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Original Article

Clinical Phenotypes of Giant Cell Arteritis: Insights into Complications and Survival Outcomes

Paula Estrada[1], Javier Narváez[2], Patricia Moya[3], Daniel Roig-Vilaseca[1], Oscar Camacho[1], Vanessa Navarro[1], Sergi Heredia[1], Dacia Cerdà[1], Delia Reina[1], Hèctor Corominas[3]

Abstract

Background: Giant cell arteritis (GCA) is a heterogeneous disease with diverse clinical presentations and varying degrees of severity. This study aimed to assess the incidence of 3 clinical subsets in GCA and analyze associated severe complications and survival rates. By identifying distinct clinical patterns, the goal is to customize treatment approaches and minimize severe complications during follow-up.
Methods: This retrospective study classified clinical manifestations of GCA into 3 major phenotypes based on the reason for consultation: i) cranial, ii) extracranial, and iii) occult GCA. These groups were analyzed and compared for acute complications, including severe ischemic complications, "true" occlusive disease, and late complications such as aortic aneurysm. Survival data were also collected during follow-up.
Results: Visual disturbances were more common in the cranial GCA group compared to other subsets ($P < .001$). Blindness and stroke showed a clinically relevant trend, although statistical differences were not significant between the cranial GCA groups. Limb claudication was significantly more prevalent in the extracranial subset compared to the cranial or occult GCA subsets (12% vs. 2.6% vs. 0% respectively). Severe ischemic complications and true occlusive disease were more frequent in the cranial GCA groups (60%, $P = .005$ and 40%, $P = 1.64$ respectively). Regarding mortality, there were no statistically significant differences in survival among the different clinical subsets. However, the occult GCA subset showed a trend towards a higher prevalence of deaths, both overall and specifically due to GCA.
Conclusion: Clinical subsets in GCA present distinct complications and survival outcomes, with the cranial subset showing a higher incidence of severe ischemic events and the occult subset associated with delayed diagnosis and increased mortality. Recognizing these subsets is crucial for tailored treatment approaches and improving patient prognosis. Further prospective studies are needed to refine diagnostic and therapeutic strategies.
Keywords: Clinical subsets, giant cell arteritis, mortality, severe ischemic complications, true occlusive disease

ORCID iDs of the authors:
P.E. 0000-0002-9827-5680;
J.N. 0000-0002-1614-8064;
P.M. 0000-0001-8339-5420;
V.N. 0000-0002-3635-7672;
S.H. 0000-0003-0911-5077;
D.C. 0000-0002-3701-6124;
D.R. 0000-0003-2587-2510;
H.C. 0000-0002-7738-6787.

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[1] Department of Rheumatology, Complex Universitari Moisès Broggi, Sant Joan Despí, Barcelona, Spain
[2] Department of Rheumatology, Hospital Universitari Bellvitge, L'Hospitalet de LLobregat, Barcelona, Spain
[3] Department of Rheumatology, Hospital Universitari Bellvitge, Universitat de Barcelona (UB), L'Hospitalet de LLobregat, Barcelona, Spain

*Paula Estrada and Javier Narváez contributed equally to this work.

Corresponding author:
Hèctor Corominas
E-mail: hcorominas@santpau.cat

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Introduction

Giant cell arteritis (GCA) is the most common primary systemic vasculitis in adults over 50 years of age. Incidence of disease increases with age, showing a peak incidence between 70 and 80 years and a 3 : 1 predominance for women.[1] According to the 1990 American College of Rheumatology classification criteria (ACR),[2] GCA should be suspected in patients older than 50 years of age who present with recent-onset headache and temporal artery abnormality with an elevated erythrocyte sedimentation rate (ESR). Different clinical onsets of disease and distinct severity of extension characterize GCA as a heterogeneous disease, sometimes with non-specific clinical manifestations.[3] A subset of patients who do not present headache at onset may take longer to diagnose.[4,5] thus, may appear with an irreversible loss of vision secondary to ischemic optic neuropathy in 15-25% of cases[5,6]

The prevalence of atypical symptoms is not well established. There is a lack of well-defined clinical tools available to accurately detect an "occult" GCA in patients who exhibit isolated polymyalgia rheumatica (PMR) or an isolated episode of arteritic optic ischemic neuropathy (AOIN). Advancements in vascular imaging techniques, such as angio-magnetic resonance imaging (MRI)/computed tomography (CT), ultrasonography (US), and fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) scans, have improved our ability to identify the presence of large-vessel vasculitis (LVV) in patients with both typical and atypical symptoms.[3,7]

