1. Title

How does age influence the clinical features of patients with giant cell arteritis?

2. Background

Giant cell arteritis (GCA) is the most common form of primary systemic vasculitis affecting patients aged ≥ 50 years [1]. It involves large- and medium-sized arteries, mainly cranial branches of the carotid artery but can also affect the aorta and its major branches. Typically, the affected segments display transmural inflammation of the arterial wall, with infiltrates of multinucleated giant cells, macrophages and CD4+ T-cells [1,2]. This causes thickening of the intima layer and fragmentation of the internal elastic lamina, which may lead to obstruction of blood flow in the affected arterial segments with consequent local ischemic manifestations [1,2].

Temporal artery biopsy (TAB) has been considered the gold standard for GCA diagnosis. It has a high specificity but low sensitivity, with false negatives occurring in up to 60% of patients [3,4]. Imaging studies have thus been increasingly used as an alternative or auxiliary tool [5–7]. The recommended first-line imaging method for evaluating patients with suspected GCA is ultrasound of the temporal arteries, particularly in individuals with cranial manifestations. This imaging method is more widely available, more readily performed and interpreted, is overall safer and has a higher sensitivity than TAB, as long as the operator is experienced [7]. For an adequate assessment in suspected GCA cases, ultrasound should include not only the temporal but also the axillary arteries, with the eventual examination of the carotid arteries and other accessible vessels according to physician's appraisal [7,8]. Other imaging methods, such as computed tomography, high-resolution magnetic resonance imaging (MRI) and positron emission tomography (PET), can also be used in selected cases and may have prominent roles in evaluating large-vessel involvement [1,7].

The most common manifestations of GCA are new-onset headache, accompanied by constitutional features, jaw claudication, visual disturbances and increased inflammatory markers [9]. Polymyalgia rheumatica (PMR)-like symptoms such as pain and stiffness of the neck, shoulder and pelvic girdles may also occur in around 30-60% of patients. In fact, these two diseases are sometimes considered within a spectrum, with 16-21% of patients with PMR eventually diagnosed with GCA [10].

If left untreated, GCA can lead to permanent visual loss and other ischemic complications in up to 20% of patients, thus prompt recognition of the disease and an aggressive therapeutic approach are fundamental [9]. High-doses of glucocorticoids are the mainstay of early treatment; however, they can lead to significant adverse effects [1,11,12].

Sex and race are known to influence the incidence of GCA, as women are 2-3 times more susceptible than men, while Caucasians (particularly those of northern European ascent) are much more commonly affected than African and Asian individuals [1].

Age is also a well-known factor for GCA's incidence with the likelihood of being diagnosed with this disease continuously increasing with age [13]. More recently, it has been studied whether age can also influence the clinical features and prognosis of GCA. A case control study showed that GCA, in patients over 85 years old, had higher rates of severe ischemic complications and an increased risk for early death compared to younger patients [14]. These results are, however, conflicting with the results of a previous study conducted in 2007 in which younger patients (<70) had more frequently PMR-like symptoms, cerebrovascular accidents and large artery stenosis. A longer delay in diagnosis was surprisingly observed in patients under 70 years old compared to older patients [15]. Moreover, large-

vessel involvement and a more refractory disease course have also been more commonly reported in younger patients with large-vessel vasculitis (LVV) than in older patients with LVV [16,17].

The new 2022 ACR-EULAR classification criteria for LVV include for the first-time age as a mandatory entry criterion. Now, patients can only be classified as having GCA if aged ≥ 50 years, and as having Takayasu's arteritis (TAK) if aged ≤ 60 years [18]. Hence, patients diagnosed between 50-60 years may present with features suggestive of both vasculitis, which should be recognized by the clinicians as it may have treatment implications.

Considering the wide clinical spectrum and the potential complications of GCA, understanding early predictors of worse prognosis and different clinical spectrums can be useful in a daily clinical setting. This study aims to increase this understanding of GCA by describing the Portuguese GCA cohort, comparing the clinical profile of patients diagnosed at <70 years old with those of patients diagnosed at an older age. The ideal cutting point would be 60 years of age, as explained beforehand; however, exploratory research was done within Reuma.pt and there seems to be a rather small group of patients diagnosed under 60 years, decreasing the likelihood of significant findings within our work. Other age intervals will also be explored. Understanding how age can affect GCA's clinical picture and prognosis can be a readily available, valuable tool to predict patients who will require closer follow-up or even earlier glucocorticoid-sparing therapeutic options, such as methotrexate or tocilizumab.

