

5.5.1 Patient population

We included 54 patients with newly diagnosed GCA patients in this study. Of these, 27 patients did not receive tocilizumab treatment for various reasons (see figure 5.15). 27 patients (49%) were suitable for 26-week glucocorticoid taper and weekly treatment with tocilizumab with a median duration of 13 months [12-20]. The mean age of GCA patients was 73.6 ± 9.1 years. 12 (44.4%) were female and 15 (55.5%) were male. Patients had a mean starting dose of $44\text{mg} \pm 8.13$ prednisolone. 3 patients required 1000mg of intravenous methylprednisolone in addition. 51% of patients had isolated

cranial disease, 7% had isolated axillary disease, and 41% had mixed cranial and large vessel disease.

5.5.2 Reasons for not initiating tocilizumab in a real-world cohort

Despite intending to treat all newly diagnosed GCA patients with a 26 week glucocorticoid taper and weekly tocilizumab as per GiACTA protocol (Stone et al., 2017b), 27 patients did not start tocilizumab treatment and were treated with a 52-week glucocorticoid taper instead. This occurred for a variety of reasons. 9 patients suffered from frailty and/or recurrent infections, 7 patients had active malignancy, 3 had a history of severe diverticulitis requiring hospitalisation, 5 did not start due to patient preference, 1 had co-existing difficult-to-treat rheumatoid arthritis for which another biologic treatment was already initiated, and 1 patient died of unrelated causes before starting tocilizumab. A further 1 patient only had one month of treatment before discontinuation for a severe drug reaction.

5.5.3 Tocilizumab spacing

17/27 (62.9%) patients were in clinical remission at one year and had subsequent treatment with every second-week tocilizumab. The median duration of every second-week tocilizumab was 10 months [3-10]. 5 remained on a weekly dose due to previous visual loss and concern about preserving the remaining eye. 2 had other coexisting inflammatory diseases for which weekly dosing was required. 1 died of natural causes before dose spacing, and 2 stopped tocilizumab before spacing due to side effects.

5.5.4 Outcomes on tocilizumab therapy

Weekly tocilizumab treatment resulted in 3/27 relapses (11.1%) and included 2 major and 1 minor relapse. This compared with a relapse rate of 3/17 (17.6%) in the reduced dose tocilizumab group (1 major and 2 minor). There was no statistically significant difference in relapse rate between the two groups, $p=0.53$. There were 2 infections each in weekly and every two-weeks dosing groups, $p=0.62$ (see table 5.6). 1 patient in the weekly dosing group required hospitalisation for severe diverticulitis. One patient had a reduction in absolute neutrophil count (ANC) on weekly tocilizumab but maintained ANC >1 and was maintained on the weekly dose.

5.5.5 OGUS results

The mean baseline OGUS for patients treated with weekly tocilizumab was 1.25 [0.34]. 20/27 (74%) had OGUS >1 at baseline. The mean OGUS at 12 months for patients who transitioned to fortnightly tocilizumab was 0.85 ± 0.14 . 3/17 (17.6%) patients had an OGUS >1 at 12 months, were in clinical remission, and had dose spacing of tocilizumab from weekly to every second week. Of these 3 patients, 1 suffered a major relapse with monocular visual loss, and 1 suffered an infection that did not require hospitalisation. Of the patients with OGUS <1 at 12 months ($n=14$), 2 suffered relapses during treatment with every second week tocilizumab (1 major with monocular vision loss; and 1 minor). 1 further patient had an infection not requiring hospitalisation. Patients with OGUS >1 at 12 months had a complication rate of 66.6% (either relapse or infection) compared with 21.4% in those with OGUS <1 at 12 months, $p=0.11$ (see table 5.5). **Figure 5.15**

Figure 5.15 Treatment of GCA patients baseline to 2 years

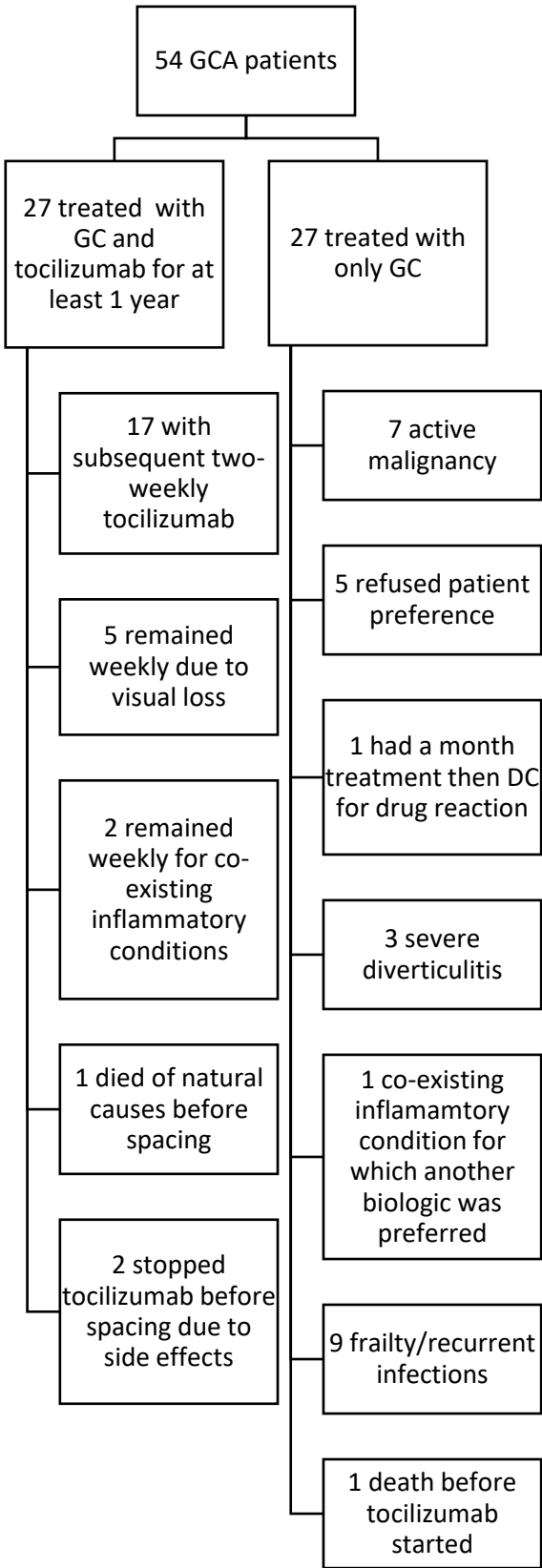


Table 5.5 Two-weekly tocilizumab treatment outcomes according to OGUS at 1 year

OGUS	OGUS <1 at 12 months	OGUS >1 at 12 months	P value
Relapse	2/14 (14.2%)	1/3 (33.3%)	0.43
Infection	1/14 (7%)	1/3 (33.3%)	0.20
Total complications	3/14 (21.4%)	2/3 (66.6%)	0.11

Table 5.6 Outcomes for GCA patients on weekly versus two-weekly tocilizumab

	Weekly tocilizumab (from baseline, n=27)	Fortnightly tocilizumab (from 12 months, n=17)	P value
Mean OGUS	1.25 [0.34]	0.85 [0.14]	<i><0.001</i>
Median [IQR] duration tocilizumab (months)	13 [12-20]	10 [3-10]	
Relapse	3/27 (11.1%)	3/17 (17.6%)	0.53
Infection	2/27 (7.4%)	2/17 (11.7%)	0.62
Overall complication rate	5/27 (18.5%)	5/17 (29.4%)	0.40

5.6 Discussion

This study has characterised the US pattern in subclinical GCA in PMR as a distinct phenotype. A higher incidence of extra-cranial involvement has been identified compared with GCA. There are only two previous publications with assessment of the cranial and extra-cranial vessels in PMR patients. Like our study, both exhibited an extracranial predilection, and this finding attained statistical significance in the De

Miguel study (De Miguel et al., 2023b, Burg et al., 2023). This may account for patients with subclinical GCA lacking the classical GCA presentation with cranial symptoms. Recognition of this pattern is important as patients with large vessel disease are more likely to follow a relapsing course (de Mornac et al., 2021). It also highlights the importance of including routine assessment of the extracranial vessels in GCA screening.

There is currently no published study documenting the change in HC, HS, and OGUS over time for patients with subclinical GCA in PMR compared with GCA. At baseline, there was no statistical difference between the HC in GCA and subclinical GCA in PMR, indicating that a similar number of vessels were involved. However, the OGUS at baseline was significantly different between the two groups, illustrating a more profound degree of inflammation in those with GCA. In the extended cohort, all three scores including HC, HS, and OGUS were significantly increased in those with GCA compared with subclinical GCA. This may suggest that subclinical GCA in PMR is a milder phenotype in the GCA-PMR spectrum of disease.

Most relapses in our subclinical GCA in PMR group were minor, with only 1/15 developing a major relapse consistent with GCA in 12 months of follow-up. Reassuringly, an increased risk of ischaemic events has not been observed in our cohort. None of the subclinical GCA patients developed blindness, stroke, or limb claudication. This is also consistent with the existing literature, and in keeping with real-world anecdotal experience of PMR patients rarely developing ischaemia.

This study has also shown that while HC, HS, and OGUS steadily decreased over the first 6 months in GCA patients, there was an overall increase in all US scores in subclinical GCA in PMR patients between 3 to 6 months of treatment, after an initial decline. This is an interesting observation and novel finding. GCA patients had significantly more glucocorticoid exposure at 3 months in comparison to their subclinical GCA counterparts at 2603mg versus 2036mg, $p=0.007$. This was also true for glucocorticoid exposure difference at the 6-month time point, 3235mg in GCA versus 2575mg in subclinical GCA, $p=0.03$. The initial decline followed by a subsequent rise in US scores in subclinical GCA in PMR may be reflective of less glucocorticoid treatment than their GCA counterparts and incomplete treatment. Relapses occurred earlier in subclinical GCA in PMR compared with GCA which may reflect this increase in HC, HS, and OGUS. It remains unclear how clinically relevant this is. Relapses up to 12 months in subclinical GCA in PMR were typically minor. Longitudinal follow-up of this cohort would be fascinating to explore the relevance of this US finding on future disease course. This study does suggest that OGUS is a responsive tool for disease monitoring.

HC, HS, and OGUS did not correlate with relapse in the GCA or subclinical GCA in PMR groups in our study. Other published studies have linked both high baseline OGUS, and failure of OGUS resolution with increased relapse in GCA (Molina-Collada et al., 2024a, Nielsen et al., 2023b). It is possible our study was underpowered to support these previously published findings. We did identify that those patients with an increase in OGUS at six months were more likely to relapse, although this didn't quite reach

significance, $p=0.09$. Our numbers of relapsing patients in subclinical GCA in PMR were small at 8/15 (53%), however, this may point to the possibility of using OGUS as a risk stratification tool. We were unable to complete this analysis in our extended subclinical GCA in PMR cohort as we only had access to baseline OGUS from the extended European cohort. OGUS has been established for monitoring purposes of GCA in clinical trials and has not yet been validated for monitoring subclinical GCA in PMR. Our larger cohort points to a potential expansion of the applicability of OGUS to patients with subclinical GCA in PMR. Larger prospective studies involving subclinical GCA in PMR patients may substantiate this.

Evidence is accumulating to support a potential role for US imaging, as a monitoring tool to assess response to treatment and detect relapses in patients with GCA (Ponte et al., 2021). The role of vascular US monitoring in GCA to guide treatment tapering or withdrawal has not been definitively proven. Currently, the only glucocorticoid-sparing agent approved for treatment of GCA is the anti-interleukin-6 receptor antagonist tocilizumab. There remains uncertainty regarding the treatment duration of tocilizumab and the optimal approach to medication withdrawal. This study assessed the OGUS in GCA patients who had dose spacing of tocilizumab to every second week at 1 year of treatment. Having an OGUS >1 at 12 months of treatment with weekly tocilizumab was associated with more relapse (33% vs 14%) but did not meet significance. Quantifying OGUS at 12 months may have a role in treatment decision-making. Larger studies are required to evaluate if OGUS at 12 months can inform treatment decisions.

A recent study has shown that all 3 scores display good sensitivity and excellent specificity for the diagnosis of GCA (Conticini et al., 2024). It also showed that a cut-off of 0.81 for OGUS, >1.5 for HC, and >14.5 for were reliable for GCA diagnosis. The HS and OGUS offer more information on the degree of intima thickness in vasculitic vessels than the halo count. In our cohort OGUS appeared to be the most clinically useful score, and predicted visual ischaemia in GCA while HS or HC did not. OGUS has also been validated for GCA disease monitoring (Dejaco et al., 2023a). In real-world cohorts, OGUS may be the most useful score to record at diagnosis and follow-up. In addition, there is an online page to assist with score calculation (<https://scoring.rheumatologie.at/omeract>) making it a quicker score to calculate than the HS.

The GiACTA extension study highlighted that stopping weekly tocilizumab in patients in clinical remission after one year resulted in 58% of patients having a GCA relapse over the second-year post-diagnosis (Stone et al., 2021). In this study, dose spacing of tocilizumab to every-other-week after at least a year of weekly treatment, maintained remission for most patients, with only 17.6% relapsing. This should be interpreted in the context of the two regimens being administered consequentially and is broadly in line with other published studies with similar numbers (Tomelleri et al., 2023a). Giant cell arteritis remains a chronic disease that entails ongoing management and careful vigilance for disease relapse and dose reduction of tocilizumab after the first year of treatment gave excellent disease control and had little safety concerns. OGUS may have a role in assisting decision-making on which patients to dose space.

In summary, vascular US quantification scores have shown promise for disease monitoring and prognostication but require external validation and longitudinal evaluation. Similarly, they have yet to be validated in subclinical GCA in PMR but our study suggests OGUS may have a role in this cohort, particularly an increase in OGUS during follow-up may point to a higher risk of relapse. Change over time with treatment in the HS, HC, and OGUS in subclinical GCA in PMR appears to differ from that of GCA. Scores in subclinical GCA in PMR initially improved, but then a subsequent rise was observed. This is a novel finding. It may reflect the earlier time to relapse in subclinical GCA in PMR and raises questions regarding the optimal treatment of subclinical GCA in PMR, which may favour a treatment protocol more in keeping with GCA. The data suggests that quantification of disease burden on US is diagnostic of both GCA and subclinical GCA in PMR, differentiates subclinical GCA from pure PMR in a PMR cohort, and may be useful tool for monitoring disease. US scores have value in research settings but may also be useful in a clinical setting. There may be a role for a prognostic scoring system that combines clinical symptoms, laboratory markers, and US scores in the future to help with disease stratification.

Chapter 6:

Pilot study of shoulder ultrasound in

Polymyalgia Rheumatica

6.1 Abstract

Introduction

Chapter 5 evaluated the role of ultrasound in the vascular assessment of PMR patients. Ultrasound also has a role in the GCA PMR spectrum of disease in identifying musculoskeletal pathology in PMR. The latest 2012 EULAR PMR classification criteria include an ultrasound domain to aid the classification of PMR into homogenous cohorts for clinical research. The role of musculoskeletal ultrasound in the diagnosis of PMR has yet to be fully defined.

Methods

A subset of PMR patients had an ultrasound of their bilateral shoulders completed at baseline visit in the PMR fast-track clinic as a pilot study. Standard musculoskeletal imaging technique following the EULAR ultrasound scanning guide was implemented. Pathology was diagnosed according to OMERACT definitions.

Results

65% of patients in the PMR cohort had bilateral subacromial subdeltoid bursitis, 45% had bilateral long head of biceps tenosynovitis, and 10% had a glenohumeral effusion. Previous glucocorticoid exposure < 4 weeks did not impact shoulder US results with no statistical difference in the prevalence of PMR-related shoulder pathology in glucocorticoid exposed versus glucocorticoid naïve patients.

Conclusions

The majority of PMR patients have ultrasound-defined pathology at presentation. Shoulder US is feasible to include in a PMR fast-track clinic care algorithm and may be a useful tool to incorporate into PMR fast-track clinics to assist diagnosis, especially in cases where patients have had glucocorticoid exposure <4 weeks.

6.2 Introduction

US is a useful tool in PMR diagnosis. Subacromial subdeltoid (SASD) bursitis appears to be the most useful finding on US in PMR patients with bilateral SASD bursitis having a sensitivity of 66% and specificity of 89% in a recent systematic review (Mackie et al., 2015a). In addition, the finding of bilateral long head of biceps tenosynovitis was associated with persistence in PMR diagnosis at follow-up, whereas the presence of glenohumeral synovitis at baseline was associated with a revised alternative diagnosis at follow-up (Conticini et al., 2023).

Hip US is somewhat less useful in detecting the typical PMR finding of bursitis compared with MRI (Huwart et al., 2018). MRI detected bursitis in 73% of hips versus only 13% detection on US (Huwart et al., 2018). This may be explained by reduced US sensitivity in deeper structures, perhaps also contributed to by scanning technique, and difficulty with positioning elderly patients. Hip scanning is also time-consuming in a fast-track clinic setting.

Knee US may also be of value in suspected PMR. Findings associated with PMR may include suprapatellar bursitis, popliteal tendonitis, and lateral and medial collateral tendonitis (Kobayashi et al., 2022). In fact, Kobayashi et al found that including an US assessment of the shoulder and knee may improve the accuracy of the 2012 EULAR/ACR provisional classification criteria for PMR (Kobayashi et al., 2022). In this study, we completed a pilot study of bilateral shoulder US to assess the findings present in our PMR cohort and determine its contribution to the diagnosis.

The objective of this pilot study was:

1. To assess shoulder ultrasound findings in PMR and examine the feasibility of including shoulder ultrasound assessment in the fast-track clinic algorithm.

6.3 Methods

6.3.1 PMR Fast-track clinic recruitment

As outlined in chapter 3, PMR fast-track clinics (FTCs) were established at TUH and SJH to establish a multicentre prospective longitudinal study. Patients with a new suspected diagnosis of PMR in primary care were recruited to the PMR FTC between July 2022 and July 2023. Patients were required to be over 50 years of age, have a new onset of bilateral shoulder or hip pain and/or stiffness, and not be on glucocorticoid treatment for >4 weeks duration. All patients were reviewed in the fast-track PMR clinic within 72 hours.