Clinical subsets in GCA refer to different subgroups of patients who present with distinct clinical manifestations, disease courses, and responses to treatment. The clinical subsets in GCA are still to be defined. Recently, Tomelleri et al published an elegant narrative review where they characterize and highlight the concept of the spectrum of disease between GCA and PMR. They describe 4 major clinically interlinked disease phenotypes: i) patients with cranial symptoms, ii) visual ischaemic symptoms, iii) constitutional symptoms, and iv) polymyalgic symptoms respectively.[7]

In our experience, clinical subsets are complicated to define, as many times, they are compounds. That said, the patient usually presents with a guiding symptom as cranial, and/or extracranial, GCA. However, we believe a special mention is necessary for an extracranial GCA subgroup called "occult GCA". The aim of this study was to investigate the incidence of these 3 clinical subsets and analyze the serious complications related to the disease and its survival. By identifying clinical patterns, we hope to tailor treatment for our patients and reduce severe complications in follow-up.

Material and Methods

We conducted a retrospective study including a cohort of 176 patients with confirmed GCA from January 1, 2005 to December 31, 2020 at 3 teaching hospitals in Barcelona, which provide healthcare to neighboring areas. The study was approved by the Institutional Review Board and Ethics Committee at our hospital (CEIm Hospital Moisès Broggi – IDIBELL, PR219/20, CSI20/58). Consent was obtained to review medical charts and collect anonymous data.

Demographic information, clinical manifestations, date of diagnosis, initial treatment, and relevant follow-up information were collected from the patients' electronic medical records. The definitive diagnosis of GCA was based on the physician's clinical judgment, supported by specific complementary tests such as vascular ultrasonography (US), PET-CT, and temporal artery biopsy (TAB), and confirmed through follow-up. All patients had a minimum of 24 months of follow-up.

Clinical manifestations were classified into 3 major phenotypes based on the reason for consultation:

Cranial Giant Cell Arteritis

This phenotype included patients with headache, jaw claudication, ocular symptoms, cerebrovascular events (stroke or transient ischemic attack), or scalp hypersensitivity, with or without PMR (Figure 1).

Extracranial Giant Cell Arteritis

This phenotype included patients with limb claudication and non-specific constitutional symptoms, or those presenting with large vessel vasculitis (LVV) relapse of PMR. This included patients initially diagnosed with apparently isolated PMR, defined by a lack of clinical evidence of GCA at diagnosis and a prompt, complete response to low-dose steroid therapy. These patients experienced arteritic relapse during follow-up, developing typical craniofacial symptoms, elevated inflammatory markers, and requiring increased glucocorticoid (GC) doses or additional immunosuppressive drugs. LVV was defined by ^{18}F-F-PET/CT involvement of large vessels, including the aorta, carotid, subclavian, axillary, humeral, iliac, and/or femoral arteries (Figure 2).

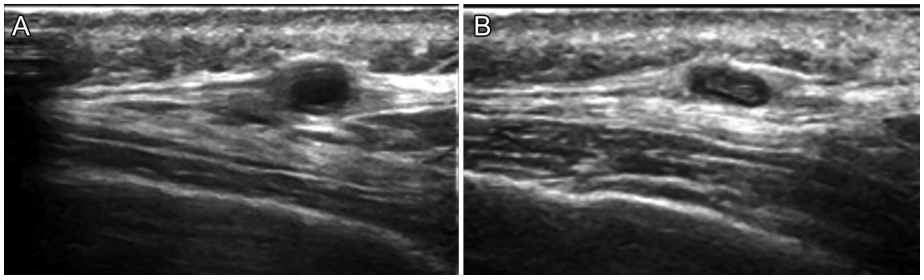

Figure 1. Temporal artery ultrasound in a patient with giant cell arteritis, cranial subset. Pathological characteristics by US in GCA: wall thickening (A), non-compressible arteries (B).

Main Points

- GCA is heterogeneous, with different clinical onsets and severity, making diagnosis challenging, especially in patients without headaches, which can delay diagnosis and lead to irreversible vision loss.
- Subsets include cranial GCA (headache, visual loss, jaw claudication) and extracranial GCA (large-vessel vasculitis, limb claudication, fever, weight loss), with a further subdivision into "occult GCA" for isolated or systemic symptoms without cranial involvement.
- Techniques like MRI, CT, ultrasonography, and PET/CT scans have improved detection of large-vessel vasculitis (LVV) in both typical and atypical cases of GCA.
- Severe ischemic complications and true occlusive disease occur across all subsets, with the highest incidence in the cranial subset due to visual loss.