3. Objectives

Primary objective

I. To thoroughly characterize the population of patients registered in the Portuguese GCA cohort, divided in patients under and over 70 years old comparing both populations regarding the following features:
   A. Clinical characteristics
   B. Treatment history and outcomes

Secondary objectives

I. To describe the influence of age at diagnosis on clinical features and outcomes, analyzing whether age is an independent predictor of different clinical phenotypes and outcomes
II. To define an age threshold with clinical significance in the patient's follow-up, if 70 years of age doesn't show any significance

4. Methods

We propose a multicenter cohort study.

Inclusion criteria

I. Patients with a clinical diagnosis of GCA by their assisting Rheumatologist, confirmed by the presence of vasculitis on at least one of the following:
   A. Temporal artery biopsy
   B. Temporal, axillary, facial, occipital, subclavian or common carotid arteries doppler ultrasound ("halo" sign)
   C. Positron emission tomography-computed tomography (PET)
   D. Computed tomography (CT)

E. High-resolution magnetic resonance imaging (MRI)

II. Patients registered in Reuma.pt, with at least one registered clinical evaluation

Data collection

- Each center will be invited to participate and register GCA patients with full clinical information into reuma.pt
- In the first phase of data completion, the center's designated local investigators will fill in all the necessary information in reuma.pt and include every patient followed in the center fulfilling inclusion criteria.
- After the first phase of data completion is concluded, an exploratory analysis of the reuma.pt data will be conducted using a preliminary export of available data
- If there is any missing information, the Principal Investigator (PI) will ask Reuma.pt to reinforce the need for this information, maintaining anonymization of the patient and respective center.

Variables to be collected

- Age (continuous variable)
- Age at beginning of symptoms (continuous variable)
- Age at diagnosis (continuous variable)
- Gender (dichotomous variable: female 0; male 1)
- Date of loss of follow-up (date)
- Cause of loss of follow-up (categorical variable)
- Date of disease onset (date)
- First disease manifestation (free text; date)
- Death (date)
    - Cause of death (free text)
    - Death related to GCA (dichotomous variable: no 0; yes 1)
- Phenotype of GCA: Exclusive large-vessel GCA (evidence of vasculitis in the imaging of large vessels without cranial features of the disease [positive TAB or positive ultrasound of the cranial arteries, or cranial symptoms), exclusive cranial-GCA (cranial features of the disease without evidence of vasculitis in the imaging of large vessels), cranial and LV-GCA (evidence of both cranial and LV involvement of the disease)
- Classification criteria:
    - Considerations when applying these criteria: these classification criteria should be applied to classify the patient as having giant cell arteritis when a diagnosis of medium- or large-vessel vasculitis has been made; alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria
    - 1990 American College of Rheumatology classification criteria for GCA[1] which mandates that a patient has GCA when in the presence of at least 3 of the following (dichotomous variables: no 0; yes 1):
        - Age at disease onset ≥ 50 years
        - New-onset headache
        - Temporal artery abnormalities (e.g., tenderness or decreased pulsation)
        - Erythrocyte sedimentation rate (ESR) > 50mm/h
        - Histologic evidence of arteritis on temporal artery biopsy
    - 2022 ACR/EULAR classification criteria for GCA[2] in which a score of ≥ 6 points is needed for the classification of giant cell arteritis:
        - Age at disease onset ≥ 50 years (required criteria)

[1] Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990;33(8):1122-1128. doi:10.1002/art.1780330810

[2] Presented in ACR Convergence 2021

- Morning stiffness in shoulder/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)
- ESR ≥ 50mm/h or CRP ≥ 10mg/L (+3)
- Positive temporal artery biopsy or halo sign on temporal artery ultrasound (+5)
- Bilateral axillary involvement (+2)
- PET activity throughout the aorta (+2)