6.3.2 Patients and study design

All patients referred underwent a thorough history and clinical examination. An extensive laboratory evaluation was also conducted to include baseline ESR, CRP, full blood count, liver profile, renal function, fibrinogen, Hba1c, lipid profile, RF, ACPA, ANCA-related antibodies, and extended myositis panel. All patients had a baseline vascular ultrasound of their cranial and axillary arteries. The diagnosis of PMR was a clinical one, made in agreement by two rheumatologists.

6.3.3 Ultrasound Procedure

A pilot study was conducted on a subset of 20 patients of our PMR cohort who had bilateral shoulder ultrasound at the baseline visit. These patients were recruited from the PMR FTC and consisted of 20 consecutive patients. The cohort included both patients with isolated PMR (17) and subclinical GCA in PMR (3). Standard shoulder images were obtained following the EULAR ultrasound scanning guide and standard imaging procedures (Backhaus et al., 2001). This was performed by a trained rheumatologist who was aware of the patient's clinical details and verified by a second rheumatologist who was blinded to the clinical details. The shoulder US evaluation included the assessment of subacromial-subdeltoid (SASD) bursitis, long head of biceps (LHB) tenosynovitis, and posterior glenohumeral (GH) synovitis.

6.3.4 Ethical considerations

Full ethical approval was obtained from the Joint Research Ethics Committee for Tallaght University Hospital and St James Hospital, Dublin, Ireland. All patients gave fully informed written consent to participate in the fast-track clinic study.

6.3.5 Statistical analysis

Descriptive analysis of the data was performed using SPSS. Data were expressed as the mean $\pm$ standard deviation (SD) for normally distributed continuous variables, as median (interquartile range) for non-normally distributed variables, and as percentages and frequencies for categorical variables. Continuous variables were compared using the independent t-test. Categorical variables are summarised by frequency and percentage (%) and compared using the chi-square test or Fisher's exact test. P values <0.05 were considered statistically significant.

6.3.5 Decision to not include US hips

US evaluation in PMR has been included in the 2012 ACR/EULAR classification criteria. In particular, the ultrasound findings of bilateral shoulder abnormalities such as subacromial-subdeltoid (SASD) bursitis, long head of biceps (LHB) tenosynovitis, and glenohumeral (GH) synovitis, or abnormalities in one shoulder and hip (hip effusion, trochanteric bursitis) may significantly improve the specificity of the clinical criteria (Dasgupta et al., 2012). In a practical sense, hip US is less useful in detecting the typical PMR finding of bursitis than MRI (Huwart et al., 2018). MRI detected bursitis in 73% of

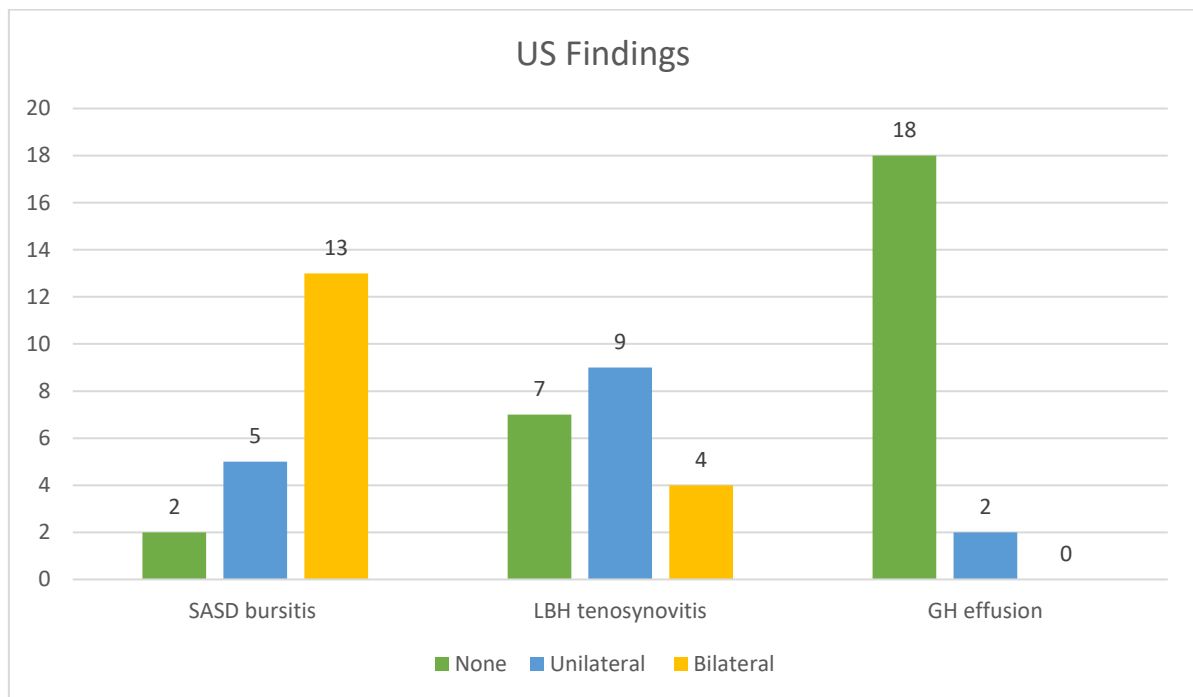
hips versus only 13% detection on US (Huwart et al., 2018). Hip US is also time-consuming in the FTC PMR setting, and many elderly patients have difficulty in attaining the necessary positioning. In addition, hip pathology is typically deeply located, and in our cohort, with most patients in the overweight or obese category, we decided to pilot shoulder US only.

6.4 Results

6.4.1 Shoulder pathology

Subacromial-subdeltoid (SASD) bursitis is one of the most helpful ultrasound features for PMR diagnosis (Mackie et al., 2015a) and this finding has also been identified in positron emission tomography (PET) studies (Owen et al., 2024b). SASD bursitis was defined as the presence of a hypoechoic line between the deltoid muscle and the supraspinatus tendon measuring ≥ 2 mm thick (Tsai et al., 2007). In total, 90% of patients had SASD bursitis, with 65% bilateral and 25% unilateral. LHB tenosynovitis was defined as the presence of an anechoic enlargement of the tendon sheath and normal tendon echotexture $\pm$ doppler activity (Iagnocco et al., 2006). 65% of patients had LHB tenosynovitis; with 45% having bilateral findings and 20% unilateral. GH effusion was defined as an anechoic enlargement/bulge at the posterior GH joint recess with the arm in external rotation. 2/20 (10%) of patients had a unilateral GH effusion on shoulder US, and none had bilateral effusions.

Figure 6.1 Shoulder Ultrasound findings in PMR



6.4.2 Inflammatory markers

There was no difference in baseline inflammatory markers in patients with either unilateral or bilateral SASD bursitis. The baseline ESR for those with unilateral SASD bursitis was 42.4 [SD29.7] compared with 48.9 [SD25.8], $p=0.68$. The baseline CRP for those with unilateral SASD bursitis was 34mg/l [SD20.45] and 19.1 [SD16.5] for those with bilateral findings, $p=0.19$. Similarly, patients with and without LHB tenosynovitis and GH effusion had no significant difference in baseline inflammatory markers (see tables 7.1, 7.2, 7.3). A previous study on MRI and US in shoulder PMR reported a similar incidence of shoulder inflammatory lesions, regardless of ESR elevation (Cantini et al., 2001).

6.4.3 Glucocorticoid exposure

40% of patients (8/20) had previous glucocorticoid exposure at the time of shoulder US. Glucocorticoid exposure before the time of US was numerically higher in those with unilateral SASD bursitis at 194mg compared with 145.7mg in those with bilateral SASD bursitis, but not statistically significant, $p=0.75$. There no significant correlation between previous glucocorticoid exposure and the presence of GH effusion ($r=-0.2$, $p=0.38$), SASD bursitis ($r=-0.1$, $p=0.64$), or LHB tenosynovitis ($r=0.13$, $p=0.58$).

Shoulder US findings do not appear to be impacted by previous glucocorticoid exposure up to 4 weeks. US shoulders in the PMR FTC setting may help make the diagnosis in patients already commenced on glucocorticoids by primary care when other clinical symptoms and laboratory markers are masked.

Table 6.1 Features of PMR patients with LBH tenosynovitis

Characteristic	No LHB (n=7)	Unilateral LHB (n=9)	Bilateral LHB (n=4)	p-value
Mean baseline ESR (mm/h)	42.4, SD = 30.27, 95% CI [19.98, 64.82]	46.67, SD = 27.2, 95% CI [28.90, 64.44]	43, SD = 23.1, 95% CI [20.36, 65.64]	.94
Mean baseline CRP (mg/l)	16.43, SD = 14.4, 95% CI [5.76, 27.10]	25.6, SD = 18.79, 95% CI [13.32, 37.88]	23.2, SD = 24, 95% CI [-0.32, 46.72]	.61

Age (years)	75.5, SD = 10.9, 95% CI [67.43, 83.57]	70.5, SD = 6.8, 95% CI [66.06, 74.94]	66.7, SD = 11.2, 95% CI [55.72, 77.68]	.31
EMS duration (mins)	109.29, SD = 89.46, 95% CI [43.02, 175.56]	103.3, SD = 92.6, 95% CI [42.80, 163.80]	63.7, SD = 77.8, 95% CI [-12.54, 139.94]	.69
GC exposure (mg)	64.6, SD = 84.78, 95% CI [1.79, 127.41]	188.8, SD = 277.5, 95% CI [7.50, 370.10]	225, SD = 450, 95% CI [-216.00, 666.00]	.56
Days symptomatic	71, SD = 55.1, 95% CI [30.18, 111.82]	103.3, SD = 73.7, 95% CI [55.15, 151.45]	109.5, SD = 67.5, 95% CI [43.35, 175.65]	.56

Table 6.2 Features of PMR patients with unilateral vs bilateral SASD bursitis

Characteristic	Unilateral SASD bursitis (n=3)	Bilateral SASD bursitis (n=13)	p-value
Mean baseline ESR (mm/h)	42.4, SD = 29.7, 95% CI [8.79, 76.01]	48.9, SD = 25.8, 95% CI [34.87, 62.93]	.68
Mean baseline CRP (mg/l)	34, SD = 20.45, 95% CI [10.86, 57.14]	19.1, SD = 16.5, 95% CI [10.13, 28.07]	.19
Age (years)	69.8, SD = 5.9, 95% CI [63.12, 76.48]	72.3, SD = 10.8, 95% CI [66.43, 78.17]	.62
EMS duration (mins)	27, SD = 22.2, 95% CI [1.88, 52.12]	107.3, SD = 84.3, 95% CI [61.47, 153.13]	.006
GC exposure (mg)	194, SD = 342.1, 95% CI [-193.12, 581.12]	145.7, SD = 266.4, 95% CI [0.88, 290.52]	.78
Days symptomatic	118.2, SD = 53.1, 95% CI [58.11, 178.29]	92.3, SD = 70.8, 95% CI [53.81, 130.79]	.42

Table 6.3 Features of PMR patient with GH effusion

Characteristic	No GH effusion (n=18)	Unilateral GH effusion (n=2)	p-value
Mean baseline ESR (mm/h)	45.89, SD = 27.2, 95% CI [33.32, 58.46]	31.5, SD = 13.4, 95% CI [12.93, 50.07]	.33
Mean baseline CRP (mg/l)	22.7, SD = 18.4, 95% CI [14.20, 31.20]	14.5, SD = 14.8, 95% CI [-6.01, 35.01]	.57
Age (years)	72.6, SD = 9.2, 95% CI [68.35, 76.85]	62, SD = 4.2, 95% CI [56.18, 67.82]	.08
EMS duration (mins)	91.67, SD = 83.4, 95% CI [53.14, 130.20]	150, SD = 127.2, 95% CI [-26.29, 326.29]	.63
GC exposure (mg)	164, SD = 279.2, 95% CI [35.02, 292.98]	50, SD = 70.7, 95% CI [-47.99, 147.99]	.21
Days symptomatic	97.5, SD = 66.9, 95% CI [66.59, 128.41]	57, SD = 38.2, 95% CI [4.06, 109.94]	.33

6.5 Discussion

Shoulder US is useful in the assessment of PMR, both in identifying alternative pathology and adding to diagnostic certainty when the presence of typical PMR findings is identified. SASD bursitis, especially when present bilaterally, appears to be the US lesion with the best diagnostic accuracy, followed by LHB tenosynovitis (Iagnocco et al., 2015). In this study, 90% of patients had SASD bursitis, with 65% of PMR patients having bilateral involvement. 65% of patients had LHB tenosynovitis; with 45% having bilateral findings and 20% unilateral, while 10% of patients had a unilateral GH effusion. This is in line with previously reported prevalence of these findings (Camellino and Cimmino, 2011, Iagnocco et al., 2015). Shoulder US findings were not impacted by previous glucocorticoid exposure <4 weeks in our study. These findings have practical clinical

applicability. Including US shoulders in the PMR FTC setting may help to establish the diagnosis of PMR in patients already commenced on glucocorticoids <4 weeks by primary care when other clinical symptoms and laboratory markers are masked.

This pilot study had some limitations. Only one-third of newly diagnosed PMR patients from our FTC had shoulder ultrasound performed. We did not include non-PMR controls to compare the incidence of shoulder findings with a similar age-matched population. This was because the full one-hour slot was filled with clinical assessment, vascular ultrasound, blood taking, and discussion with the patient regarding diagnosis and treatment at the initiation phase of the FTC. As time went on, the clinician sonographer was more efficient with time in the one-hour clinical slot, and shoulder US was also included in the protocol. In addition, the first clinician sonographer was the treating physician and was not blinded to the clinical details of the case. We accounted for this by having a second clinician sonographer, blinded to the clinical details of the cases, review and verify all the images.

Finally, hip ultrasound was not performed on this cohort. Several recent studies have reported a distinctive pattern of hip pathology in PMR involving extracapsular structures including tendons, bursae, and entheses (Mackie et al., 2015b, Owen et al., 2024a, Owen et al., 2017). The reported prevalence of hip pathology in PMR is 92-100% on MRI (Fruth et al., 2020). These values contrast with an ultrasound study performed by the EULAR/ACR Working Group for the development of PMR classification criteria which found a much lower rate of trochanteric bursitis at only 20% in PMR patients (Dasgupta

et al., 2012). Most of our PMR patients were overweight or obese which posed difficulty in correctly positioning the patients and attaining quality images at sufficient tissue depth. The reduced sensitivity of US for hip pathology was also a factor.

This pilot study also had many strengths. We consecutively included patients with newly diagnosed PMR, including both those with pure PMR and subclinical GCA in PMR. This is representative of a real-world PMR cohort. A standardised shoulder imaging protocol was followed and could be easily replicated and may be adopted into other PMR FTCs.

This pilot confirmed that performing shoulder US is feasible in the FTC setting in addition to clinical assessment and vascular ultrasound screening once clinicians have sufficient experience running the clinic. It has shown utility in assisting diagnosis where patients have had previous GC exposure < 4 weeks. Making a clinical diagnosis may be more challenging in this group as symptoms may have resolved and laboratory markers may have normalised with glucocorticoid treatment. The majority of patients with PMR have shoulder pathology on ultrasound at the time of presentation. The commonest site of involvement for inflammation is the subdeltoid bursa. This data may be useful in defining the clinical phenotypes in GPSD but did not differentiate patients according to response to therapy.

Chapter 7:

Serum biomarkers in GCA-PMR

Spectrum Disease

7.1 Abstract

GPSD remains a difficult complex of diseases to diagnose, differentiate, and prognosticate. There is currently a paucity of validated biomarkers to aid clinical decision-making.

Methods

Serum biomarker analysis for angiopoietin-1, angiopoietin-2, CXCL-9, osteopontin, IL-6, IL-17 and IL-23 was completed on patients recruited via fast-track GCA and PMR clinics. Samples from baseline, remission states, and relapse states were analysed. Remission was defined as the absence of clinical symptoms and systemic inflammation. Relapse was defined as new disease activity after a period of remission or worsening disease activity. Samples included baseline PMR (n=53), remission PMR (n=53), relapse PMR (n=11), baseline subclinical GCA in PMR (n=13), remission subclinical GCA in PMR (n=31), relapse subclinical GCA in PMR (n=5), baseline GCA (n=59), remission GCA (n=71), and relapse GCA serum (n=11). All samples underwent one freeze-thaw cycle and were analysed with the BioTechne ELISA screening assay kits following the manufacturer's protocol recommendations and reported as mean $\pm$ standard deviation or median $\pm$ interquartile range.

Results

Angiopoietin-1 was significantly elevated in subclinical GCA in PMR compared with PMR patients at baseline $p < 0.001$. A cut-off of 21,408 pg/ml produced a sensitivity of 84.6%

and a specificity of 70% for differentiating subclinical GCA in PMR from pure PMR. IL-17 levels were significantly more elevated in subclinical GCA in PMR compared with isolated PMR. ROC analysis demonstrated an AUC of 0.892, with a cut-off of 5pg/ml giving a sensitivity of 84.6%, and specificity of 79.2%. Osteopontin levels were significantly elevated in subclinical GCA in PMR compared with isolated PMR and ROC analysis found the AUC to be 0.814. A cut-off of 2766pg/ml gave a sensitivity of 84.6% and a specificity of 72.7%. ROC analysis of CXCL-9 levels between PMR and subclinical GCA in PMR gave an AUC of 0.752 with cut off of 107.8pg/ml giving 92.3% sensitivity and 62.3% specificity. GCA serum was significantly different from PMR serum at time of diagnosis, with GCA exhibiting significant elevations in angiopoietin-1 ($p<0.001$), angiopoietin-2 ($p<0.001$), CXCL-9 ($p<0.001$), osteopontin ($p<0.001$), IL-6 ($p=0.02$), and IL-17 ($p<0.001$) compared with PMR. Small numbers of relapsing tocilizumab-treated GCA patients limited the biomarker analysis in this cohort, but no biomarker appeared as useful as ESR or CRP in this group.

Conclusion

Overall, analysis of baseline serum of patients with GCA, PMR, and subclinical GCA has demonstrated potential for disease stratification in GPSD. Angiopoietin-1, angiopoietin-2, CXCL-9, osteopontin, IL-6, and IL-17 were significantly different between PMR and GCA serum at baseline. Angiopoietin-1, CXCL-9, osteopontin, and IL-17 discriminated between PMR and subclinical GCA in PMR, with angiopoietin-1, IL-17, and osteopontin showing excellent AUC on ROC analysis. The only biomarker to discriminate between

GCA and subclinical GCA was IL-17. Subclinical GCA in PMR has a distinct biochemical profile from PMR, more akin to that of GCA.