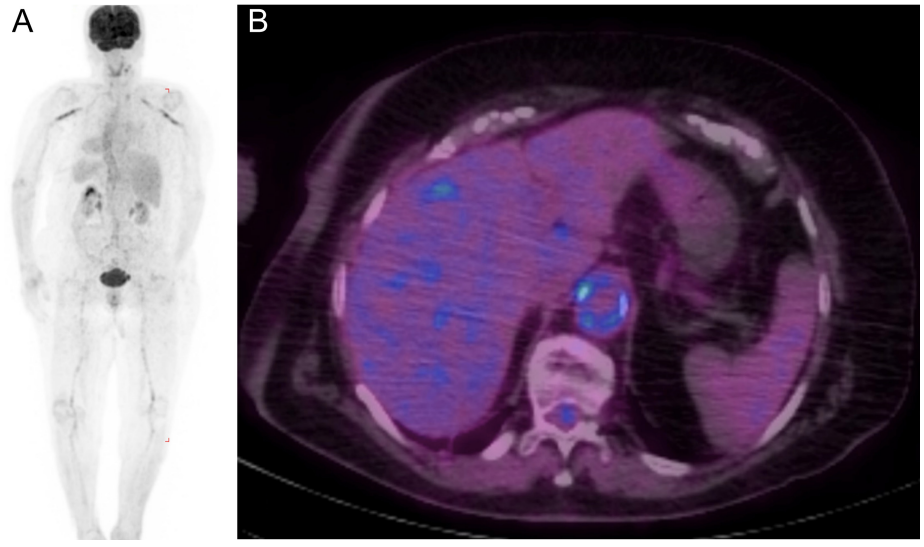

Figure 2. ^{18}F-FDG-PET/TC in a patient with giant cell arteritis, extracranial subset. Vascular hypermetabolism compatible with vasculitis. (A) Whole body ^{18}F-FDG PET/TC with ^{18}F-FDG uptake, gray scale. High ^{18}F-FDG uptake in the aorta and main arterial branches was detected, including subclavian, carotid, internal mammary, thoracic aorta, iliac, femoral, tibial arteries, and periarticular hypermetabolism in shoulders due to polymyalgia rheumatica, in relation to extracranial GCA subset. (B) Axial slices, spectrum color scale, with hypermetabolism in the thoracic aorta.

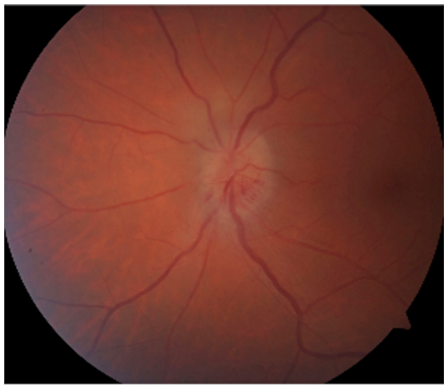

Figure 3. Retinography of a patient with acute ischemic optic neuropathy and giant cell arteritis. Retinography with changes that reflect the impact of reduced blood flow to the optic nerve due to the inflammatory process associated. The optic disc (optic nerve head) appears swollen or edematous, with blurring of the optic disc margins.

Occult Giant Cell Arteritis

This phenotype included patients with systemic symptoms such as fever or weight loss, or isolated ophthalmic GCA with visual impairment due to anterior or posterior ischemic optic neuropathy confirmed by ophthalmology, with elevated acute phase reactants and exclusion of other causes by MRI, presenting with an altitudinal defect (Figure 3).

The groups were analyzed and compared for acute complications, including severe ischemic complications and "true" occlusive disease; and late complications such as aortic aneurysm (Figure 4). Survival data were also collected during follow-up.

Patients were considered to have severe ischemic complications if they experienced visual manifestations (transient visual loss, including amaurosis fugax, permanent visual loss, or diplopia), cerebrovascular accidents (stroke and/or transient ischemic attacks), jaw claudication, or large-artery stenosis of the extremities causing occlusive manifestations (limb claudication) of recent onset. These ischemic complications were attributed to GCA if they occurred between the onset of GCA symptoms and 1 month after the onset of corticosteroid therapy.

Patients were classified as having "true" occlusive disease if they presented with permanent visual loss, stroke, and/or limb occlusive disease related to GCA, excluding transient visual loss, diplopia, transient ischemic attacks, and jaw claudication.