- Disease manifestations:
  - Constitutional involvement
    - Fatigue / asthenia (dichotomous variable: no 0; yes 1)
    - Fever, temperature ≥ 38ºC (dichotomous variable: no 0; yes 1)
    - Unintentional weight loss ≥ 2 kg (dichotomous variable: no 0; yes 1)
    - Lymphadenopathies (dichotomous variable: no 0; yes 1)
    - Nocturnal sweating (dichotomous variable: no 0; yes 1)
  - Musculoskeletal involvement
    - Arthralgia (dichotomous variable: no 0; yes 1)
    - Arthritis (dichotomous variable: no 0; yes 1)
    - Myalgia (dichotomous variable: no 0; yes 1)
    - Polymyalgia Rheumatica-like symptoms:
      - Prolonged morning stiffness/bilateral shoulder/hip arthralgia and stiffness (dichotomous variable: no 0; yes 1)
  - Neuro-ophthalmic/ischemic symptoms:
    - Scalp tenderness (dichotomous variable: no 0; yes 1)
    - New-onset headache (dichotomous variable: no 0; yes 1)
      - Respective topography (categorical variable: frontal, occipital, temporal or other location)
      - Jaw claudication
      - Tongue claudication
    - Cerebral ischemic events (dichotomous variables: no 0; yes 1):
      - Arteritic ischemic optic neuropathy (AION), central retinal artery occlusion, cilioretinal artery occlusion, choroidal ischemia
      - Transient ischemic attack and ischemic stroke
    - Visual loss (dichotomous variable: no 0; yes 1)
    - *Amaurosis fugax* (dichotomous variable: no 0; yes 1)
    - Diplopia/blurred vision (dichotomous variable: no 0; yes 1)
  - Dermatological symptoms
    - Skin ulcers or necrosis, e.g., necrosis of the scalp and tongue (dichotomous variable: no 0; yes 1)
  - Other symptoms (dichotomous variables: no 0; yes 1)
    - Sensorineural hearing loss (worsening of hearing acuity due to inner ear damage)
    - Ischemic cardiac pain, arm claudication, leg claudication, loss of pulses (absence of palpable peripheric arterial pulses), heart murmur (new onset since GCA diagnosis), abnormal exam of temporal arteries or other arteries, ischemic abdominal pain
- Large-vessel involvement confirmed at diagnosis either by ultrasound, PET, MRI (A) or CT (A)

- Complementary diagnostic exams:
  - Laboratory values (continuous variables):
    - Erythrocyte sedimentation rate (ESR)
    - C-reactive protein (CRP)
    - Hemoglobin
    - Platelet count

  - Temporal artery biopsy (date; findings: positive/negative, comment – free text)
  - Color doppler ultrasonography (date; findings: positive/negative, comment – free text)
    - Compatible arterial CDUS (temporal and axillary more commonly but also, if available, facial, occipital, subclavian or common carotid arteries) - defined as evidencing of "halo" sign[3]
  - PET scan (date; findings: positive/negative, comment – free text)
  - CT scan (date; findings: positive/negative, comment – free text)
  - MRI (date; findings: positive/negative, comment – free text)

- Previous medications
  - Initial daily prednisolone or equivalent dose (continuous variable)
  - Intravenous glucocorticoid pulses (dichotomous variable: no 0; yes 1; date)
  - Oral glucocorticoids (dichotomous variable: no 0; yes 1; date)
  - Glucocorticoid cumulative dose (continuous variable)
  - Methotrexate (dichotomous variable: no 0; yes 1; date)
  - Tocilizumab SC (dichotomous variable: no 0; yes 1; date)
  - Tocilizumab EV (dichotomous variable: no 0; yes 1; date)
  - Other DMARDs (dichotomous variable: no 0; yes 1; date)
  - Antiplatelet agents (dichotomous variable: no 0; yes 1; date)
  - Anticoagulants (dichotomous variable: no 0; yes 1; date)
  - Statins (dichotomous variable: no 0; yes 1; date)
  - Fibrates (dichotomous variable: no 0; yes 1; date)
  - Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) (dichotomous variable: no 0; yes 1; date)
  - Beta-blockers (dichotomous variable: no 0; yes 1; date)
  - Other antihypertensive agents not included in previous categories (dichotomous variable: no 0; yes 1; date)
  - Oral antidiabetics (dichotomous variable: no 0; yes 1; date)
  - Insulin (dichotomous variable: no 0; yes 1; date)
  - Bisphosphonates (dichotomous variable: no 0; yes 1; date)
  - Non-steroidal anti-inflammatory drugs (NSAIDs) (dichotomous variable: no 0; yes 1; date)
  - Others (dichotomous variable: no 0; yes 1; date)