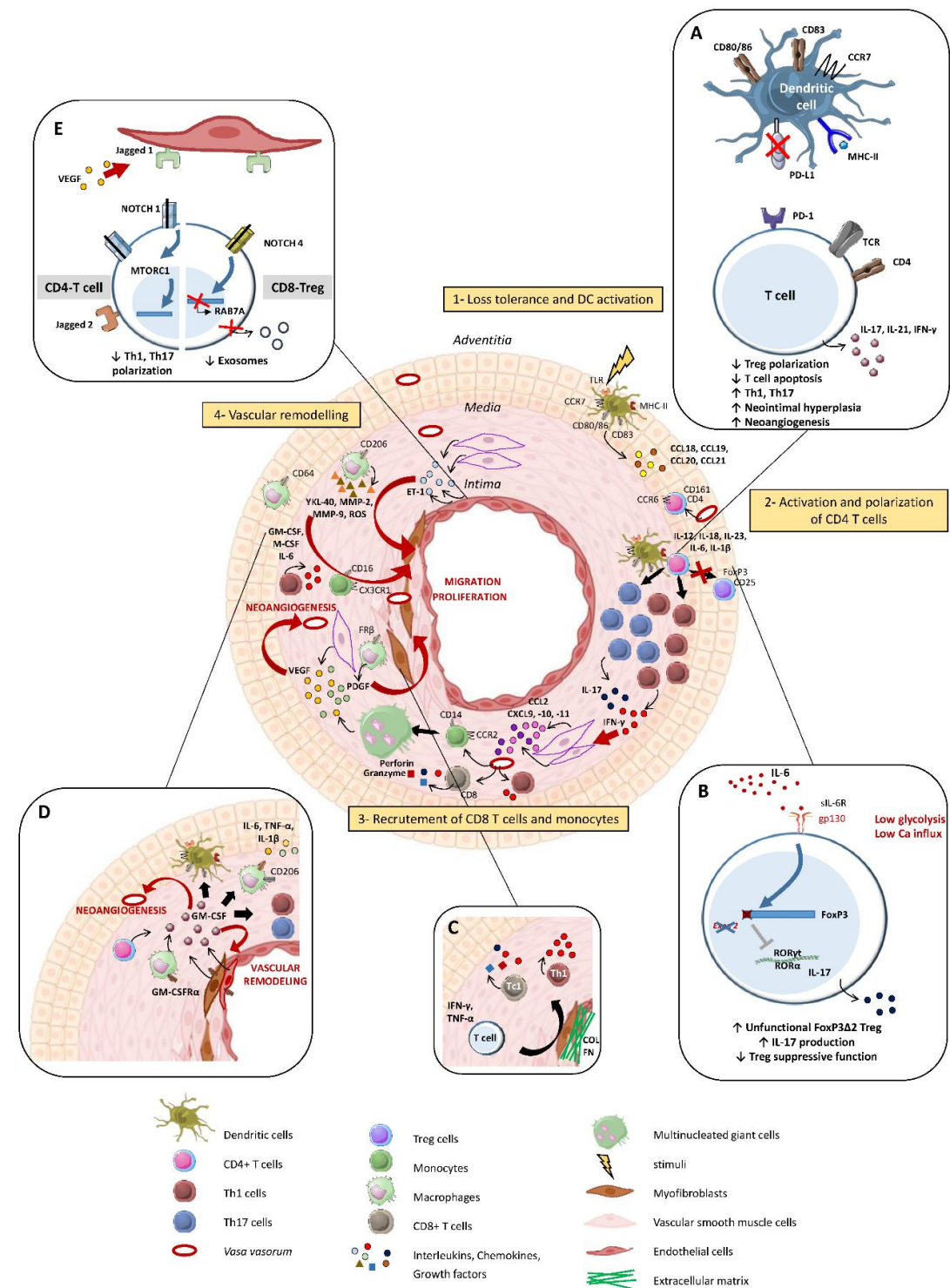
7.2 Introduction

The GCA PMR Spectrum of disease encompasses GCA, PMR, GCA-PMR overlap, and subclinical GCA in PMR. Significant homogeneity exists between these conditions linked by common genetics, inflammatory mediated response, IL-6 signature, and therapeutic response to glucocorticoid treatment. Equally, heterogeneity exists in their propensity for vascular inflammation and end-organ damage, differential dose response to glucocorticoid-sparing agents, and risk of relapse. Stratifying patients with GPSD may assist with predicting the disease course and delivering individualised patient treatment. There is growing interest in biomarkers that may help with disease assessment, categorisation, monitoring, prognostication, and the delivery of targeted therapy. This is particularly important in the era of anti-interleukin-6 receptor treatment for GCA and PMR, where traditional inflammatory biomarkers such as ESR and CRP are of limited value in monitoring for disease relapse.

There are still many unanswered questions in the monitoring and treatment of GCA. While ESR and CRP have been the principal biomarkers, both are indirect measures of cytokine directed inflammation, and their utility is reduced in patients on selective cytokine inhibitors such as tocilizumab. Novel biomarkers that may predict disease complications or relapse are highly anticipated as they could potentially be incorporated into treatment stratification. Biomarkers that measure actual disease activity, preferably not directly influenced by the IL-6 pathway or blunted with glucocorticoid and anti-IL6

receptor treatment, and baseline parameters that may predict outcomes are all of huge interest. Similarly, in PMR, biomarkers are being pursued to predict which PMR patients have concomitant GCA or will go on to develop GCA during their disease course. To date, no new reliable biomarkers have been validated for clinical use, however, there have been several biomarkers of interest noted in various studies (see table 7.1). No study to date has examined cohorts of PMR patients categorised by temporal artery ultrasound. This study investigates the differences and similarities in the inflammatory profiles of PMR and GCA using serum biomarkers and assesses diagnostic biomarkers of subclinical vascular inflammation in patients with PMR.

Figure 7.1 Immunopathological Model of GCA



(Greigert et al., 2022)

7.2.1 Vascular Markers

It seems logical that vascular markers may have the propensity to delineate GCA from PMR and identify PMR patients with GCA. Vascular endothelial growth factor (VEGF) is elevated in treatment naïve GCA patients diagnosed on TAUS compared with healthy age-matched controls (Burja et al., 2019, van Sleen et al., 2022). VEGF serum concentrations are also higher in untreated PMR patients than in normal control subjects (Meliconi et al., 2000) but this has not been correlated with concomitant GCA or future GCA development. Angiopoietin-1 (ang-1) levels do not appear to be elevated in patients with GCA, and high levels at baseline were associated favourable prognosis with a shorter time to glucocorticoid-free remission (van Sleen et al., 2019). Conversely, elevated angiopoietin-2 (ang-2) levels were shown to be associated with an imminent relapse during treatment for GCA (van Sleen et al., 2019). While individually less useful in PMR, the Ang 2:1 ratio also identifies concomitant GCA in PMR patients (van Sleen et al., 2022).

7.2.2 Monocyte/macrophage involvement

Macrophage infiltration and giant cell formation are diagnostic histological features in vessel wall inflammation (van Sleen et al., 2017). There may be a role for the measurement of factors secreted by monocytes and macrophages, and/or factors with upstream regulation of these cells in assessing disease activity and phenotype.

Chitinase 3-like protein 1 also known as YKL-40, is secreted by macrophages, neutrophils, chondrocytes, endothelial, vascular smooth muscle, and cancer cells. High

serum YKL-40 is a biomarker of poor prognosis in patients with cancer and inflammation (Roslind and Johansen, 2009). It has also been shown to be more elevated in GCA patients at baseline compared to healthy controls (van Sleen et al., 2019), and does not appear to be down-regulated by glucocorticoid treatment.

Granulocyte-macrophage colony stimulating factor (GM-CSF) is expressed in the adventitia of temporal artery biopsies (TABs), and likely contributes to macrophage heterogeneity in the vascular wall (Jiemy et al., 2020). Blocking the GM-CSF receptor alpha with mavrilimumab reduces infiltrating cells and neo-angiogenesis in the neo-intimal layer of cultured arteries with GCA (Corbera-Bellalta et al., 2022) and may be a therapeutic option in GCA. In serum, this marker is less helpful with no significant elevation compared with controls (van der Geest et al., 2015b).

Monocyte chemotactic protein-3 (MCP-3), also known as Chemokine (C-C motif) ligand 7 (CCL-7) was associated with an increased risk of developing GCA in prospective population studies with samples taken from the Malmo Diet Cancer Study (Wadström et al., 2023). Levels of the mannose receptor (soluble cluster of differentiation 206, *sCD206*) are elevated in both GCA and isolated PMR (van Sleen et al., 2022) as compared with normal controls.

7.2.3 Extracellular remodelling

Matrix metalloproteinases (MMPs) have been postulated to have a role in GCA pathogenesis due to their ability to degrade elastin. Degradation of the internal elastic lamina is characteristic of GCA (Rodríguez-Pla et al., 2005). MMP-1, and MMP-9 have been proven to be elevated in GCA compared with matched healthy controls, while MMP-2 is decreased compared with healthy controls (Burja et al., 2019). MMP-3 has pro-inflammatory and anti-inflammatory effects (Wan et al., 2021). MMP-3 has potential utility in identifying PMR patients at risk of GCA, with lower MMP-3 levels previously reported in PMR patients with concomitant GCA (van Sleen et al., 2022). In addition, low MMP-3 levels may assist in differentiating GCA from infection (van Sleen et al., 2022).

7.2.4 Neutrophil involvement

Neutrophil infiltration is observed on histological analysis of temporal artery biopsy in GCA (Hernández-Rodríguez et al., 2016), suggesting that neutrophils have a role in GCA pathogenesis. Activated neutrophils result in the local release of pro-inflammatory cytokines (Paroli et al., 2024). Possible neutrophil-related factors that may have a role in GCA-related inflammation include calprotectin, elastase, and anti-proteinase-3. Neutrophil release of calprotectin is well-recognised as a clinical biomarker in inflammatory bowel disease pathogenesis, but calprotectin is elevated in multiple inflammatory states including GCA. It is a calcium- and zinc-binding protein that plays a key role in innate immunity and the recruitment of inflammatory cells. Calprotectin has been demonstrated to be elevated in both GCA and isolated PMR, with GCA exhibiting higher levels than PMR (van Sleen et al., 2022).

Elastase is a proteinase with a primary role in the breakdown of elastin. It has been identified as a potential differentiator between PMR and healthy controls with elevated levels in patients with PMR (van Sleen et al., 2022). Anti-proteinase-3 (PR3) is elevated in both the serum of GCA and isolated PMR compared with healthy controls (van Sleen et al., 2022).

7.2.5 Cytokines / lymphocyte activation

Cytokine profiles and lymphocyte activation factors may help to distinguish GCA and PMR or predict which patients are at high risk of developing ischemic complications. B-cell activating factor (BAFF) is a critical factor that supports the maturation of B cells. Increased serum BAFF is elevated in GCA and PMR (van der Geest et al., 2015a, Burja et al., 2019) and has an association with disease activity. Interferon alpha (IFN-alpha) levels have proven to be elevated in giant cell arteritis aortitis tissue (Vieira et al., 2022) but not in serum from GCA or PMR patients (van der Geest et al., 2015b).

Osteopontin is a multifunctional glycoprotein expressed by a wide range of cells in states of tissue injury and inflammation by several cells, including lymphocytes. It acts as a chemotactic molecule to promote the migration of inflammatory cells and functions as an adhesive protein to retain cells at the site of inflammation. It also enhances Th1 differentiation (Lund et al., 2009) and Th17 differentiation, promote inhibition of Th2-mediated responses and contributes to angiogenesis and vascular remodelling

(Tomelleri and DeJaco, 2024). Osteopontin has been found to correlate with CRP and ESR in one study, with levels attenuating with GC therapy, however, not appearing to be affected by IL-6 blocking agents (Prieto-González et al., 2017). Another study indicated high serum levels of osteopontin in GCA were associated with a relapsing disease course (Prieto-González et al., 2017).

Cytokines including interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-17 (IL-17) and interleukin-23 (IL-23) are also of interest in GPCD. IL-6 has a well-established role in the pathophysiology of GCA and PMR, first identified as an elevated factor in 1990 (Dasgupta and Panayi, 1990). Levels have been shown to correlate with ESR (Roche et al., 1993), and blocking this pathway has proven to be a successful treatment option for both GCA and PMR (Stone et al., 2017a, Spiera et al., 2023). IL-1 is also of interest, showing elevation in treatment naïve GCA (Burja et al., 2019). IL-10 is also elevated in newly diagnosed GCA, but not PMR (van der Geest et al., 2015a). Serum levels of IL-17 do not appear to be elevated in GCA or PMR patients compared with healthy controls (van der Geest et al., 2015a). However, incubation of vascular myofibroblasts from healthy arteries with IL-17 has a direct effect on the production of pro-inflammatory cytokines, including IL-6, VEGF-A, GM-CSF, CCL2 and CCL20 (Greigert h, 2023). Increased IL-17A expression on TABs is also associated with sustained response to GC (Espígol-Frigolé et al., 2013). IL-23 is also proven to be elevated in newly diagnosed GCA patient serum compared with normal healthy controls (Burja et al., 2019).

7.2.6 Cell migration

Chemokine (C-X-C motif) ligand 9 (CXCL-9) is an interferon-triggered chemokine that induces chemotaxis and differentiation of leukocytes. It is secreted by leukocytes, macrophages, and fibroblasts (Zhou et al., 2023). It has been previously identified as a chemokine with elevations in newly diagnosed GCA and PMR patients compared to healthy controls (van der Geest et al., 2015b).

Table 7.1 Summary of biomarkers in GCA/ PMR

Biomarker	References	Findings
Vascular		
VEGF	(Burja et al., 2019) (van Sleen et al., 2022) (Meliconi et al., 2000)	Elevated in treatment naïve GCA patients. Elevated in treatment naïve PMR
Angiopoietin-1	(van Sleen et al., 2019)	Elevated levels with a shorter time to GC-remission in GCA
Angiopoietin-2	(van Sleen et al., 2019)	Elevated levels with a shorter time to relapse in GCA. Ang2: Ang 1 ratio predicts vascular involvement in PMR
Monocyte/Macrophage Involvement		
YKL-40	(van Sleen et al., 2019)	Elevated in GCA patients; not downregulated by glucocorticoid treatment
GM-CSF	(van der Geest et al., 2015b) (Jiemy et al., 2020) (Jiemy et al., 2023)	Not elevated in GCA serum Expressed in the vessel wall of GCA Expressed in the synovium of PMR patients
MCP-3	(Wadström et al., 2023)	Associated with developing GCA in the future
sCD206	(van Sleen et al., 2022)	Elevated in serum of GCA and isolated PMR
Extracellular Remodelling		

MMP-1	(Burja et al., 2019)	Levels elevated in GCA vs healthy controls
MMP-2	(Burja et al., 2019)	Levels elevated in GCA vs healthy controls
MMP-3	(van Sleen et al., 2022)	Lower MMP-3 levels are observed in PMR patients with concomitant GCA. Low levels may differentiate GCA from infections.
MMP-9	(Burja et al., 2019)	Levels elevated in GCA vs healthy controls.
Neutrophil involvement		
Calprotectin	(van Sleen et al., 2022)	Elevated in GCA and isolated PMR
Elastase	(van Sleen et al., 2022)	Elevated in isolated PMR
PR3	(van Sleen et al., 2022)	Elevated in GCA and isolated PMR
Cytokines / lymphocyte activation		
BAFF	(Burja et al., 2019) (van der Geest et al., 2015a)	Increased in newly diagnosed GCA and PMR patients.
IFN-alpha	(van der Geest et al., 2015a) (Vieira et al., 2022)	Serum levels not elevated in GCA / PMR vs healthy controls. Elevated in giant cell arteritis aortitis
Osteopontin	(Prieto-González et al., 2017)	High serum levels in GCA associated with a relapsing course
IL-1	(Burja et al., 2019)	Elevated in treatment naïve GCA patients
IL-6	(Dasgupta and Panayi, 1990) (Jiemy et al., 2023)	Elevated in GCA and PMR Expressed in synovium of PMR patients
IL-10	(van der Geest et al., 2015b)	Elevated in newly diagnosed GCA but no PMR

IL-17	(van der Geest et al., 2015b) (Greigert h, 2023) (Espígol-Frigolé et al., 2013)	No elevation in GCA/PMR serum Treatment of negative TABs with il-17 upregulates several pro-inflammatory markers. Increased il-17A expression on TABs associated with sustained response to GC.
IL-23	(Burja et al., 2019)	Increased in GCA patient serum
Cell migration		
CXCL9	(van der Geest et al., 2015b)	Elevated in newly diagnosed GCA and PMR patients.

Currently, no studies have directly compared the serum protein biomarker profiles of patients with PMR, GCA and subclinical GCA in PMR as defined by vascular imaging. This research aims to compare the biomarker profile of these GPSD phenotypes by analysing serum biomarkers. The aim is to identify specific serum biomarkers that can help diagnose and differentiate between PMR, GCA, and subclinical GCA in PMR. In this study, we have decided to analyse IL-6, IL-17, IL-23, osteopontin, CXCL-9, angiopoietin-1, and angiopoietin-2 as candidate biomarkers in our patients with GCA, PMR, and subclinical GCA in PMR. IL-6 is integral to the inflammatory process in GCA and PMR, and blockade of this pathway has proven to be an effective treatment in both GCA and PMR, so, logically, there may be some utility in measuring this biomarker. Similarly, IL-17 blockade is a promising therapeutic option for GCA, with IL-17 having a direct effect on the production of pro-inflammatory cytokines including IL-6, VEGF-A, and GM-CSF (Greigert h, 2023), hence the logic to choose this as a candidate biomarker. IL-23 blockade has also been shown to play a key pathogenic role in inflammatory and proliferative pathways of GCA (Conway et al., 2018b), which prompted the inclusion of this biomarker

to assess its utility in disease monitoring. Angiopoietin-1 and Angiopoietin-2 have a role in vascular remodelling. As subclinical GCA in PMR and GCA exhibit vascular remodelling and intima-media proliferation these factors were chosen to examine their utility in diagnosis and disease monitoring. CXCL-9 was chosen as it has previously been shown to be elevated in newly diagnosed GCA and PMR patients (van der Geest et al., 2015b). This study sought to test the replicability of this result and further explore its utility in disease monitoring. Similarly, osteopontin was chosen as it has previously been shown to have some utility in predicting disease course in GCA (Prieto-González et al., 2017, van der Geest et al., 2015a). This study aimed to replicate this and investigate it as a diagnostic marker in GPSD.