Continuous variables are presented as mean with standard deviation (SD) or as median with interquartile range (IQR) depending on data distribution. Categorical variables are presented as percentages. For group comparisons, the Chi-squared statistic was used, with a *P*-value of < .05 considered significant. Statistical survival analysis considered death as the primary outcome, using the Kaplan–Meier survival curve. Statistical analysis was performed using SPSS version 18.0.

Results

The demographic characteristics of the patients and follow-up times are presented in Table 1. The majority of patients (59.1%) were female, with a median age of 75.9 years (SD 7.8). The median follow-up duration was 46.5 months [IQR 25-75%: 23.7-79], with no significant difference in follow-up time between the groups.

All patients received initial treatment with glucocorticoids (GC). During follow-up, methotrexate was added for 35.6% of the patients, and tocilizumab was added for 28.4% due to persistent disease activity, relapses, or the need for GC sparing due to comorbidities or complications, at the discretion of the treating physician. Notably, half of the patients in the extracranial GCA subset received tocilizumab (*P* = .008) (Table 2).

Table 1. Baseline Demographics

Demographic Data, n = 176	
Sex (female, %)	59.1
Age, years (SD)	75.9 (7.8)
Follow-up, months [IQR 25-75%]	46.5 [23.7-79]
Clinical subset, n (%)	
Cranial +/- PMR	114 (64.8)
Extracranial GCA	34 (19.3)
Occult GCA	28 (15.9)
Follow-up, months [IQR 25-75%]	
Cranial +/- PMR	40.5 [25-65]
Extracranial GCA	46.5 [23-79]
Occult GCA	39.5 [23-55.5]

Regarding complications across different subsets, visual disturbances were more frequent in the cranial GCA group, with or without PMR (*P* < .001). Although blindness and stroke were more common in the cranial group, the differences were not statistically significant but indicated a clinically relevant trend. Limb claudication was significantly more prevalent in the extracranial subset compared to the cranial or occult GCA groups, at 12% vs. 2.6% vs. 0% respectively. Severe ischemic complications and true occlusive disease were more frequent in the cranial GCA group, with or without PMR, at 60% (*P* = .005) and 40% (*P* = .164) respectively (Table 3).

When analyzing causes of death, whether overall or solely due to GCA, no statistically significant differences in survival were observed between the different clinical subsets. However, there was a trend towards a higher prevalence of death in the occult GCA subset (Table 3). In our cohort, occult GCA was associated with more deaths from any cause or specifically due to GCA (Table 4). The causes of death included 2 subarachnoid hemorrhages secondary to the rupture of a middle cerebral artery aneurysm, 2 fatalities due to stroke (one from extensive infarction of the middle cerebral artery in a patient who had discontinued GC treatment, and the other from not initiating GC treatment), and one patient who died postoperatively following aortic aneurysm surgery.

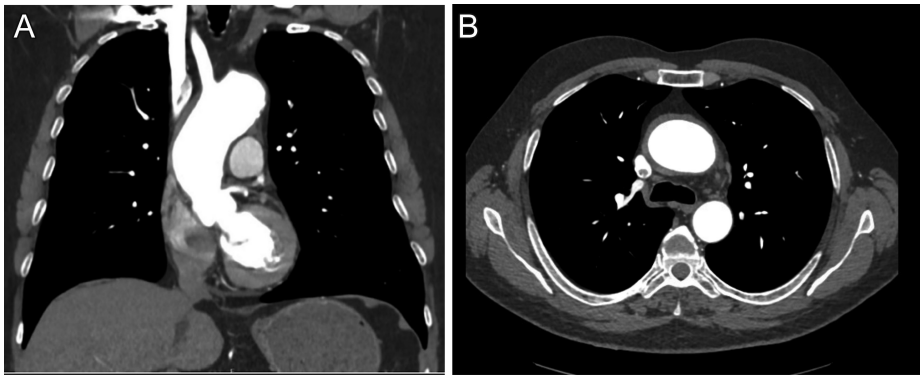

Figure 4. Computerized tomography with contrast, coronary view (A), axial view (B). Ascending aorta with circumferential thickening of the vascular wall and an aneurysm as a late complication of a patient with giant cell arteritis.

Table 2. Treatment for Patients with GCA in Our Cohort

	Cranial +/- PMR N = 114	Extracranial GCA N = 34	Occult GCA N = 28	*P*
Glucocorticoids*	63 (55.3%)	22 (64.7%)	18 (64.3%)	.492
Methotrexate	35 (30.7%)	17 (50%)	10 (35.7%)	.158
Tocilizumab	27 (23.9%)	17 (50%)	6 (21.4%)	.008

The value in bold indicates statistical significance.
*In those patients with a follow-up longer than 24 months.