- Ongoing medications
  - Intravenous glucocorticoid pulses (dichotomous variable: no 0; yes 1; date)
  - Oral glucocorticoids (dichotomous variable: no 0; yes 1; date)
  - Glucocorticoid cumulative dose at 2-years and at the last time point (continuous variable)
  - Methotrexate (dichotomous variable: no 0; yes 1; date)
  - Tocilizumab SC (dichotomous variable: no 0; yes 1; date)

[3] Monti S, Floris A, Ponte C, et al. The use of ultrasound to assess giant cell arteritis: review of the current evidence and practical guide for the rheumatologist. Rheumatology (Oxford). 2018;57(2):227-235. doi:10.1093/rheumatology/kex173

- Tocilizumab EV (dichotomous variable: no 0; yes 1; date)
- Other DMARDs (dichotomous variable: no 0; yes 1; date)
- Antiplatelet agents (dichotomous variable: no 0; yes 1; date)
- Anticoagulants (dichotomous variable: no 0; yes 1; date)
- Statins (dichotomous variable: no 0; yes 1; date)
- Fibrates (dichotomous variable: no 0; yes 1; date)
- Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) (dichotomous variable: no 0; yes 1; date)
- Beta-blockers (dichotomous variable: no 0; yes 1; date)
- Other antihypertensive agents not included in previous categories (dichotomous variable: no 0; yes 1; date)
- Oral antidiabetics (dichotomous variable: no 0; yes 1; date)
- Insulin (dichotomous variable: no 0; yes 1; date)
- Bisphosphonates (dichotomous variable: no 0; yes 1; date)
- Non-steroidal anti-inflammatory drugs (NSAIDs) (dichotomous variable: no 0; yes 1; date)
- Others (dichotomous variable: no 0; yes 1; date)

- Comorbidities of interest (dichotomous variables: no 0; yes 1; date)
    - Obesity, hypertension, hypercholesterolemia, hypertriglyceridemia, hyperuricemia, diabetes mellitus, ischemic heart disease, cerebrovascular disease, atrial fibrillation, carotid atherosclerosis, peripheral artery disease, chronic kidney disease, thyroid disease, osteoporosis

- Tobacco and Alcohol habits
    - Tobacco (categorical variable: unknown, never smoked, former smoker, current smoker)
        - If former smoker, year in which stopped smoking (continuous variable)
        - Units per day (continuous variable)
        - Years smoking (continuous variable)
        - Type of tobacco (categorical variable: cigarettes, cigars, other)
    - Alcohol (categorical variable: unknown, never/social drinker, former drinker, current drinker)
        - Units of alcohol per day (continuous variable)
- Number of disease relapses at 2-years and at the last time point (continuous variable)
- Time to first relapse at 2-years and at the last time point (continuous variable)
    - Definition of relapse: recurrence of GCA-related symptoms or increased levels of acute-phase reactants (CRP ≥1 mg/dL and/or ESR ≥30 mm/hour) not otherwise explained and requiring glucocorticoid increase [19]
- Time to first-time glucocorticoid discontinuation at 2-years and at the last time point (continuous variable)

<u>Statistical analysis</u>

Multicenter open cohort study, including patients registered in the vasculitis module of the Rheumatic Diseases Portuguese Register (Reuma.pt) with the diagnosis of GCA until May 2022. The data will be analyzed using SPSS. Descriptive statistics will be presented as mean ± standard deviation for continuous and normal variables, as median (interquartile range) for continuous non-normal variables, and as absolute and relative frequencies for categorical variables. Associations between the different categorical or dichotomous variables will be tested using Chi-Square Test or Fisher's Exact Test, as appropriate. For statistically significant associations, the odds ratio will be calculated as a measure of

the effect size of the association. The associations of continuous variables with categorical or dichotomous variables will be tested using Student's t-Test or Mann-Whitney Test, as appropriate (normality and variance homogeneity will be calculated). Cohen's D will be used as a measure of the effect size of the differences. Time to first-time glucocorticoid discontinuation and time until first relapse will be analyzed using Kaplan-Meier analysis, and differences between the groups assessed via log-rank test.
Age at diagnosis will be analyzed as an independent predictor of different clinical manifestations and outcomes, adjusted for sex, through binomial logistic regression modelling. The linearity of the continuous variables with respect to the logit of the dependent variable will be assessed via the Box-Tidwell procedure. Correlated variables, cases with missing information and outliers will be excluded from the multivariate analysis in order to fulfil all assumptions necessary to assure the validity of the regression.
Statistical significance will be set at $p < 0.05$.