The objectives of this study were:

1. To determine if analysis of serum biomarkers in PMR, subclinical GCA in PMR, and GCA may help differentiate between these related conditions.
2. To compare multiple serum biomarkers for their ability to detect active disease in patients with GCA, PMR, and subclinical GCA in PMR.
3. To assess if serum biomarkers identify increased disease activity in relapsing GCA patients on treatment with tocilizumab.
4. To correlate serum biomarkers with OGUS score.

7.3 Methods

7.3.1 Design and study population

As outlined in detail in chapter 2 and 3, fast-track GCA and PMR clinics were established at TUH and SJH to establish a multicentre prospective longitudinal study. Patients with a new suspected diagnosis of GCA or PMR in primary care were recruited between July 2022 and July 2023. All patients were reviewed in the fast-track GCA clinic with 24 hours and PMR clinic within 72 hours. All patients were reviewed at baseline, 1-month, 3-month, 6-month, and 12-month timepoints, with clinical assessment, ultrasound assessment and serum biobanking at each visit.

7.3.2 Biomarker analysis

Baseline blood samples were drawn from patients before initiation of treatment. Serum samples were stored at -80°C until analysis was conducted. Samples included baseline PMR serum (n=53), remission PMR (n=53), relapse PMR (n=11), baseline subclinical GCA in PMR (n=13), remission subclinical GCA in PMR (n=31), relapse subclinical GCA in PMR (n=5), baseline GCA (n=59), remission GCA (n=71), and relapse GCA serum (n=11). Remission samples were from either 3- or 6-month timepoints. Relapse may have occurred at any timepoint up to 12 months follow-up.

Samples went through one freeze-thaw cycle. In all cohorts (GCA, PMR, and subclinical GCA in PMR), serum levels of selected biomarkers including angiopoietin-1, angiopoietin-2, IL-6, IL-17A, IL-23, osteopontin, and CXCL-9 were measured using the BioTechne ELISA screening assay kits following the manufacturer protocol recommendations. Solid phase sandwich ELISA measured cytokines with an assay range of 9.38-600 pg/ml for IL-6, 31.2-2000 pg/mL for IL-17, and 39-2500 pg/mL for IL-23. The assay range of angiopoietin-1 was 62.5 - 4,000 pg/mL, angiopoietin-2 was 46.9 - 3,000

pg/mL, CXCL-9 was 19.9 - 30,400 pg/mL, and osteopontin was 0.312-20 ng/mL. Absorbance was measured at 450nm in a microtiter plate spectrophotometer. Patients with PMR, subclinical GCA in PMR, and GCA had duplicate analysis of baseline, remission, and relapse samples with the mean absorbance of each sample reported.

7.3.3 Ethical considerations

Full ethical approval was obtained from the Joint Research Ethics Committee for Tallaght University Hospital and St James Hospital, Dublin, Ireland (reference number ID 2150). All patients gave fully informed written consent to participate in the fast-track clinic study.

7.3.4 Statistical analysis

Biomarker levels were reported as mean $\pm$ standard deviation or median $\pm$ interquartile range. T-tests or Mann-Whitney U tests were performed to compare biomarker expression values, with p-value <0.05 deemed significant. Biomarker utility was assessed by receiver operating characteristic (ROC) and area under the ROC curve (AUC). The Pearson or Spearman correlation coefficient was used to measure linear correlation between two variables.

7.4 Results

Analysis of baseline biomarkers in PMR, GCA and subclinical GCA in PMR.

7.4.1 Angiopoietin-1

Patients with subclinical GCA had significantly higher baseline levels of angiopoietin-1 compared to their PMR counterparts (see table 7.2), $p < 0.001$. ROC analysis showed AUC to be 0.801 (see figure 7.2). An angiopoietin-1 level of 21,408pg/ml gives a sensitivity of 84.6% and a specificity of 70% for subclinical GCA in PMR. Similarly, baseline angiopoietin-1 levels were significantly more elevated in GCA compared with PMR, $p < 0.001$ (see table 7.4).

Interestingly, there was no significant difference between baseline angiopoietin-1 levels in subclinical GCA and GCA groups (see table 7.3), $p = 0.45$. This may suggest that subclinical GCA in PMR serum is more like GCA than PMR serum regarding angiopoietin-1 circulating levels at baseline.

7.4.2 Angiopoietin-2 and Angiopoietin Ratios

Angiopoietin-2 was significantly higher in GCA than PMR at baseline, $p < 0.001$ (see table 7.4). This is in line with a previous study, indicating higher levels of angiopoietin-2 in patients with both GCA and PMR clinically, compared with those with isolated PMR, suggesting vascular involvement may increase angiopoietin-2 levels (van Sleen et al., 2020). Despite this, there was no significant difference in levels between subclinical GCA in PMR and either GCA or PMR, indicating that it is not a useful marker for differentiating subclinical GCA in PMR from other GPSD phenotypes.

Ang1:2 and Ang2:1 ratio were significantly different between GCA and PMR (see table 7.4). There was no significant difference between these ratios and subclinical GCA in PMR and either PMR or GCA (see tables 7.2-7.3), again indicating a distinct biochemical

phenotype of subclinical GCA in PMR. Angiopoietin-2 levels correlated with ESR and CRP at baseline in GCA patients (see table 7.8), but not in subclinical GCA in PMR (table 7.7), or PMR patients (table 7.5).

7.4.3 Interleukin-6

Interleukin-6 levels were elevated at baseline in subclinical GCA in PMR patients when compared with the normal range adapted from the Immunology laboratory at SJH and established in-house at 0.00 - 7.26 pg/ml using the maximum and minimum values $\pm$ 2 SD from 30 healthy adult controls. IL-6 was not a useful biomarker to differentiate subclinical GCA in PMR from pure PMR patients, $p=0.11$. There was no significant difference between baseline IL-6 levels in subclinical GCA in PMR and GCA ($p=0.73$). However, PMR and GCA groups exhibited a difference in baseline levels of IL-6, with higher levels in GCA, $p=0.02$, which fits with the theory of an increased IL-6-mediated inflammatory response in GCA compared with PMR.

IL-6 correlated moderately with ESR levels in PMR patients at baseline/time of diagnosis ($r=0.382$; $p=0.005$) and correlated with CRP in glucocorticoid-naïve PMR patients ($r=0.415$, $p=0.02$). There was no significant correlation with IL-6 and ESR or CRP in GCA or subclinical GCA in PMR (see tables 7.7-7.9).

Overall, IL-6 levels were more elevated in patients without glucocorticoid exposure, suggesting IL-6 levels were glucocorticoid sensitive in these patient groups. Glucocorticoid naïve GCA patients had a higher baseline IL-6 level than glucocorticoid-exposed GCA patients without meeting significance, $p=0.13$. In PMR patients, there was

high variability in baseline IL-6 levels, with an abnormal distribution. There was a significant difference in median baseline IL-6 levels in glucocorticoid naïve patients at 5.01 pg/ml [1.99 – 66.52] compared with steroid-exposed patients 1.78 [0.38 – 16.95], $p < 0.001$. Patients with subclinical GCA in PMR also exhibited higher mean baseline IL-6 levels in glucocorticoid naïve patients compared with their glucocorticoid exposed counterparts, however due to small numbers in the steroid naïve group ($n=3$), this was not significant; $p=0.23$.

7.4.4 Interleukin-17

Baseline interleukin-17 levels in our cohort were significantly different at baseline between all three groups (see figure 7.3). Highest levels were observed in GCA at 10.03pg/ml [7.01-16.60], followed by subclinical GCA in PMR at 7.08pg/ml [6.62-9.41], followed by PMR at 2.47 pg/ml [1.20-4.53]. This supports the hypothesis of a distinct biomarker profile of subclinical GCA in PMR.

IL-17 may be a useful biomarker to differentiate between PMR and subclinical GCA in PMR as defined with vascular ultrasound. ROC analysis of IL-17 levels in PMR and subclinical GCA in PMR demonstrated an AUC of 0.892, and a cut-off of 5pg/ml gave a sensitivity of 84.6%, and specificity of 79.2% for subclinical GCA in PMR (see figure 7.2).

Baseline IL-17 levels did not, however, correlate with ESR or CRP in PMR, subclinical GCA in PMR, or GCA patients (see tables 7.5-7.9).

Table 7.2 Baseline biomarker levels in PMR and subclinical GCA in PMR

Biomarker	PMR, n= 53 (median, IQR)	Subclinical GCA in PMR, n=13 (median, IQR)	P-value	FDR- adjusted p value
Ang-1 (pg/ml)	19,774.46 [18,051.58 - 22140.71]	25,548.48 [22,471.30- 26468.36]	<0.001*	0.003
Ang-2 (pg/ml)	12.37 [6.26- 51.52]	11.33 [9.52- 31.48]	0.68	0.874
Ang 1:2 Ratio	1388	1949	0.99	0.99
Ang2:1 Ratio	0.0007	0.0005	0.99	0.99
CXCL9: MIG (pg/ml)	66.55 [33.27- 336.82]	497.55 [218.98- 1665.03]	0.004*	0.009*
OPN (pg/ml)	2334.01 [1277.28- 2953.30]	3634.82 [3241.65- 4744.42]	<0.001*	0.003*
IL-6 (pg/ml)	4.07 [0.72- 21.64]	10.84 [3.28- 32.77]	0.11	0.198
IL-17 (pg/ml)	2.47 [1.20- 4.53]	7.08 [6.62- 9.41]	<0.0001 *	0.0009*
IL-23 (pg/ml)	81.46 [39.01- 399.20]	44.97 [19.45- 280.87]	0.24	0.36

Legend: * refers to results of statistical significance. FDR-adjusted p values were calculated with Benjamini–Hochberg, q = 0.05

Table 7.3 Baseline biomarker levels in GCA and subclinical GCA in PMR

Biomarker	GCA, n=59 (median, IQR)	Subclinical GCA in PMR, n=13 (median, IQR)	P value	FDR adjusted p- value
Ang-1 (pg/ml)	27,018.00 [21,869.75- 29,493.74]	25,548.48 [22,471.30- 26468.36]	0.74	0.83
Ang-2 (pg/ml)	38.01 [17.35- 64.93]	11.33 [9.52- 31.48]	0.08	0.13
Ang 1:2 ratio	747	1949	0.04*	0.13
Ang2:1 ratio	0.001	0.0005	0.06	0.13
CXCL9: MIG (pg/ml)	301.77 [191.63- 799.59]	497.55 [218.98- 1665.03]	0.09	0.135
OPN (pg/ml)	3182.41 [2382.02- 4176.93]	3634.82 [3241.65- 4744.42]	0.09	0.13
IL-6 (pg/ml)	6.58 [3.06- 23.77]	10.84 [3.28- 32.77]	0.73	0.83
IL-17 (pg/ml)	10.03 [7.01- 16.60]	7.08 [6.62-9.41]	<0.001*	0.009*
IL-23 (pg/ml)	31.11 [14.67- 199.94]	44.97 [19.45- 280.87]	0.85	0.85

Legend: * refers to results of statistical significance. FDR-adjusted p values were calculated with Benjamini–Hochberg, q = 0.05

Table 7.4 Baseline biomarker levels in PMR and GCA

Biomarker	PMR, n= 53 (median, IQR)	GCA, n=59 (median, IQR)	P-value	FDR-adjusted p value
Ang-1 (pg/ml)	19,774.46 [18,051.58 - 22140.71]	27,018.00 [21,869.75- 29,493.74]	<0.001*	0.0015*
Ang-2 (pg/ml)	12.37 [6.26- 51.52]	38.01 [17.35- 64.93]	<0.001*	0.0015*
Ang 1:2 ratio	1388	747	<0.01*	0.0129*
Ang2:1 ratio	0.0007	0.001	<0.001*	0.0015*
CXCL9: MIG (pg/ml)	66.55 [33.27- 336.82]	301.77 [191.63- 799.59]	<0.001*	0.0015*
OPN (pg/ml)	2334.01 [1277.28- 2953.30]	3182.41 [2382.02- 4176.93]	<0.001*	0.0015*
IL-6 (pg/ml)	4.07 [0.72- 21.64]	6.58 [3.06- 23.77]	0.02*	0.02*
IL-17 (pg/ml)	2.47 [1.20- 4.53]	10.03 [7.01- 16.60]	<0.001*	0.0015*
IL-23 (pg/ml)	81.46 [39.01- 399.20]	31.11 [14.67- 199.94]	0.11	0.02*

Legend: * refers to results of statistical significance. FDR-adjusted p values were calculated with Benjamini–Hochberg, q = 0.05

7.4.5 Interleukin-23

Baseline levels of IL-23 showed no statistical difference between PMR, GCA, or subclinical GCA in PMR (see figure 7.3). There was no correlation between IL-23 and ESR or CRP in GCA, PMR or subclinical GCA in PMR (see tables 7.5-7.9).

7.4.6 Osteopontin

Osteopontin is a partially IL-6 independent biomarker (Tombetti et al., 2021). It is present in a large number of tissues including skeletal muscle and endothelial cells (Icer and Gezmen-Karadag, 2018). Elevated levels have been associated with aging, T-cell senescence, atherosclerosis, skeletal muscle regeneration, osteoporosis, and neurodegenerative changes (Du et al., 2022). It plays a key role in secretion levels of interleukin-10 (IL-10), interleukin-12 (IL-12), interleukin-3 (IL-3), interferon- γ (IFN- γ), integrin α vB3, nuclear factor kappa B (NF- κ B), macrophage and T cells, and regulating the osteoclast function (Icer and Gezmen-Karadag, 2018). The normal range of osteopontin in healthy controls has been reported to be very variable (Filia et al., 2013, Salem et al., 2013). It has also been reported previously to be associated with a relapsing course in GCA (Prieto-González et al., 2017).

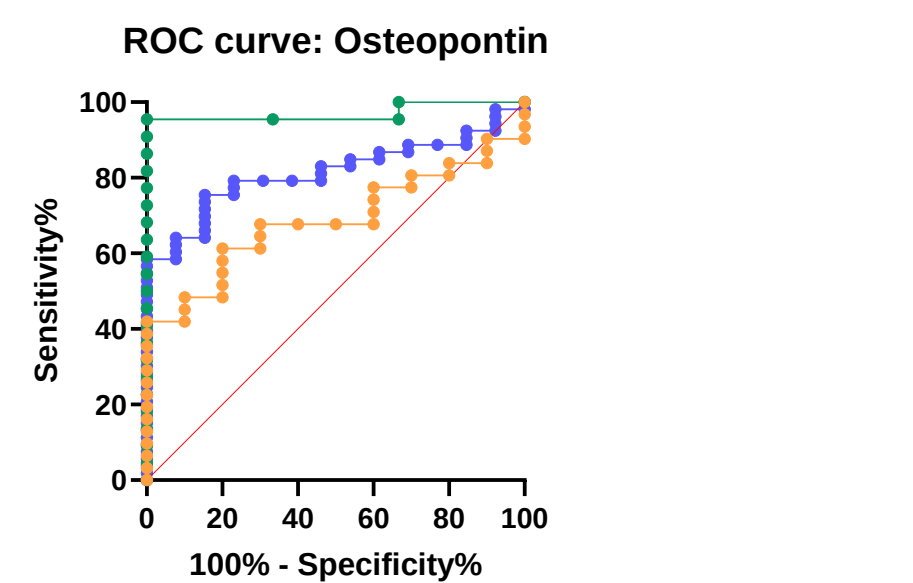
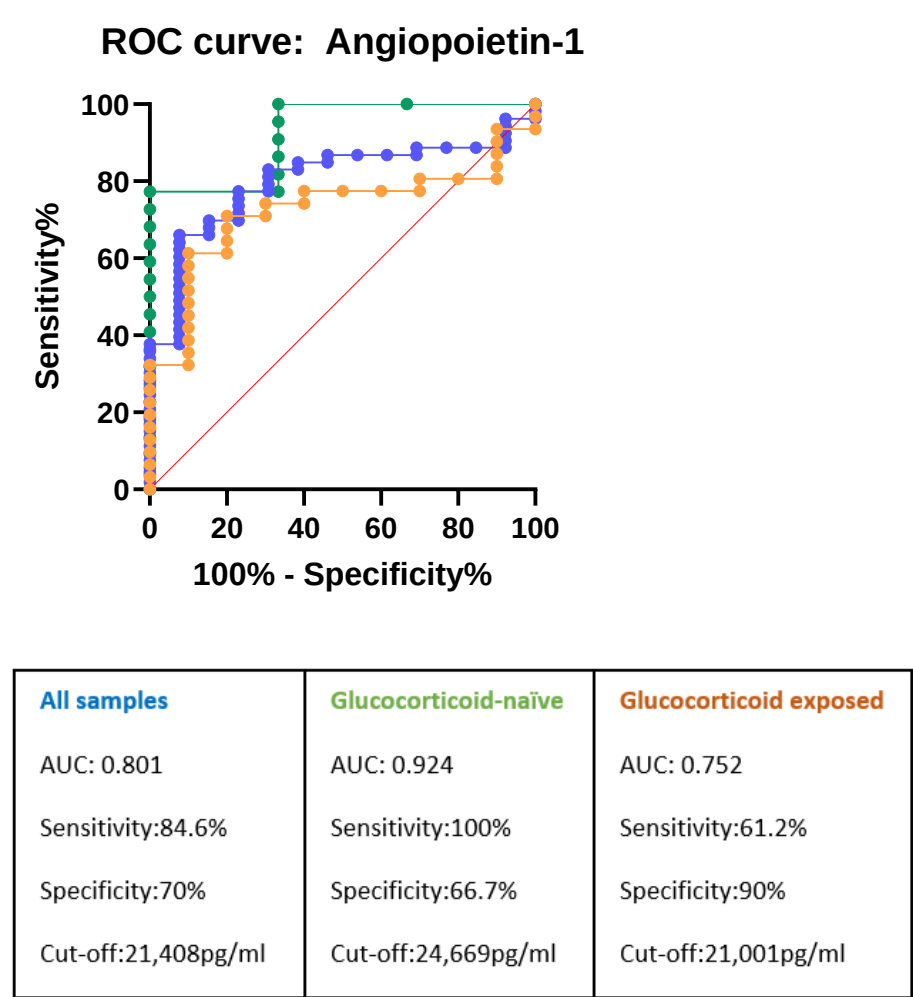
In this study, baseline osteopontin levels were significantly higher in subclinical GCA in PMR compared with PMR patients (see table 7.2), $p < 0.001$. ROC analyses found the AUC to be 0.814. A cut-off of 2,766pg/ml gave a sensitivity of 84.6% and a specificity of 72.7% for subclinical GCA in PMR (see figure 7.2).