Discussion

Vascular inflammation in GCA can disrupt the integrity of elastin and collagen fibers within the walls of blood vessels, resulting in mechanical vulnerability.[8,9] The impact of GCA on morbidity and mortality remains controversial, with medium- to long-term complications reflecting the global vascular inflammatory process.

Severe Complications and Survival

Breuer et al. recently concluded that survival and outcomes in patients with GCA vary considerably depending on the clinical subset.[10] Some studies report survival rates comparable to the general population,[11] while others find higher overall mortality rates, particularly among younger patients or those with aortic involvement within the first or second year of diagnosis.[12] Conversely, a systematic review and meta-analysis by Hill et al. found that global and long-term mortality is not increased in GCA patients, although those recruited through hospital admission exhibit much higher mortality rates.[13]

The prognosis for GCA patients with aortitis remains uncertain. The prevalence of aortitis in GCA is estimated to be between 33% and 65%, with approximately 10-15% of GCA patients developing an aortic aneurysm or ectasia. The potential severity of aortic involvement in GCA should not be underestimated, as studies indicate an increased incidence of aortic aneurysm or dissection occurring 5 years post diagnosis.[14]

Table 3. Incidence of Complications and Death for Our GCA Cohort

	Cranial +/- PMR N = 114	Extracranial GCA N = 22	Occult GCA N = 28	*P*
Visual Alterations	47 (41%)*	5 (15%)	8 (29%)	.013*
Blindness	27 (24%)	3 (9%)	6 (21.4%)	.601
Stroke	19 (17%)	1(3%)	3 (11%)	.133
Limb claudication	3 (2.6%)	2 (12%)	0 (0%)	.029*
Aortic aneurism/aortic dilatation	12 (10.5%)	4 (12%)	2 (7%)	.823
Severe ischemic complications[a]	68 (60%)	10 (29%)	12 (43%)	.005*
True occlusive disease[b]	46 (40%)	7(20.5%)	9 (32%)	.164
Death due to any cause	17 (15%)	4(12%)	9 (32%)	.062
Death due to GCA	3 (2.6%)	0 (0%)	2 (7.1%)	.228

Values in bold indicate statistical significance.
[a]Severe ischemic complication: if they suffered visual manifestations (i.e., transient visual loss, including amaurosis fugax, permanent visual loss, or diplopia), cerebrovascular accidents (i.e., stroke and/or transient ischemic attacks), jaw claudication, or large-artery stenosis of the extremities that caused signs of occlusive manifestations (i.e., limb claudication) of recent onset. [b]True occlusive disease: if they presented permanent visual loss, stroke, and/or limb occlusive disease related to GCA. *$P < .05$.

Table 4. Mortality Due to Any Cause in GCA

Clinical Phenotype	Follow-Up Months [IQR 25-75%]	Death		
		N	Crude (%)	Annual* (%)
Cranial +/- PMR	40.5 [25-65]	17	15	4.4
Extracranial GCA	46.5 [23-71]	4	12	3.2
Occult GCA	39.5 [23-55.5]	9	32	9.7

*Annual mortality rate: dividing the total mortality by the number of years of follow-up.

Our data show a higher rate of deaths from any cause and specifically due to GCA in the occult GCA subset (Table 4), although this did not reach statistical significance, likely due to our sample size. We attribute this to diagnostic delays, as occult GCA often falls under the differential diagnosis for infections and neoplasms. Additionally, patients presenting with isolated arteritic anterior ischemic optic neuropathy require higher cumulative doses of GC, including methylprednisolone boluses at diagnosis.

Clinical Subsets

Clinical subsets for GCA include cranial and extracranial GCA with or without PMR symptoms.[15] However, differentiating these subsets is complex due to overlapping clinical features. Criteria such as new-onset headache, temporal artery abnormality, scalp tenderness, jaw and tongue claudication, and visual loss classify patients into the cranial subset. Extracranial GCA includes patients with predominant large-vessel vasculitis, often presenting as PMR, with arm or leg claudication, fever, and/or weight loss. The exact prevalence of large vessel involvement varies widely, with systemic screening yielding a prevalence of 29-83%.[3,14]

We further subdivided the extracranial GCA subset into a smaller category, occult GCA, for patients presenting with isolated arteritic anterior ischemic optic neuropathy (AION) or systemic symptoms without cranial symptoms, PMR, or limb claudication (Table 1). This differentiation helped us better understand these patients' clinical presentations.