5.

a. Expected Results

With this study we expect to analyze how age at diagnosis can influence GCA clinical phenotype and be a prognostic factor.

b. Possible limitations

Sample size

There will be an effort to include the largest number of rheumatology centers, regardless of size, nature or geographic location, in order to maximize our sample size. Nevertheless, we expect to have a small number of patients with GCA who are aged below 60 and/ or 65 years to test other potential cut-off points for age.

Missing data/Typing errors

All participating centers will be asked to complete the missing information with data from patients' medical records whenever such information is available. To minimize the influence of typing errors, outlier cases will be analyzed individually.

6. Calendar of assignments

- Literature review, study design and elaboration of research protocol: February-March 2022
- Submission of research protocol to Reuma.pt and Ethics Commission: April 2022
- Invitation of all national centers to participate in this project: March-May 2022
- Data completion by all participating centers: June 2022
- First data extraction and database compilation: June-July 2022
- Data analysis: July 2022
- Preparation of the final manuscript and abstract submissions for presentation at national/international congresses as well as publication: August 2022 - January 2023

7. Ethical considerations

The study will be conducted according to the principles of the Declaration of Helsinki (revised in Fortaleza – 2013) and submitted for evaluation and approval to the Ethics Committee of *Centro Académico de Medicina de Lisboa (CAML)* and the Reuma.pt National Committee. This work's databases and all steps of the research process will be fully anonymized and all patients included will have signed the Reuma.pt informed consent.

8. Research team

a. Proponent

Matilde Bandeira[1,2]

b. Research team

The project will be coordinated by the proponent (first author) and the senior author (last author). The project is open to all national centers willing to participate, which will all be formally invited. Currently, the research team is the following (some names/order of the co-authors may change after the collection of data):

Matilde Bandeira[1,2], Diana Raimundo[3], Joana Martins-Martinho[1,2], Eduardo Dourado[1,2], Adriana Carones[4], Jorge Pestana[5], Mariana Santos[6], Ana Rita Machado[1,2], Sofia Bandeira[1,2], Nikita Khmelinskii[1,2], Carla Macieira [1,2], Luís Inês[4], João Eurico Fonseca[1,2,3], Vasco Romão[1,2,3], Cristina Ponte[1,2,3]

c. Institutions

1. Rheumatology Department, Centro Hospitalar Universitário Lisboa Norte, Centro Académico de Medicina de Lisboa (CAML), Lisbon, Portugal
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5. Rheumatology Department, Hospital Garcia de Orta, Almada, Portugal.
6. Rheumatology Department, Hospital Egas Moniz, Centro Hospitalar de Lisboa Ocidental, Lisbon, Portugal

d. Co-authorship

Clinicians who actively collaborate in the project will be co-authors, according to the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (Vancouver Convention). Authorship rules are as follows:

- The investigators who will take the lead of the project (MB, DR), and who will be responsible for organizing the distribution tasks and writing the manuscript, will share first authorship of the manuscript (MB, DR).
- A total of 15 patients with complete data registered at reuma.pt per center will be the minimum requirement for co-authorship.
- For each additional 15 valid patients after the 16th patient, one additional co-author may be proposed for inclusion.
- The centers that include less than 15 patients, but with at least 5 patients with complete data, will be listed at the end of the manuscript as members of the "reuma.pt task force", following

descending alphabetical order. This listing at the end of the manuscript allows investigators to define themselves appropriately as a co-author of the manuscript under generally accepted rules of academic authorship for large multicenter studies, ensuring their appearance in Pubmed as co-authors of the manuscript.

9. Other

a. Funding

This project is currently not funded.

b. Conflicts of interest

There are no conflicts of interest to be declared.