Osteopontin levels in GCA were also significantly higher than PMR at baseline, $p<0.001$. Interestingly, there was no significant difference between baseline osteopontin levels comparing subclinical GCA with GCA, $p=0.09$, suggesting more biochemical similarity between subclinical GCA in PMR and GCA serum than with PMR.

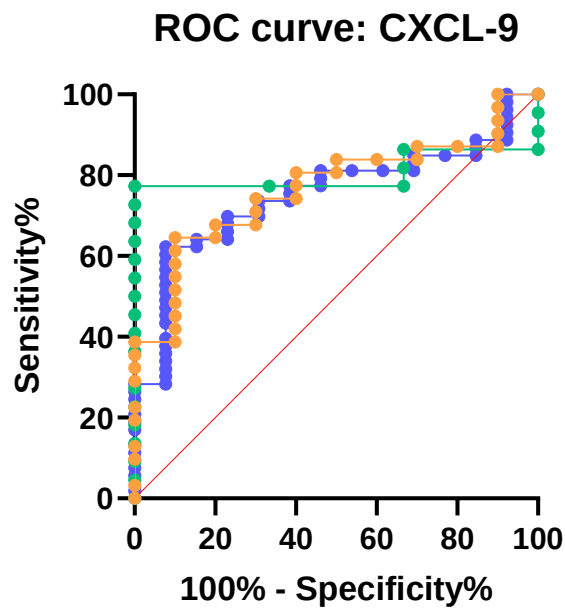
7.4.7 CXCL-9

CXCL-9 has been previously identified to be elevated in both newly diagnosed GCA and PMR (van der Geest et al., 2015b). Levels of CXCL-9 were significantly higher at baseline in GCA compared with PMR, $p<0.001$ (see table 7.4), and higher in subclinical GCA in PMR compared with isolated PMR, $p=0.004$ (see table 7.2). There was no significant difference in CXCL-9 levels between GCA and subclinical GCA, $p=0.09$ (see table 7.3).

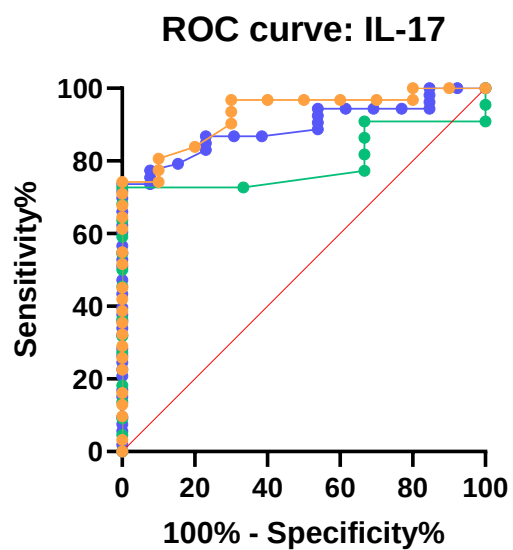
Figure 7.2 ROC analysis of angiopoietin-1, IL-17, osteopontin, and CXCL-9 in subclinical GCA in PMR and isolated PMR



All Samples	Glucocorticoid-naïve	Glucocorticoid exposed
AUC: 0.814	AUC: 0.969	AUC: 0.687
Sensitivity:84.6%	Sensitivity: 95.45%	Sensitivity:48.4%
Specificity:72.7%	Specificity:100%	Specificity:90%
Cut-off:2,766pg/ml	Cut-off:3,198pg/ml	Cut-off:2,587pg/ml



All samples	Glucocorticoid-naïve	Glucocorticoid exposed
AUC: 0.752	AUC :0.803	AUC: 0.767
Sensitivity:92.3%	Sensitivity:77.3%	Sensitivity: 61.2%
Specificity:62.3%	Specificity:66.7%	Specificity: 90%
Cut-off:107.8pg/ml	Cut-off:517.3pg/ml	Cut-off: 102.1pg/ml



All samples	Glucocorticoid-naïve	Glucocorticoid exposed
AUC:0.892	AUC:0.795	AUC: 0.927
Sensitivity:84.6%	Sensitivity:72.7%	Sensitivity: 80.65%
Specificity:79.2%	Specificity: 66.6%	Specificity: 90%
Cut-off:5pg/ml	Cut-off: 7.01pg/ml	Cut-off: 4.77pg/ml

- All patients
- Glucocorticoid exposed
- Glucocorticoid-naïve

Legend: ROC curves reflect the ability of each biomarker to detect arterial inflammation in PMR patients. The optimal sensitivity, specificity and cut-off value are established by identifying the Youden index. AUC, sensitivity, specificity and optimal cut-off value for each marker are depicted on the graphs. AUC: area under the curve; ROC: receiver operating characteristic.

Table 7.5 Biomarker correlation with ESR/CRP in baseline PMR samples

Biomarker (n=53)	ESR R-value	ESR p-value	CRP R-value	CRP p-value
Ang-1 (pg/ml)	.167	.23	.185	.190
Ang-2 (pg/ml)	.251	.073	. -0.033	0.816
CXCL9:MIG (pg/ml)	.253	.070	.035	.805
OPN (pg/ml)	-.026	.969	.076	.592
IL-6 (pg/ml)	.382**	.005**	.149	.291
IL-17 (pg/ml)	.216	.123	.083	.558
IL-23 (pg/ml)	.157	.266	-.055	.699

Table 7.6 Biomarker correlation with ESR/CRP in baseline steroid naïve PMR samples

Biomarker (n=22)	ESR R-value	ESR p-value	CRP R-value	CRP p-value
Ang-1 (pg/ml)	-.117	.530	-.117	.308
Ang-2 (pg/ml)	.121	.517	.251	.181
CXCL9: MIG (pg/ml)	.053	.777	.190	.315
OPN (pg/ml)	-.608*	<0.001	.022	.908
IL-6 (pg/ml)	.331	.069	.415*	.023*
IL-17 (pg/ml)	-.072	.700	.122	.520
IL-23 (pg/ml)	1	—	.138	.457

Table 7.7 Biomarker correlation with ESR/CRP in subclinical GCA in PMR

Biomarker (n=13)	ESR R-value	ESR p-value	CRP R-value	CRP p-value
Ang-1 (pg/ml)	.341	.255	.220	.471
Ang-2 (pg/ml)	.253	.405	-.154	.616
CXCL9: MIG (pg/ml)	.099	.748	-.049	.873
OPN (pg/ml)	.099	.748	-.044	.887
IL-6 (pg/ml)	.418	.155	.171	.577
IL-17 (pg/ml)	.173	.571	.176	.565
IL-23 (pg/ml)	.503	.079	.322	.284

Table 7.8 Biomarker correlation with ESR/CRP in GCA

Biomarker (n=59)	ESR R-value	ESR p-value	CRP R-value	CRP p-value
Ang-1 (pg/ml)	.120	.387	.287*	.034*
Ang-2 (pg/ml)	.346*	.010*	.293*	.030*
CXCL9: MIG (pg/ml)	-.058	.677	-.104	0.450
OPN (pg/ml)	.025	.859	-.013	.924
IL-6 (pg/ml)	-.079	.568	-.037	.786
IL-17 (pg/ml)	-.005	.971	.014	.918
IL-23 (pg/ml)	-.162	.243	-.220	.107

Table 7.9 Biomarker correlation with ESR/CRP steroid naïve in GCA

Biomarker (n=29)	ESR R-value	ESR p-value	CRP R-value	CRP p-value
Ang-1 (pg/ml)	.301	.119	.182	.355
Ang-2 (pg/ml)	.321	.096	.450*	.016*
CXCL9: MIG (pg/ml)	-.160	.416	-.043	.827
OPN (pg/ml)	-.138	.482	-.028	.888
IL-6 (pg/ml)	-.125	.462	.087	.661
IL-17 (pg/ml)	.038	.849	.069	.729
IL-23 (pg/ml)	-.340	.077	-.197	.315

In summary, this analysis has demonstrated a distinct biochemical profile of subclinical GCA in PMR compared with PMR with normal vascular ultrasound. A high sensitivity and specificity were demonstrated with angiopoietin-1, IL-17, CXCL-9, and osteopontin in differentiating these two entities. These biomarkers may have diagnostic utility for subclinical GCA in PMR, particularly in centres with limited access to vascular ultrasound.

A considerable proportion of patients had prior glucocorticoid exposure. Analysis of glucocorticoid-naïve patients was performed to compare the reliability of these biomarkers (angiopoietin-1, osteopontin, and CXCL-9 glucocorticoid-naïve patients all had greater AUC compared with analysis of glucocorticoid-exposed patients (see figure 7.2) suggesting greater discrimination of vasculitis in PMR patients prior to glucocorticoid exposure. IL-17 demonstrated excellent AUC for both glucocorticoid naïve and glucocorticoid-exposed patients with slightly higher AUC in the glucocorticoid-exposed group.

PMR and GCA serum were distinct from each other, with significant differences in baseline levels of angiopoietin-1, angiopoietin-2, IL-6, IL-17, osteopontin, and CXCL-9. Interestingly, despite being significantly different between the two groups, and having an integral role in the pathogenesis of both conditions, IL-6 was less sensitive than the other biomarkers to differentiate between GCA and PMR. It was also heavily influenced by previous glucocorticoid exposure.

Overall, all selected biomarkers, apart from IL-23, demonstrated some potential in differentiating GCA-PMR spectrum diseases at the time of diagnosis.

7.5 Correlation of Objective Ultrasound Scores: Halo Count, Halo Score and OGUS with serum biomarkers.

Overall, there was poor correlation between biomarkers and halo count, halo score, and OGUS in both subclinical GCA in PMR and GCA. There was a significant correlation between angiopoietin-1 in subclinical GCA in PMR and halo count, however, angiopoietin-1 did not correlate with halo score or OGUS. Other biomarkers failed to correlate with halo score, halo count, and OGUS (see tables 7.10 – 7.13).

Table 7.10 Biomarker correlation with Halo Count, Halo Score, and OGUS in subclinical

GCA

Biomarker (n=13)	Halo count R- value	Halo count p-value	Halo score R- value	Halo score p- value	OGUS R- value	OGUS p- value
Ang-1 (pg/ml)	-.673*	.012*	-.396	.180	-.198	.517
Ang-2 (pg/ml)	.194	.526	-.093	.764	.269	.375
CXCL9: MIG (pg/ml)	.069	.824	.005	.987	.272	.369
OPN (pg/ml)	-.259	.394	.170	.579	.063	.838
IL-6 (pg/ml)	.180	.557	-.096	.755	.264	.384
IL-17 (pg/ml)	.183	.549	-.126	.683	.234	.441
IL-23 (pg/ml)	.188	.539	-.076	.805	.276	.362

Table 7.11 Biomarker correlation with Halo Count, Halo Score, and OGUS in steroid

naïve subclinical GCA

Biomarker (n=3)	Halo count R- value	Halo count p-value	Halo score R- value	Halo score p- value	OGUS R- value	OGUS p- value
Ang-1 (pg/ml)	-.968	.161	-.653	.547	-.653	.547
Ang-2 (pg/ml)	-.709	.498	-.181	.884	-.181	.884
CXCL9: MIG (pg/ml)	-.586	.602	-.020	.987	-.020	.987
OPN (pg/ml)	-.324	.790	.273	.824	.273	.824
IL-6 (pg/ml)	-.624	.571	-.068	.957	-.068	.957
IL-17 (pg/ml)	-.617	.576	-.060	.962	-.060	.962
IL-23 (pg/ml)	-.577	.608	-.009	.994	-.009	.994

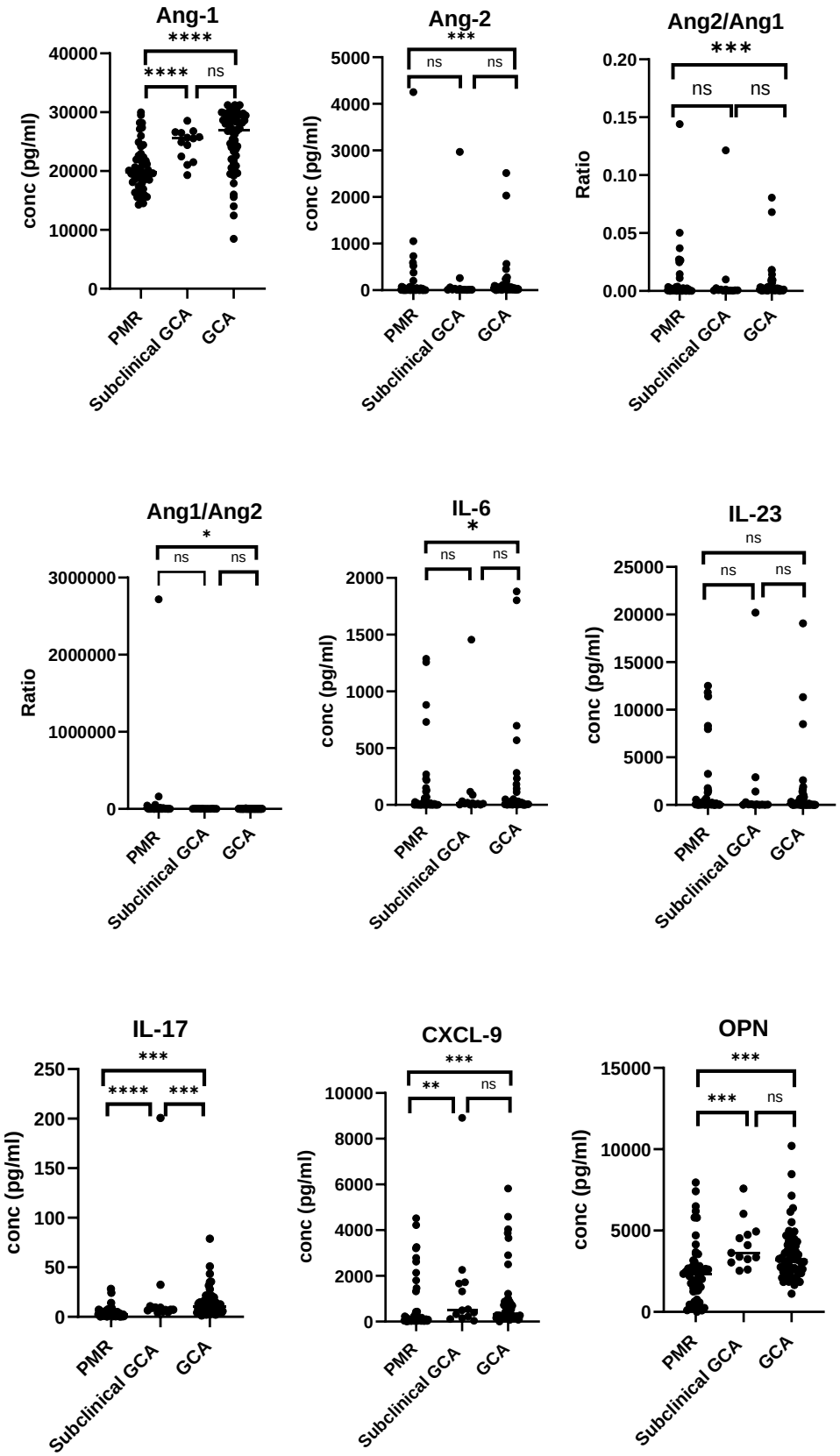
Table 7.12 Biomarker correlation with Halo Count, Halo Score, and OGUS in GCA

Biomarker (n=59)	Halo count R- value	Halo count p-value	Halo score R- value	Halo score p- value	OGUS R- value	OGUS p- value
Ang-1 (pg/ml)	-.137	.305	-.014	.919	-.126	.347
Ang-2 (pg/ml)	.046	.734	-.067	.619	-.096	.472
CXCL9: MIG (pg/ml)	-.025	.855	.043	.751	-.105	.433
OPN (pg/ml)	.125	.349	-.051	.705	.135	.313
IL-6 (pg/ml)	.096	.476	.131	.328	-.022	.868
IL-17 (pg/ml)	.041	.757	-.023	.864	-.047	.725
IL-23 (pg/ml)	.032	.812	.141	.292	-.017	.900

**Table 7.13 Biomarker correlation with Halo Count, Halo Score, and OGUS in steroid
naïve GCA**

Biomarker (n=29)	Halo count R- value	Halo count p-value	Halo score R- value	Halo score p- value	OGUS R- value	OGUS p- value
Ang-1 (pg/ml)	-.238	.213	-.098	.613	-.238	.356
Ang-2 (pg/ml)	-.021	.914	-.218	.256	-.137	.478
CXCL9: MIG (pg/ml)	.083	.668	.167	.387	-.036	.851
OPN (pg/ml)	.110	.569	-.165	.392	.027	.891
IL-6 (pg/ml)	.253	.186	.311	.101	.115	.553
IL-17 (pg/ml)	.025	.896	-0.56	.773	-.014	.944
IL-23 (pg/ml)	.266	.164	.365	.051	.149	.441

Figure 7.3 Serum markers in newly diagnosed GCA, PMR, and subclinical GCA in PMR.



Legend: Serum levels of angiopoietin-1, angiopoietin-2, ang1:2 ratio, ang 2:1 ratio, IL-6, IL-17,

*IL-23, osteopontin, and CXCL-9 in GCA, PMR, and subclinical GCA in PMR. The horizontal line represents the median. Statistical significance is denoted as NS =not significant difference, * = significant difference with $p < 0.05$, ** = significant difference with $p < 0.01$, ***= significant difference with $p < 0.001$, **** =significant difference with $p < 0.001$.*

7.6 Analysis of biomarkers in the context of remission and relapse

There is a need to identify and introduce into clinical practice reliable disease markers, other than classic inflammatory markers, particularly for disease monitoring in patients with GPSD. This study has assessed angiopoietin-1, angiopoietin-2, IL-6, IL-17, IL-23, osteopontin, and CXCL-9 in the context of active disease (baseline and relapse states) and remission.