This categorization is crucial for improving the surveillance of complications. For example, visual alterations are predominantly associated with the cranial subset, while limb claudication is typical of the extracranial subset. Severe ischemic complications and true occlusive disease were present across all subsets, with the highest incidence in the cranial subset, likely due to the serious consequences of visual manifestations leading to permanent visual loss (Table 3).

Imaging Considerations

The choice between PET/CT and ultrasound varies based on the healthcare setting, available expertise, and the patient's clinical presentations.[16] Following ACR/EULAR recommendations, temporal artery ultrasound is a reliable first-line diagnostic method for GCA.[15] In our experience, temporal artery ultrasound has a sensitivity of 81.8% and specificity of 93.3%, with a positive predictive value of 90% in a high-suspicion cohort.[17] As expertise with

ultrasound has grown, it has also become useful for assessing large vessels accessible with a linear probe. Recent studies indicate that ultrasound examinations of the temporal, axillary, subclavian, and vertebral arteries can achieve sensitivities and specificities exceeding 90%. Additionally, a novel scoring system using the intima-media thickness of the temporal and axillary arteries enables tracking of structural alterations during treatment.[18]

While ^{18}F-PET/CT has not traditionally been a first-line diagnostic technique for GCA due to difficulties in visualizing cranial arteries,[19] it is particularly valuable for diagnosing extracranial and occult GCA, given the nonspecific symptoms in these patients.[15,20] This technique allows synchronized examination of the aorta and its branches, with high sensitivity and specificity for early diagnosis. Studies suggest performing an ^{18}F-FDG PET-CT scan preferably within the first 3 days of symptom onset, as GC therapy can reduce FDG uptake.[21] Narvaez et al. recently demonstrated that even with reduced vascular wall uptake of FDG due to GC treatment, a late ^{18}F-FDG PET-CT beyond the initial 10 days can still provide valuable information in many cases.[22]

Treatment Approach

Patients with GCA are generally treated similarly regardless of the clinical subset. However, retrospective analyses suggest that patients with large vessel GCA exhibit more treatment-resistant characteristics and may require individualized therapy.[23] In our cohort, half of the patients with the extracranial subset were prescribed tocilizumab (Table 2), potentially due to the association of fever with pro-inflammatory cytokines, likely IL-6.[24]

Study Limitations and Strengths

Our study has several limitations. As a retrospective cohort study based on daily clinical practice and clinical records, our sample size was limited, and we were unable to adjust for other risk factors such as comorbidities present at diagnosis. Additionally, ischemic events and complications were not adjusted for cardiovascular risk factors, and inflammation of large vessels was not routinely investigated in all patients with GCA. Despite these limitations, our study included both outpatients and hospitalized patients, providing an overview of different degrees of disease severity.

As diagnostic approaches for GCA evolve, new challenges emerge in improving long-term outcomes and patient survival. Effective management of GCA depends on prompt diagnosis and early treatment initiation, ongoing monitoring for comorbidities, and complications related to immunosuppressive therapy with GC. Many unanswered questions remain about individualizing treatment, identifying clinical factors associated with poor prognosis, and characterizing disease features.

Future research should focus on prospective studies using gold-standard imaging techniques and seeking prognostic biomarkers.[25] Risk stratification and identifying specific patient subsets in GCA can help determine those who would benefit from more intensive treatment. Given the disease's significant heterogeneity, implementing a chronic damage index could effectively monitor the presence and progression of severe complications.

Ethics Committee Approval: This study was approved by Ethics Committee of Bellvitge University Hospital (approval number: PR219/20 (CSI 20/58); date: 06/03/2020).

Informed Consent: Since our study was performed retrospectively, we were exempted by the ethics committee from obtaining informed consent. Patient information were pseudonymized prior to analysis.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – P.E., J.N.; Design – P.E., J.N., H.C.; Supervision – J.N., H.C.; Resources – D.R.-V., P.M.; Materials – J.N., D.R.-V., H.C.; Data Collection and/or Processing – P.E., J.N., P.M., D.R.-V., V.N., O.C., S.H., D.C., D.R.; Analysis and/or Interpretation – P.E., J.N., D.R.-V.; Literature Search – P.E., P.M., D.R.; Writing – P.E., J.N., H.C.; Critical Review – J.N., D.R., P.M., H.C.

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