10. References

1. Borchers AT, Gershwin ME. Giant cell arteritis: a review of classification, pathophysiology, geoepidemiology and treatment. Autoimmunity reviews 2012;11:A544-54.

2. Younger DS. Giant Cell Arteritis. Neurologic clinics 2019;37:335–44.

3. Rubenstein E, Maldini C, Gonzalez-Chiappe S, Chevret S, Mahr A. Sensitivity of temporal artery biopsy in the diagnosis of giant cell arteritis: a systematic literature review and meta-analysis. Rheumatology (Oxford, England) 2020;59:1011–20.

4. Davies CG, May DJ. The role of temporal artery biopsies in giant cell arteritis. Annals of the Royal College of Surgeons of England 2011;93:4–5.

5. Monti S, Floris A, Ponte C, Schmidt WA, Diamantopoulos AP, Pereira C, et al. The use of ultrasound to assess giant cell arteritis: review of the current evidence and practical guide for the rheumatologist. Rheumatology (Oxford, England) 2018;57:227–35.

6. Ponte C, Monti S, Scirè CA, Delvino P, Khmelinskii N, Milanesi A, et al. Ultrasound halo sign as a potential monitoring tool for patients with giant cell arteritis: a prospective analysis. Annals of the rheumatic diseases 2021;80:1475–82.

7. Dejaco C, Ramiro S, Duftner C, Besson FL, Bley TA, Blockmans D, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Annals of the rheumatic diseases 2018;77:636–43.

8. Ponte C, Martins-Martinho J, Luqmani RA. Diagnosis of giant cell arteritis. Rheumatology (Oxford, England) 2020;59:iii5–16.

9. Hellmich B, Agueda A, Monti S, Buttgereit F, de Boysson H, Brouwer E, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Annals of the rheumatic diseases 2020;79:19–30.

10. Dejaco C, Brouwer E, Mason JC, Buttgereit F, Matteson EL, Dasgupta B. Giant cell arteritis and polymyalgia rheumatica: current challenges and opportunities. Nature reviews. Rheumatology 2017;13:578–92.

11. Hill CL, Black RJ, Nossent JC, Ruediger C, Nguyen L, Ninan J V, et al. Risk of mortality in patients with giant cell arteritis: A systematic review and meta-analysis. Seminars in arthritis and rheumatism 2017;46:513–9.

12. Proven A, Gabriel SE, Orces C, O'Fallon WM, Hunder GG. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. Arthritis and rheumatism 2003;49:703–8.

13. Nordborg C, Johansson H, Petursdottir V, Nordborg E. The epidemiology of biopsy-positive giant cell arteritis: special reference to changes in the age of the population. Rheumatology (Oxford, England) 2003;42:549–52.

14. Liozon E, Delmas C, Dumonteil S, Dumont A, Gondran G, Bezanahary H, et al. Features and prognosis of giant cell arteritis in patients over 85 years of age: A case-control study. Seminars in arthritis and rheumatism 2019;49:288–95.

15. Lopez-Diaz MJ, Llorca J, Gonzalez-Juanatey C, Peña-Sagredo JL, Martin J, Gonzalez-Gay MA. Implication of the age in the clinical spectrum of giant cell arteritis. Clinical and experimental rheumatology 2008;26:S16-22.

16. Morinaka S, Tsuboi H, Hagiwara S, Sugita T, Tabuchi D, Sato R, et al. Clinical features of large vessel vasculitis (LVV): Elderly-onset versus young-onset. Mod Rheumatol 2021;31:1129–34.

17. Delaval L, Daumas A, Samson M, Ebbo M, De Boysson H, Liozon E, et al. Large-vessel vasculitis diagnosed between 50 and 60 years: Case-control study based on 183 cases and 183 controls aged over 60 years. Autoimmunity Reviews 2019;18:714–20.

18. Ponte C, Grayson P, Suppiah R, Robson J, Gribbons K, Craven A, et al. 077. Classification criteria for large-vessel vasculitis. Rheumatology [Internet] 2019 [cited 2020 Mar 18];58. Available from: https://academic.oup.com/rheumatology/article/doi/10.1093/rheumatology/kez058.017/5421891

19. Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, et al. Trial of Tocilizumab in Giant-Cell Arteritis. N Engl J Med 2017;377:317–28.