7.6.1 Angiopoietin-1

In GCA, angiopoietin-1 levels significantly dropped between baseline and remission, $p < 0.001$, indicating higher levels in active disease. Previous studies have shown that elevated angiopoietin levels at baseline were associated with a shorter time to glucocorticoid remission in GCA (van Sleen et al., 2019). In our cohort, there was no correlation between baseline angiopoietin-1 level and time to relapse in GCA, $r = 0.01$, $p = 0.93$. Similarly, there was no correlation between baseline angiopoietin-1 and halo count in GCA ($r = -0.23$; $p = 0.21$), halo score ($r = -0.98$; $p = 0.61$), or OGUS ($r = -0.17$; $p = 0.35$).

Angiopoietin-1 was not a useful marker of disease activity in PMR. There was no significant difference in PMR groups between baseline and relapse levels of angiopoietin-1.

There was a significant reduction in angiopoietin-1 levels in subclinical GCA in PMR between baseline and remission, $p=0.02$, and baseline and relapse states, $p=0.0002$. This is difficult to interpret as the relapse number was small, $n=5$, and both baseline and relapse groups represented active disease. If the relapse group is excluded due to small numbers, it appears that active disease is associated with higher angiopoietin-1 levels in subclinical GCA in PMR patients.

7.6.2 Angiopoietin-2 and Angiopoietin Ratios

Angiopoietin-2 levels increased in remission in subclinical GCA in PMR compared with baseline, $p=0.03$ (see table 7.14). Similarly, a significant increase was observed in remission in PMR patients compared with baseline levels, <0.001 (see table 7.16). Angiopoietin-2 did not prove a useful marker to differentiate between GCA activity states, with no significant difference in levels between disease states (see figure 7.6).

There was a positive correlation between baseline angiopoietin-2 in GCA patients and time to relapse, $r=0.34$; $p=0.008$. Similarly, baseline levels of the angiopoietin 2: 1 ratio correlated with time to relapse in GCA, $r=0.32$, $p=0.01$. This finding was also reported in previous studies (van Sleen et al., 2019). There was no significant correlation between angiopoietin 2: 1 ratio and relapse in PMR $r=0.12$; $p=0.35$, or subclinical GCA, $r=0.24$; $p=0.42$.

In PMR, angiopoietin-2 levels increased significantly in remission when compared to baseline, $p < 0.001$. Comparing relapse and remission, levels also increased in remission when compared to relapse 40.07pg/ml [24.41-128.88] vs 27.85pg/ml [8.34-44.66], but this did not reach statistical significance, $p = 0.08$ (see table 7.17).

7.6.3 Interleukin-6

IL-6 levels were elevated in subclinical GCA patient serum at baseline when compared to the SJH immunology laboratory normal range. In GCA, IL-6 levels increased in remission as compared with baseline; $p = 0.02$, however, this is likely an effect mediated by tocilizumab treatment, as a majority of GCA patients were initiated on this medication after diagnosis. This effect has been well described in the literature for several diseases treated with tocilizumab (Liang et al., 2024, Berger et al., 2019, Nishimoto et al., 2008). There were no significant differences in IL-6 levels in subclinical GCA in PMR or PMR comparing different states of disease activity making it a less useful biomarker to differentiate between these disease phenotypes (figure 7.3-7.6).

7.6.4 Interleukin-17

IL-17 plays a role in the pathogenesis of GCA and PMR having a direct effect on the production of pro-inflammatory cytokines including IL-6, VEGF-A, GM-CSF, CCL2, and CCL20 (Greigert h, 2023). In subclinical GCA in PMR patients, IL-17 levels did not change significantly between active disease and remission states (see tables 7.14 and 7.15), indicating it is not a useful marker to monitor disease activity.

In GCA patients IL-17 levels significantly dropped in remission compared with baseline, $p < 0.001$. It is difficult to determine if this indicates a potential utility for monitoring IL-17 levels in GCA for disease monitoring as tocilizumab treatment has been shown to reduce serum IL-17 levels (Meyer et al., 2023) and this significant difference may be due to tocilizumab treatment rather than a direct measure of disease activity.

Conversely, in PMR, levels of IL-17 significantly increased in remission states compared with baseline and relapse states (see tables 7.16-7.17). This indicates that lower IL-17 serum levels were associated with increased disease activity in PMR, which is surprising given the known proinflammatory effect of IL-17 (Amatya et al., 2017). This study measured IL-17A and the IL-17 cytokine family is composed of six structurally related molecules: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25) and IL-17F (Kolls and Lindén, 2004). It is possible another IL-17 molecule may be a more relevant biomarker in PMR. There was no significant correlation between cumulative glucocorticoid dose pre-assessment and baseline IL-17 level; $r = -0.16$; $p = 0.25$ or between remission dose glucocorticoid and IL-17 levels in PMR; $r = 0.05$, $p = 0.72$.

7.6.5 Interleukin-23

IL-23 levels showed no significant difference between the different disease activity states in GCA, PMR, or subclinical GCA in PMR (see figures 7.4-7.6). Furthermore, there was no correlation between IL-23 and ESR or CRP in any disease subgroup. There was no correlation between baseline IL-23 levels and future relapse in subclinical GCA ($r = 0.42$; $p = 0.21$), PMR ($r = 0.15$; $p = 0.27$), and GCA ($r = -0.04$, $p = 0.71$). Serum IL-23 levels appear to be of limited utility in GPSD.

7.6.6 Osteopontin

In subclinical GCA in PMR, osteopontin levels significantly decreased in remission compared with baseline levels, $p=0.007$. There was no correlation between baseline osteopontin levels and future relapse in subclinical GCA in PMR ($r=-0.17$; $p=0.56$), GCA ($r=0.06$; $p=0.63$). Conversely in PMR, osteopontin levels significantly increased in remission compared with baseline, $p<0.0001$. There was no correlation between baseline osteopontin levels and future relapse in PMR ($r=0.02$; $p=0.84$). In GCA, there were no significant changes in osteopontin levels with various states of disease activity.

7.6.7 CXCL-9

CXCL-9 levels were not useful in determining disease activity in subclinical GCA in PMR with no significant differences between the groups. In PMR, CXCL-9 levels significantly increased in remission, $p<0.001$. A previous study showed CXCL-9 levels to be elevated in newly diagnosed GCA and PMR patients and remained elevated despite glucocorticoid-induced remission (van der Geest et al., 2015b). Conversely in GCA, there was no significant difference between baseline and remission levels of CXCL-9, $p=0.84$, while levels decreased in remission compared with relapse, $p=0.03$. A majority of our relapse and remission patients in GCA were on tocilizumab treatment. IL-6 has been shown previously to inhibit secretion of IFN-responsive chemokines including CXCL-9 (Huseni et al., 2023). Therefore, treatment with IL-6 blockade may have impacted levels in GCA remission and relapse patients.

In summary, this study has shown that angiopoietin-1 and IL-17 may have utility to monitor disease activity in GCA with significant reductions in levels in remission. Angiopoietin-2, IL-17, CXCL-9, and IL-17 may have utility in assessing disease activity in PMR with elevations observed in these biomarkers in remission.

Table 7.14 Remission and relapse biomarker levels in subclinical GCA in PMR

Biomarker	Remission subclinical GCA in PMR, n= 31 (median, IQR)	Relapse subclinical GCA in PMR, n=5 (median, IQR)	P value	FDR- adjusted p- value
Ang-1 (pg/ml)	21,661.24 [18,866.04- 24,233.90]	19,108.14 [18,958.26- 19895.09]	0.16	0.72
Ang-2 (pg/ml)	31.00 [18.21- 55.25]	23.11 [19.70- 32.73]	0.79	0.83
Ang 1:2 ratio	734.8	775	0.99	0.72
Ang2:1	0.001	0.001	1.00	1.0
CXCL9:MIG (pg/ml)	305.09 [217.62- 538.67]	228.53 [135.40- 348.97]	0.50	0.90
OPN (pg/ml)	2742.52 [2327.03- 3471.90]	3182.96 [2947.52- 3412.20]	0.69	0.93
IL-6 (pg/ml)	17.67 [2.35- 60.34]	17.67 [4.65- 72.73]	0.62	0.93
IL-17 (pg/ml)	8.95 [5.77- 13.78]	5.69 [4.76-25.61]	0.79	0.83
IL-23 (pg/ml)	55.00 [27.20- 361.79]	35.05 [31.11- 239.01]	0.85	0.95

Legend: * refers to results of statistical significance. FDR-adjusted p values were calculated with Benjamini–Hochberg, q = 0.05

Table 7.15 Baseline and remission biomarker levels in subclinical GCA in PMR

Biomarker	Baseline subclinical GCA in PMR, n=13 (median, IQR)	Remission subclinical GCA in PMR, n= 31 (median, IQR)	P value	FDR- adjusted p value
Ang-1	25,548.48 [22,471.30- 26468.36]	21,661.24 [18,866.04- 24,233.90]	0.02*	0.05
Ang-2	11.33 [9.52- 31.48]	31.00 [18.21- 55.25]	0.03*	0.05
Ang 1:2 ratio	1949	734.8	0.03*	0.05
Ang2:1 ratio	0.0005	0.001	0.03*	0.05
CXCL9: MIG	497.55 [218.98- 1665.03]	305.09 [217.62- 538.67]	0.31	0.46
OPN	3634.82 [3241.65- 4744.42]	2742.52 [2327.03- 3471.90]	0.007*	0.05
IL-6	10.84 [3.28- 32.77]	17.67 [2.35- 60.34]	0.96	0.96
IL-17	7.08 [6.62-9.41]	8.95 [5.77- 13.78]	0.95	0.96

Legend: * refers to results of statistical significance. FDR-adjusted p values were calculated with Benjamini–Hochberg, q = 0.05

Table 7.16 Remission and relapse biomarker levels in PMR

Biomarker	Remission PMR, n=53 (median, IQR)	Relapse PMR, n=11 (median, IQR)	P value	FDR-adjusted p value
Ang-1 (pg/ml)	22,372.63 [17,796.39-25,310.18]	21,961.93 [18,252.82-24,967.55]	0.74	0.83
Ang-2 (pg/ml)	40.07 [24.41-128.88]	27.85 [8.34-44.66]	0.08	0.13
Ang 1:2 ratio	499.8	912.1	0.06	0.13
Ang2:1 ratio	0.002	0.0009	0.06	0.13
CXCL9: MIG (pg/ml)	211.90 [150.86-377.46]	464.09 [297.71-698.84]	0.09	0.13
OPN (pg/ml)	3005.48 [2267.08-4239.04]	3873.72 [3459.00-4483.09]	0.09	0.13
IL-6 (pg/ml)	8.61 [2.84 – 81.50]	5.01 [4.13-6.09]	0.73	0.33
IL-17 (pg/ml)	14.09 [10.03-20.07]	5.07 [4.07-6.08]	<0.001***	0.009*
IL-23 (pg/ml)	39.00 [19.45 – 473.74]	37.02 [26.22-66.13]	0.85	0.85

Legend: * refers to results of statistical significance. FDR-adjusted p values were calculated with Benjamini–Hochberg, q = 0.05

Table 7.17 Baseline and remission biomarker levels in PMR

Biomarker	Baseline PMR, n= 53 (median, IQR)	Remission PMR, n=53 (median, IQR)	P value	FDR-adjusted p value
Ang-1 (pg/ml)	19,774.46 [18,051.58 - 22140.71]	22,372.63 [17,796.39- 25,310.18]	0.08	0.10
Ang-2 (pg/ml)	12.37 [6.26- 51.52]	40.07 [24.41- 128.88]	<0.001*	0.0015*
Ang 1:2 ratio	1388	499.8	<0.0001*	0.0004*
Ang2:1 ratio	0.0007	0.002	<0.001*	0.0004*
CXCL9: MIG (pg/ml)	66.55 [33.27- 336.82]	211.90 [150.86- 377.46]	<0.001*	0.0015*
OPN (pg/ml)	2334.01 [1277.28- 2953.30]	3005.48 [2267.08- 4239.04]	<0.001*	0.0015*
IL-6 (pg/ml)	4.07 [0.72- 21.64]	8.61 [2.84 – 81.50]	0.56	0.56
IL-17 (pg/ml)	2.47 [1.20-4.53]	14.09 [10.03- 20.07]	<0.001*	0.0015*
IL-23 (pg/ml)	81.46 [39.01- 399.20]	39.00 [19.45 – 473.74]	0.23	0.25

Legend: * refers to results of statistical significance. FDR-adjusted p values were calculated with Benjamini–Hochberg, q = 0.05

Table 7.18 Remission and relapse biomarker levels in GCA

Biomarker	Remission GCA, n=71 (median, IQR)	Relapse GCA, n=11 (median, IQR)	P value	FDR- adjusted p value
Ang-1 (pg/ml)	22,110.54 [18,859.33- 24,475.85]	22,000.42 [20.634- 23,681.96]	0.85	0.95
Ang-2 (pg/ml)	25.41 [17.03- 54.15]	35.46 [16.06- 54.88]	0.57	0.85
Ang2:1 ratio	0.001	0.001	0.54	0.85
Ang 1:2 ratio	903.2	580	0.55	0.85
CXCL9: MIG (pg/ml)	418.98 [228.65- 636.19]	643.46 [481.42- 993.55]	0.03*	0.27
OPN (pg/ml)	3559.32 [2417.17- 4963.44]	3886.21 [2609.68- 5058.00]	0.74	0.95
IL-6 (pg/ml)	22.68 [4.36- 56.60]	13.84 [3.33- 123.90]	0.96	0.96
IL-17 (pg/ml)	6.16 [4.61-7.55]	6.46 [5.23- 13.78]	0.34	0.85
IL-23 (pg/ml)	31.11 [13.72- 101.17]	23.31 [18.49- 91.50]	0.94	0.85

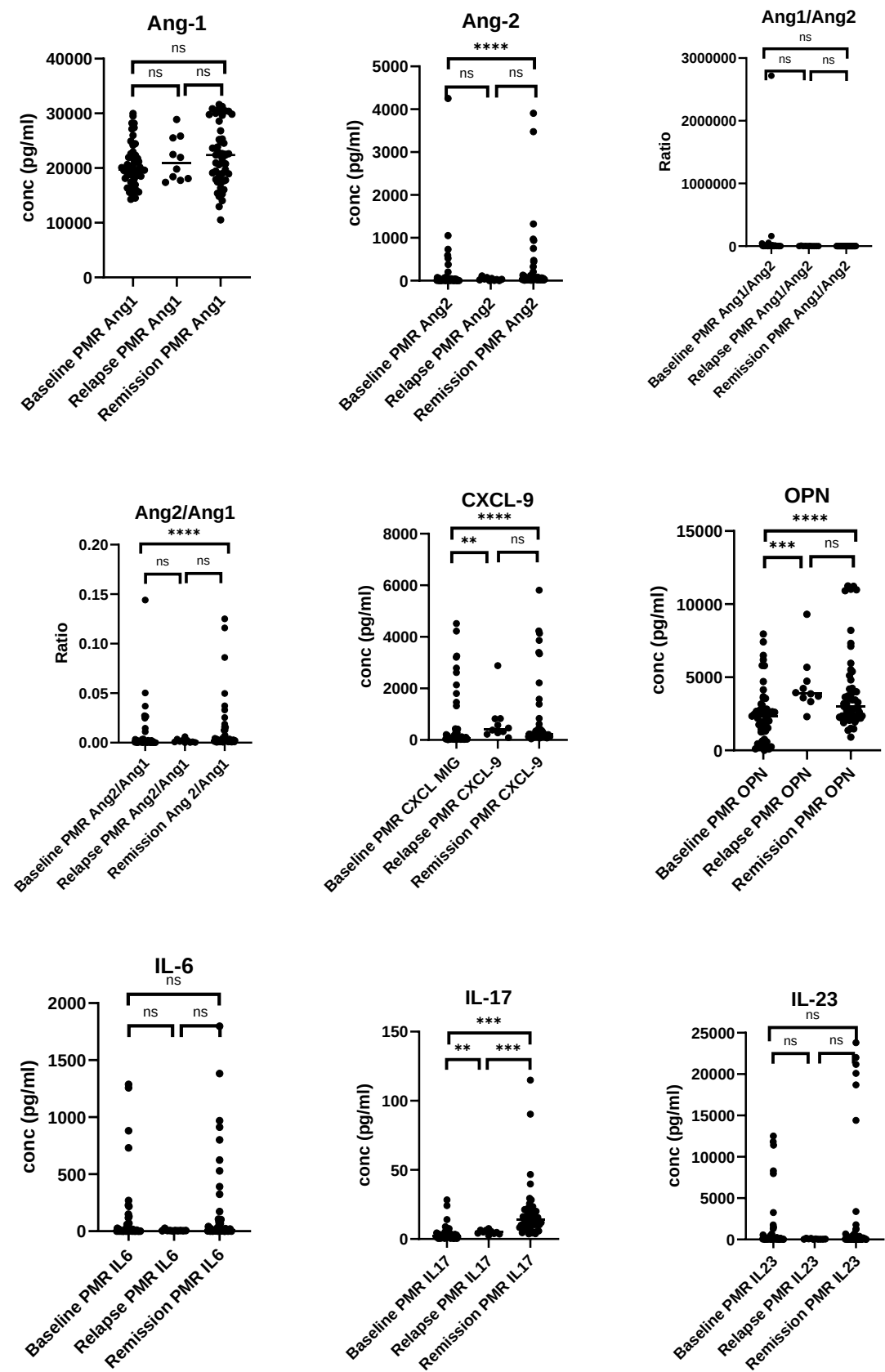
Legend: * refers to results of statistical significance. FDR-adjusted p values were calculated with Benjamini–Hochberg, q = 0.05

Table 7.19 Baseline and remission biomarkers in GCA

Biomarker	Baseline GCA, n=59 (median, IQR)	Remission GCA, n=71 (median, IQR)	P value	FDR- adjusted p value
Ang-1 (pg/ml)	27,018.00 [21,869.75- 29,493.74]	22,110.54 [18,859.33- 24,475.85]	<0.001*	0.004*
Ang-2 (pg/ml)	38.01 [17.35- 64.93]	25.41 [17.03- 54.15]	0.13	0.25
Ang 1:2 ratio	747.5	903.2	0.38	0.25
Ang 2:1 ratio	0.001	0.001	0.37	0.48
CXCL9: MIG (pg/ml)	301.77 [191.63- 799.59]	418.98 [228.65- 636.19]	0.84	0.94
OPN (pg/ml)	3182.41 [2382.02- 4176.93]	3559.32 [2417.17- 4963.44]	0.21	0.33
IL-6 (pg/ml)	6.58 [3.06- 23.77]	22.68 [4.36- 56.60]	0.02*	0.06
IL-17 (pg/ml)	10.03 [7.01- 16.60]	6.16 [4.61-7.55]	<0.001*	0.004*
IL-23 (pg/ml)	31.11 [14.67- 199.94]	31.11 [13.72- 101.17]	0.94	0.94

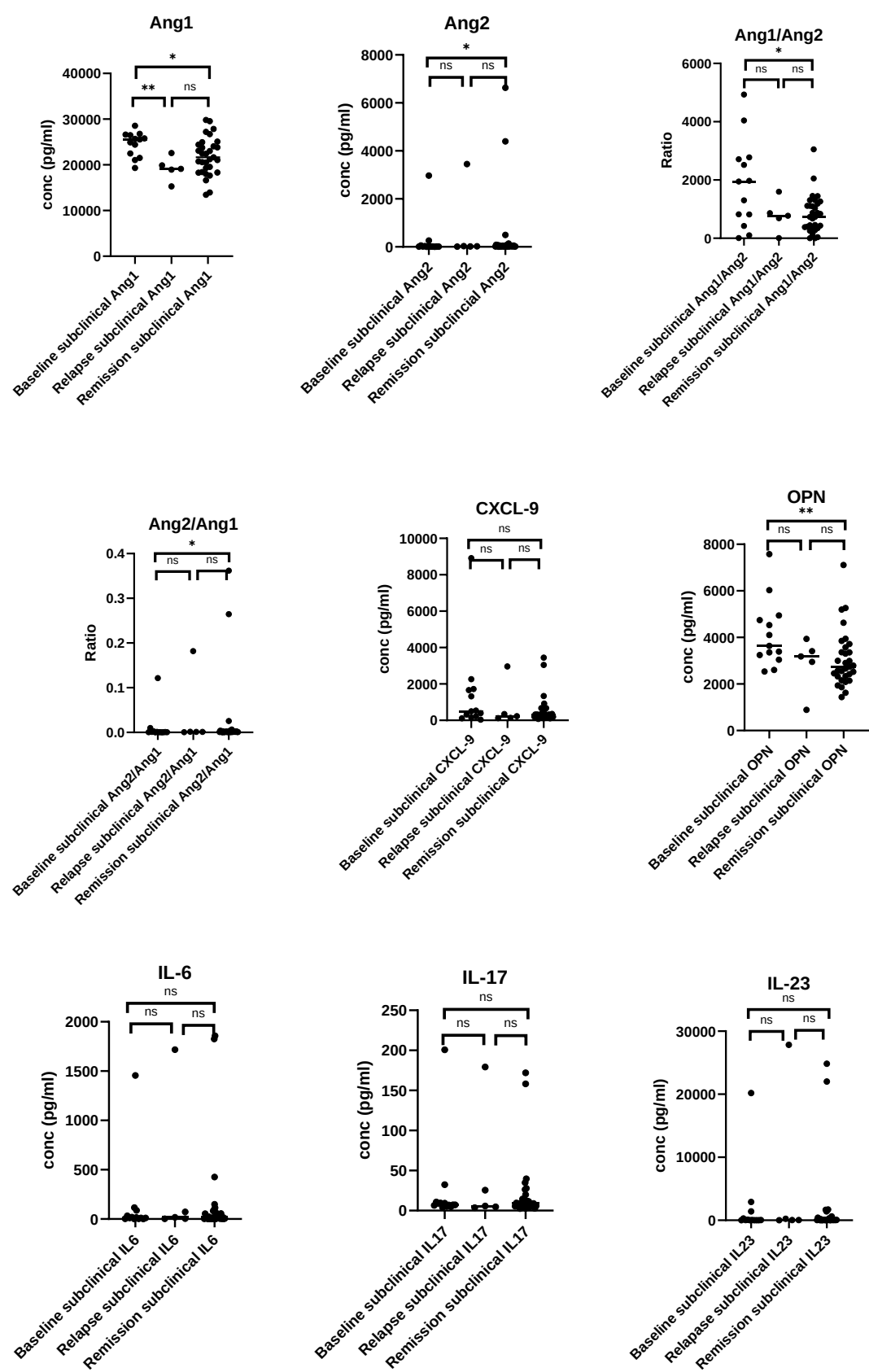
Legend: * refers to results of statistical significance. FDR-adjusted p values were calculated with Benjamini–Hochberg, q = 0.05

Figure 7.4: Serum biomarkers in PMR at baseline, remission and relapse.



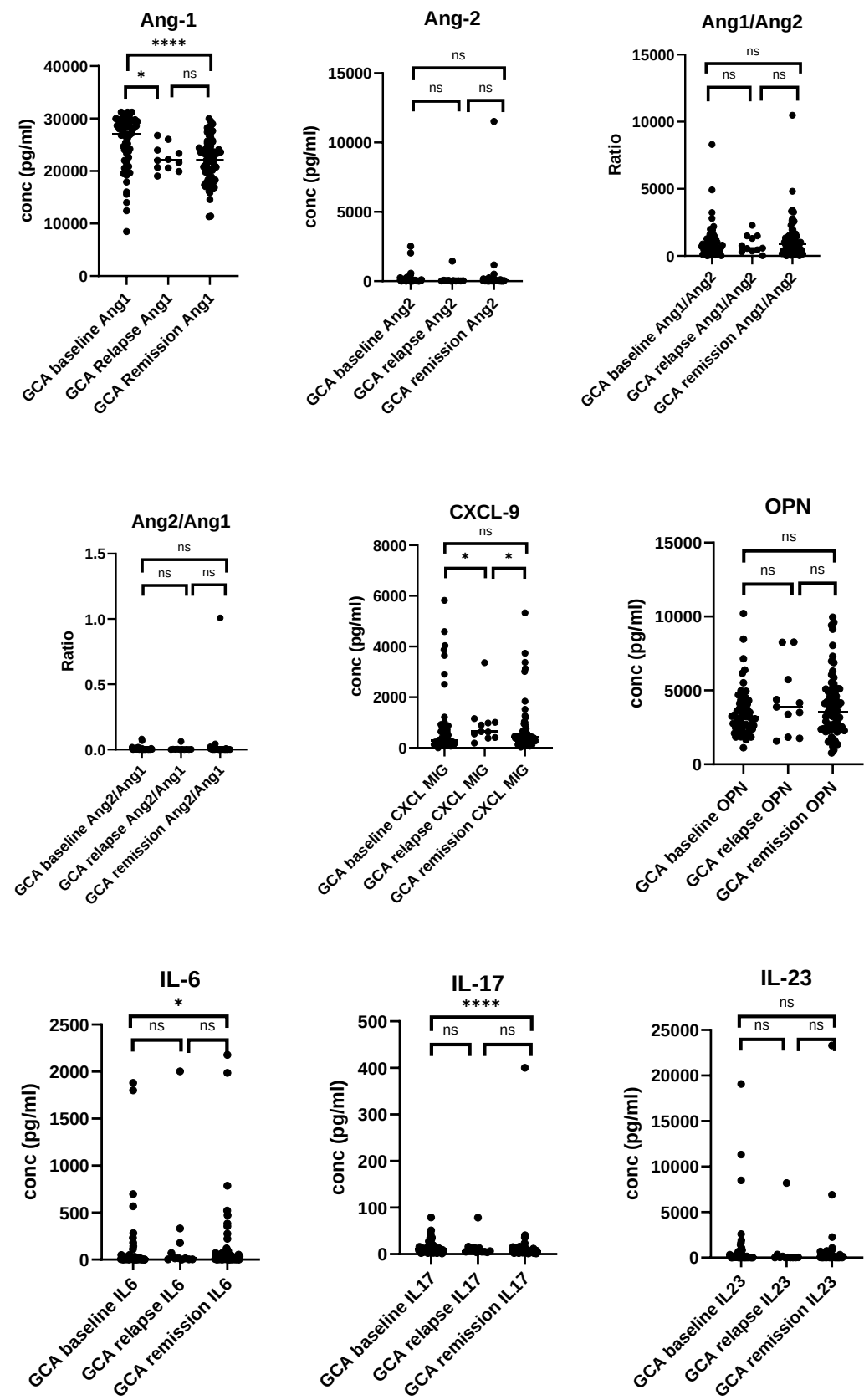
Legend: Serum levels of angiopoietin-1, angiopoietin-2, ang1:2 ratio, ang 2:1 ratio, IL-6, IL-17, IL-23, osteopontin, and CXCL-9 in PMR disease states. The horizontal line represents the median. Statistical significance is denoted as NS =no significant difference, * = significant difference with $p < 0.05$, ** = significant difference with $p < 0.01$, ***= significant difference with $p < 0.001$, **** =significant difference with $p < 0.001$

Figure 7.5 Serum biomarkers in subclinical PMR at baseline, remission and relapse.



Legend: Serum levels of angiopoietin-1, angiopoietin-2, ang1:2 ratio, ang 2:1 ratio, IL-6, IL-17, IL-23, osteopontin, and CXCL-9 in subclinical GCA in PMR disease states. The horizontal line represents the median. Statistical significance is denoted as NS =no significant difference, * = significant difference with $p < 0.05$, ** = significant difference with $p < 0.01$, ***= significant difference with $p < 0.001$, **** =significant difference with $p < 0.001$

Figure 7.6: Serum biomarkers in GCA at baseline, remission and relapse.



Legend: Serum levels of angiopoietin-1, angiopoietin-2, ang1:2 ratio, ang 2:1 ratio, IL-6, IL-17, IL-23, osteopontin, and CXCL-9 in GCA disease states. The horizontal line represents the median. Statistical significance is denoted as NS =no significant difference, * = significant difference with $p < 0.05$, ** = significant difference with $p < 0.01$, ***= significant difference with $p < 0.001$, **** =significant difference with $p < 0.001$.

7.7 Analysis of biomarkers in the context of tocilizumab

In GCA patients on tocilizumab, biomarkers were analysed to compare states of remission and relapse. There were no significant differences between relapse and remission serum in all biomarkers (see table 7.20). Small numbers of tocilizumab-treated GCA patients who relapsed (n=3) limited the analysis.

Table 7.20 Remission and relapse on tocilizumab treatment

Biomarker	Relapse Tocilizumab ± glucocorticoid treated GCA, n=3 (median, IQR)	Remission Tocilizumab ± glucocorticoid treated GCA, n=35 (median, IQR)	P value	FDR- adjusted p value
Angiopoietin-1 (pg/ml)	24723.58 [22044.62- 26413.76]	22993.75 [22051.75- 24,321.69]	0.11	0.35
Angiopoietin-2 (pg/ml)	51.68 [26.04- 753.25]	30.83 [26.37- 57.38]	0.99	0.99
CXCL-9 (pg/ml)	1082.76 [779.38- 2262.49]	366.72 [151.42- 652.40]	0.37	0.64
OPN (pg/ml)	3941.87 [2666.64- 6317.07]	4946.35 [3010.28- 7526.63]	0.95	0.99

IL-6 (pg/ml)	42.29 [9.51-1036.53]	53.78 [42.19-58.92]	0.58	0.81
IL-17 (pg/ml)	11.22 [5.31-47.26]	4.30 [3.14 – 10.68]	0.78	0.38
IL-23 (pg/ml)	91.50 [29.26-4173.73]	21.47 [7.23-98.26]	0.64	0.60

Legend: FDR-adjusted p values were calculated with Benjamini–Hochberg, q = 0.05

7.8 Discussion

The GCA PMR spectrum of diseases are clinical diagnoses with significant overlap between GCA, PMR, and subclinical GCA in PMR. This is significant as early recognition of GCA is key given the potential serious complications that may arise. Currently, ESR and CRP are the principal biomarkers relied upon as an adjunct to clinical evaluation. While they are a useful diagnostic aid, they have limitations as they are not specific to GPSD activity and may be blunted by glucocorticoid exposure. There is a need for additional biomarkers with more specificity to GPSD, including those involved in vascular inflammation. In addition, monitoring of disease activity on IL-6R antagonists is difficult and warrants investigation for useful biomarkers. This study chose to evaluate angiopoietin-1, angiopoietin-2, IL-6, IL-17, IL-23, osteopontin, and CXCL-9 in the context of differentiating GCA, PMR, and subclinical GCA in PMR and in evaluating disease activity in patients treated with glucocorticoids and IL-6R antagonists. This study did not include any healthy control blood donor samples and comparison was made between PMR, GCA, and subclinical GCA in PMR serum to assess the utility of the selected biomarkers in differentiating these GPSD subtypes.

The major finding of this study was that the biomarker profile of subclinical GCA in PMR was found to be distinct from that of PMR, and more closely in keeping with GCA serum. Analysis of subclinical GCA in PMR serum demonstrated significant differences in levels of angiopoietin-1, angiopoietin-2, IL-6, IL-17, osteopontin, and CXCL-9 with PMR. In particular, angiopoietin-1, IL-17, and osteopontin levels were significantly higher in subclinical GCA in PMR compared with PMR, with ROC analysis displaying excellent AUC. This is significant as both subclinical GCA in PMR and PMR patients could not be differentiated clinically, or with ESR/CRP, and vascular ultrasound was the only method of accurately determining subclinical GCA in PMR. Many centres lack access to bedside vascular ultrasound in a fast-track clinic setting and this biomarker may have the potential to aid the selection of PMR patients that require further investigation. Conversely, there was no significant difference between any of the biomarkers in GCA and subclinical GCA in PMR apart from IL-17, indicating subclinical GCA in PMR serum may be more akin to GCA than PMR. As expected, GCA and PMR serum exhibited significant differences in biomarker levels. Angiopoietin-1, angiopoietin-2, CXCL-9, osteopontin, IL-6 and IL-17 were all statistically significantly more elevated in GCA serum at baseline when compared with PMR.

Angiopoietin-1 was particularly useful in differentiating subclinical GCA in PMR in patients presenting with symptoms of PMR clinically, and a cut-off of 21,408pg/ml produced a sensitivity of 84.6% and a specificity of 70% for differentiating subclinical GCA in PMR from pure PMR. Angiopoietin-1 also showed a potential utility in GPSD to indicate disease activity. In both GCA and subclinical GCA in PMR patients, angiopoietin-1 levels significantly dropped in remission states. We did not observe a correlation between angiopoietin-1 levels and time to remission in GCA unlike another recently

published study (van Sleen et al., 2019) despite having larger numbers in our study numbers (n=59 versus n=41). This is likely because most GCA patients in our study were treated with tocilizumab if there were no contraindications, while the comparative study provided treatment with glucocorticoids alone and only added disease modifying treatment in the event of relapse. This suggests angiopoietin-1 may be less useful in predicting disease course when tocilizumab treatment is instigated, but may have utility in identifying relapse and remission states in GCA and subclinical GCA in PMR.

Angiopoietin-2 also demonstrated a potential utility in differentiating between PMR and GCA, with levels significantly higher in GCA than PMR at baseline, $p < 0.001$ (see table 7.4). This is in line with a previous study, indicating higher levels of angiopoietin-2 in patients with both GCA and PMR clinically, compared with those with isolated PMR, suggesting vascular involvement may increase angiopoietin-2 levels (van Sleen et al., 2020). Angiopoietin-2 levels may also have some utility in disease monitoring of PMR, with levels increasing significantly in disease remission compared with their baseline levels. In conclusion, these findings for angiopoietin-1 and angiopoietin-2 add to previous studies demonstrating potential utility in measuring vascular biomarkers in GPSD.

Blockade of the interleukin-6 pathway is a proven treatment in both GCA and PMR. In our cohort, GCA, PMR, and subclinical GCA in PMR all had elevated IL-6 levels at baseline when compared with the St James Hospital immunology laboratory normal range, indicating active disease at the time of diagnosis. Regarding disease monitoring, IL-6 was not a reliable marker for discerning a clinical relapse in our cohorts. This was

not in keeping with previous studies, where significant elevations in IL-6 were observed in relapse (Roche et al., 1993, van der Geest et al., 2015a). However, IL-6 is lower in patients with ischaemic complications of GCA (Hernández-Rodríguez et al., 2003). The current hypothesis of GCA pathogenesis implicates dual T-lymphocyte pathways of Th-17 and Th-1 (Deng et al., 2010). High IL-6 response in GCA is associated with the Th-17 pathway mediates high acute phase reactants, constitutional symptoms, polymyalgia symptoms and myofibroblast differentiation and invasion, while the Th-1 pathway promotes ischaemia and intimal hyperplasia (Weyand and Goronzy, 2013b). This may explain why IL-6 is not a good differentiator between GCA and PMR, as a proportion of GCA patients will have an ischaemic phenotype and lower IL-6 levels.

Specifically analysing tocilizumab-treated GCA patients, IL-6 levels were observed to increase numerically in relapse, but this did not reach significance. While IL-6R blockade is known to increase serum IL-6 levels, previous studies have been inconsistent in displaying whether further elevation of IL-6 is characteristic of relapse in tocilizumab-treated GCA patients (Berger et al., 2019). Our cohort was too small to determine the additional effect of glucocorticoid dose on IL-6 variability in tocilizumab-treated patients which may have implications on its ability to identify relapse in this cohort. In conclusion, IL-6 levels at baseline were elevated in PMR, GCA and subclinical GCA in PMR but its functionality to identify disease relapse was not borne out and was likely complicated by anti-IL6R treatment.

Serum measurement of interleukin-17 exhibited diagnostic significance in GPSD. Levels were significantly elevated at baseline in GCA and subclinical GCA in PMR compared to

patients with isolated PMR. This finding may be useful to aid stratification between PMR and subclinical GCA in PMR with ROC analysis showing excellent AUC. In GCA patients, IL-17 levels significantly dropped in remission compared with active disease at baseline, in keeping with IL-17 levels contributing to the pro-inflammatory cascade and consistent with the success of IL-17 blockade in the treatment of GCA in a clinical trial (Venhoff et al., 2023). However, it is difficult to determine if measurement of IL-17 levels in real-world clinical practice for disease monitoring of GCA is worthwhile. Tocilizumab treatment has been shown to reduce serum IL-17 levels (Meyer et al., 2023). The significant difference identified in this study may have been amplified by tocilizumab treatment.

Interleukin-23 levels did not prove a useful biomarker in GPSD. Levels were not significantly different between GCA, PMR, and subclinical GCA in PMR at baseline. Similarly in relapse, there was no significant change in serum IL-23 levels to prove utility in monitoring disease activity. IL-23 has previously been proven to have increased expression in positive temporal artery biopsies for GCA and to play a distinct role in GCA pathogenesis (Conway et al., 2018b). One other study also found it to be more elevated in GCA than in normal controls (Burja et al., 2019). However, previous studies have reported contrasting results for IL-12/23 blockade in GCA treatment (Matza et al., 2021, Conway et al., 2018a). This serum study has not demonstrated a utility for measuring serum IL-23 to differentiate between GCA and PMR or for disease monitoring.

Osteopontin showed good potential in differentiating subclinical GCA in PMR from PMR. Baseline osteopontin levels were significantly higher in subclinical GCA in PMR compared with PMR patients, with excellent AUC on ROC analysis. Osteopontin levels were also significantly elevated in PMR in remission compared with baseline serum. Despite its promise as a differentiator between PMR and subclinical GCA in PMR, the real-world utility of measuring osteopontin in PMR for disease activity remains unclear. Osteopontin is secreted for many reasons including muscle catabolism and muscle injury (Hoffman et al., 2013) and this may be a confounding factor, considering the length of glucocorticoid treatment in an elderly population for PMR.

CXCL-9 levels were significantly more elevated in GCA and subclinical GCA compared with PMR. Unlike angiopoietin-1, IL-17, and osteopontin, ROC analysis of CXCL-9 levels between PMR and subclinical GCA in PMR was a good discriminator with an AUC of 0.752. The utility of CXCL-9 in disease monitoring of GCA or PMR however was unconvincing with levels increasing in remission in PMR and decreasing in remission in GCA. Tocilizumab treatment may have impacted these results as IL-6 has been shown previously to inhibit secretion of IFN-responsive chemokines including CXCL-9 (Huseni et al., 2023). Based on this study, CXCL-9 has less utility in GPSD than some of the aforementioned biomarkers.

The OGUS score has been developed as a clinical tool to aid diagnosis and potentially monitor vascular inflammation in GCA. While the OGUS score has previously been shown to correlate moderately with ESR but not CRP (Dejaco et al., 2023a), this study did not show any significant correlation between OGUS and serum angiopoietin-1, angiopoietin-2, IL-6, IL-17, IL-23, osteopontin, or CXCL-9 in GCA or subclinical GCA in PMR. This was disappointing given that biomarkers angiopoietin-1, IL-17, and IL-6 showed significant differences in levels in active and inactive disease states. As OGUS assesses a limited number of arteries this may limit its assessment of the total arterial disease burden, which serum biomarkers may more accurately reflect. Alternatively, further evaluation of an extended panel of vascular-specific biomarkers may have greater potential to correlate with the vascular thickening of the intima-media complex measured by OGUS.

In summary this study has identified a cytokine signature or profile for GCA compared to PMR that may aid in identifying patients with vascular involvement in PMR. The most useful biomarkers for the diagnosis of subclinical GCA in PMR were angiopoietin-1, IL-17, and osteopontin, with excellent ROC curve sensitivity and specificity. These may be useful to combine as screening tool to identify PMR patients that would benefit from vascular ultrasound.

Regarding monitoring disease in the GPSD spectrum, the use of biological treatment, particularly IL-6R blockade is becoming more frequent and interferes with laboratory monitoring of ESR/CRP. There is a need for an accurate biomarker of disease activity as

many centres do not yet have access to bedside ultrasound, which also requires equipment, training, time, and expertise. Our analysis of tocilizumab-treated GCA patients did not highlight any utility in measuring angiopoietin-1, angiopoietin-2, IL-6, IL-17, IL-23, CXCL-9 or osteopontin. None of these markers proved more useful than ESR or CRP. However, our low numbers of relapsing patients on tocilizumab meant that this analysis was limited.

PMR remains a difficult disease to treat, with a relapsing course. PMR patients are older with many comorbidities and frequently suffer glucocorticoid-induced side-effects which can be difficult to discriminate from relapse. Several biomarkers showed promise in identifying active disease in PMR with significant elevations in remission for CXCL-9, angiopoietin -2, osteopontin, and IL-17. These findings merit further research and development.

Overall, this serum analysis of selected biomarkers in patients with GCA, PMR, and subclinical GCA has contributed to disease stratification in GPSD. It suggests that subclinical GCA in PMR has a distinct biochemical phenotype and is more akin to GCA than PMR serum. A limitation of this study was the lack of healthy blood donors to ascertain the normal range of the tested biomarkers. Apart from IL-6, which is now measured more frequently in clinical practice since the COVID-19 pandemic, reported normal levels of the other biomarkers are highly variable in literature to date. Chapter 4 of this study has previously shown the incidence of subclinical GCA in PMR (as identified by vascular ultrasound) as 1 in 5 PMR patients. This is a significant proportion of patients.

Not every rheumatology centre has the access, expertise, or clinic capacity to perform vascular ultrasound. In particular angiopoietin-1, IL-17, and osteopontin may have diagnostic value in PMR to identify patients who may benefit from vascular ultrasound evaluation for subclinical GCA.

Chapter 8:

Final Discussion

The diagnostic approach to GCA is changing with fast-track clinics becoming more mainstream. Imaging guidelines have endorsed US as the first-line investigation in suspected large vessel vasculitis, and this lends itself perfectly to the fast-track clinic model of care. There is less reliance on temporal artery biopsy, resulting in a quicker time to diagnosis. Chapter 2 of this study proved that rheumatologists can be adequately trained in vascular ultrasound following the EFSUMB Level 1 training program for performing vascular ultrasound with two half-day ultrasound clinics per week over a six-month period with approximately 4-6 examinations performed at each session under supervision, and subsequent validation examination by experienced providers. This approach can be emulated in other centres. In our cohort, only 12.5% of patients required admission for temporal artery biopsy after fast-track clinic US to confirm the diagnosis of GCA, resulting in significant cost-savings for the hospital.

This study has shown that the Southend Pretest Probability Score (SPTPS), applied to a real-world cohort, is an excellent stratification tool for GCA FTC referrals into low-risk, intermediate risk, and high-risk of GCA. It achieved a sensitivity of 100%, specificity of 73%, positive predictive value of 54%, and negative predictive value of 100% in this cohort, which is comparable to the validation study. It outperformed both the 1990 and 2022 GCA classification criteria, highlighting the known limitations of relying on these criteria to be met to accept patients for FTC referral. We would strongly advocate incorporating this scoring system into the process of FTC referrals. The Southend PTPS stratified referrals and excluded mimics, offering a reliable stratification of which patient requires a temporal artery ultrasound. If we had incorporated it into the FTC from 2022-

2023, we would have eliminated the need to review patients classified as low risk. These represented 52% of overall referrals and a substantial burden of work. This would require detailed referral information including all known co-morbidities in order to accurately compute the score.

In 2023, the international GCA/PMR study group developed international consensus-based recommendations for early referral of individuals with suspected PMR (Keller et al., 2023a). They advised that all patients with suspected or recently diagnosed PMR should be considered for specialist evaluation, however this recommendation has not yet been implemented as the standard of care. To our knowledge, the study in chapter 3 is the first report of a fast-track PMR clinic in Ireland or the UK. By adopting the GCA FTC model of care and replicating it in a PMR cohort, we had a template to facilitate rapid referrals, perform vascular US in all patients to screen for underlying GCA, and initiate protocolised PMR treatment regimens when appropriate. Significantly, almost 40% of patients had an alternative diagnosis to PMR after specialist evaluation. The FTC service correctly diagnosed these patients, allowed for faster instigation of appropriate treatment, avoided incorrect treatment with PMR dose glucocorticoids, and provided follow-up as required in the appropriate rheumatology clinic. While osteoarthritis and seronegative inflammatory arthritis were the commonest alternative diagnoses, many patients with a diagnosis of PMR in the community had serious pathology, including ANCA vasculitis, polyarteritis nodosa, myositis, and malignancy, which may have been difficult to diagnose in primary care.

The PMR FTC study proved that more communication and education are required with primary care regarding PMR diagnosis, referral, and management. Overall, PMR patients and patients with suspected PMR benefited from the FTC model of care with prompt diagnosis, excluding of mimics, screening for underlying GCA, stratifying PMR patients regarding GCA risk, and implementing a treatment plan to include appropriate follow-up. The commencement of glucocorticoid therapy should ideally be deferred until after specialist evaluation to enable more accurate clinical diagnosis and prevent masking of laboratory and US parameters which may be useful for prognosis. However, a delay in therapy can only realistically be avoided if GPs have access to a fast-track PMR clinic. We believe that rheumatologists should consider establishing fast-track PMR clinics and this study provides a compelling case and a template to support this practice innovation.

As detailed in chapter 4, vascular ultrasound examination of patients with PMR was worthwhile. It was feasible to perform this alongside clinical assessment in the FTC setting with a 45-minute time slot per new patient. 20% of PMR patients had subclinical GCA identified on ultrasound, representing a substantial burden of disease. While we observed a statistically significantly higher frequency of subclinical GCA in PMR in male patients, other trends, including a tendency towards shorter duration of early morning stiffness, more hip girdle symptoms, and constitutional symptoms, did not meet statistical significance. Overall, clinical features were not particularly useful in differentiating these patients from those with pure PMR, and vascular US was the only reliable method of identifying subclinical GCA in PMR. Glucocorticoid resistance was observed frequently in our patients with subclinical GCA in PMR and may indicate

vascular involvement. We recommend that in centres without access to vascular US imaging at the time of PMR diagnosis, a failure to respond to the initial dose of PMR glucocorticoids should prompt careful evaluation for subclinical GCA.

This longitudinal study on subclinical GCA in PMR detailed in chapter 5 conducted serial vascular ultrasound at intervals up to 12 months. Ultrasound was superior to clinical features in differentiating subclinical GCA, and a distinct ultrasound pattern was observed. PMR patients with subclinical GCA had a higher frequency of extracranial involvement with lower halo scores and OGUS than their GCA counterparts. One could speculate that the predominant extracranial pattern with less vessel oedema may produce fewer symptoms and explain why these findings are subclinical. Our study illustrated novel ultrasound findings in subclinical GCA with an initial improvement in halo count, halo score, and OGUS from baseline, followed by a later deterioration, suggesting that PMR dose glucocorticoids were not sufficient to treat the underlying inflammation. These patients also relapsed slightly earlier than their pure PMR counterparts and required an overall higher glucocorticoid treatment dose than those with pure PMR, with a greater need for glucocorticoid-sparing agents. This raises serious considerations for clinicians deciding how to treat this cohort. Our study suggests that a PMR dose treatment protocol is insufficient. Larger multicentre longitudinal studies are needed to validate this finding.

The pilot study in chapter 6 confirmed that performing shoulder US is feasible in the FTC setting in addition to clinical assessment and vascular ultrasound screening, once clinicians have sufficient experience running the clinic. Shoulder ultrasound was useful

in assisting diagnosis where patients have had previous GC exposure < 4 weeks, and most patients with PMR had shoulder pathology on ultrasound at the time of presentation. The commonest site of involvement for inflammation is the subdeltoid bursa. This data may be useful in defining the clinical phenotypes in GPSD and future cohorts in our centre will explore ultrasound shoulder and hip findings in patients presenting solely with GCA, to delineate the true prevalence of GCA-PMR overlap.

Analysis of baseline serum of patients with GCA, PMR, and subclinical GCA in chapter 7 of this study has contributed to understanding the biomarker profile of subclinical GCA in PMR. Our findings suggest that subclinical GCA has a serum biomarker profile more akin to GCA serum than PMR serum. Baseline levels of angiopoietin-1, IL-17, CXCL-9, and osteopontin may help identify PMR patients with vascular inflammation. Angiopoietin-1, IL-17, CXCL-9 and osteopontin were the best markers to discriminate subclinical GCA in PMR from pure PMR, with excellent ROC curve sensitivity and specificity. Fast-track PMR clinics with access to vascular ultrasound are not widely available, and these markers may be a useful screening tool to identify PMR patients who would benefit from vascular ultrasound.

Objective markers of disease activity in GCA and PMR are important as an adjunct to clinical practice and may identify future therapeutic targets. At present, ESR and CRP are heavily relied upon despite being imperfect markers; some patients have no elevation of ESR/CRP, and they are attenuated with anti-IL-R agents. Consequently, active disease may go undetected. Among the biomarkers analysed in this study, angiopoietin-1 and

IL-17 may have utility to monitor disease activity in GCA, with significant reductions in levels in remission. In PMR, angiopoietin-2, IL-17, and CXCL-9 may have utility in assessing disease activity with significant elevations observed in remission. While none of these markers in isolation may suffice as a clinical tool, there may be potential for a panel of biomarkers to assist clinical practice, particularly if these findings are replicated in other studies. Further evaluation of these biomarkers is required in GCA and PMR patients treated with anti-IL6-R agents. The analysis of serum biomarkers in the tocilizumab-treated patient group was limited by the small number of relapsing patients.

This study had some limitations. We scored every ultrasound in PMR using GCA-established ultrasound definitions regardless of whether patients had a suspicion of GCA clinically. The halo count, halo score, and OGUS are technically validated for use in patients presenting with a clinical suspicion of GCA. However, it was useful to objectively compare the ultrasound features of PMR patients with subclinical GCA with GCA patients. We decided not to perform temporal artery biopsy in patients with subclinical GCA in PMR as it is invasive, requires admission in our hospital, and often has little effect on diagnostic sensitivity (Luqmani et al., 2016). Ultrasound had the additional benefit of examining the superficial temporal artery along its entire length. Ultrasound cut-off values together with the OMERACT ultrasound definitions (Dejaco et al., 2023a) were also applied, already displayed a sensitivity over 99% (Schäfer et al., 2017).

Another limitation of the study was that the primary clinician in the fast-track clinic was not blinded to the clinical details of the cases before performing the ultrasound.

However, this was mitigated for by having a second clinician sonographer review the images without access to clinical particulars. There was also some difficulty in recruiting completely glucocorticoid naïve patients, particularly for the PMR FTC, and referral criteria made glucocorticoid exposure up to 4 weeks permissible for inclusion. This was a potential limitation as various studies have reported halo sign regression after glucocorticoid treatment anywhere from a few days to several weeks (Schmidt et al., 1997, Soares et al., 2021, Seitz et al., 2021). It may have resulted in an underestimation of positive vascular ultrasound and reduced baseline ultrasound scores, and may be a reason why we did not see a correlation between OGUS and ESR/CRP.

The strengths of this study included the prospective study design with standardised data collection. We also endeavoured to attain referrals directly from primary care, which, without the FTC, would have been ordinarily treated in primary care. This allowed for referrals representative of the entire PMR population, not only those with severe disease that would have previously been referred to rheumatology. We observed a rate of subclinical GCA in PMR in keeping with the two recently published studies.

Another strength of this study was that patients with subclinical GCA in PMR were initially treated with a PMR treatment protocol. This allowed for observation of the natural history of PMR with subclinical GCA, comparison of relapse with pure PMR patients, and comparison of progression to GCA and overall glucocorticoid requirement. However, baseline glucocorticoid doses were not standardised as clinical judgement impacted the choice of 12.5-25mg. Many patients also had significant glucocorticoid

exposure in primary care before referral to the fast-track clinic, often with starting doses >25mg. This impacted the overall glucocorticoid taper and cumulative glucocorticoid exposure at 12 months. Despite this, we identified earlier relapse time, higher glucocorticoid requirement, and a higher rate of progression to GCA than those with pure PMR. All patients had their diagnosis re-evaluated at 6 and 12-month timepoints, which offered further robustness to the study.

This study is more complete than previous similar studies due to biomarker analysis on all patient samples. This analysis has contributed to the characterisation of subclinical GCA in PMR as a phenotype in the GPSD spectrum. We identified a cytokine profile that may aid in identifying patients with subclinical GCA in PMR from those with pure PMR. Angiopoietin-1, IL-17, CXCL-9 and osteopontin demonstrated promising performance to delineate PMR patients with subclinical GCA. This may be useful for centres with limited access to vascular ultrasound in PMR, to identify PMR patients that would benefit from vascular ultrasound.

This research will make a valuable contribution to international collaborative research studies and further research locally at TUH and SJH. We have collaborated with European colleagues to expand the cohort of newly-diagnosed PMR patients to be assessed with vascular US. This will increase the sample size, facilitate recruitment from various international centres with expertise in vascular US, and further contribute towards identifying the optimal vascular screening protocol for newly-diagnosed PMR patients. This research is also contributing towards a multicentre international collaboration of prospective cohort of GCA patients to determine the utility of an

ultrasound-based quantification of vascular inflammation using the OGUS for prognostication and predicting GCA relapses. Furthermore, this research is also contributing towards a European collaborative effort to investigate serum biomarkers in GCA and PMR. The aim of this study with colleagues in the Netherlands and Switzerland is to investigate the differences and similarities of the inflammatory characteristics between PMR and GCA using serum protein profiles and to identify potential diagnostic biomarkers uncovering occult vascular inflammation in patients with PMR. This will contribute towards understanding the GCA-PMR spectrum of disease and will meaningfully contribute to advancing the broader research agenda focused on improving diagnosis, treatment, and long-term outcomes for both conditions.

In conclusion, we have proven the hypothesis that subclinical GCA in PMR has a distinct phenotype from pure PMR. It has a prevalence of 20.5% in patients presenting with PMR, an ultrasound pattern with slightly more extracranial involvement than classic GCA, a propensity for earlier relapse than pure PMR, a higher glucocorticoid requirement than pure PMR, and a biomarker profile distinct from pure PMR. As such, subclinical GCA in PMR should be acknowledged as distinct from PMR and a separate phenotype in the GCA-PMR disease spectrum. We also strongly advocate for the diagnosis and treatment of suspected GCA and PMR to be performed in fast-track clinics. We advocate that rheumatology centres with both the technology and the clinician sonographers should consider including vascular ultrasound in the initial assessment of PMR, and preferably as part of prospective outcome studies. Patients with US identified subclinical GCA in PMR demonstrated a higher requirement for glucocorticoid-sparing

agents and biological therapies, which warranted closer follow-up. Based on this study, patients with subclinical GCA in PMR may benefit from GCA protocol treatment from the time of diagnosis, however, we acknowledge that further long-term prospective studies are required to establish the optimal glucocorticoid therapy.

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