Summary tables of evidence SLR focused on diagnosis/monitoring – results on GCA

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LIST OF ABBREVIATIONS

ABA: abatacept

aCL: anti Cardiolipin antibodies

ACR: American college of Rheumatology

ADA: adalimumab

AE: adverse event(s)

AION: anterior ischaemic optic neuropathy

ALP: alanine aminotransferase

APR: acute phase reactants

ASA=acetylsalycilic acid

AZA: azathioprine

bDMARDs: biologic disease-modifying anti-rheumatic drugs

BP: blood pression

BVAS: Birmingham vasculitis activity score

CABG: coronary artery bypass grafting CDS: colour duplex sonography

CDS: color doppler sonography

C-GCA: cranial pattern GCA

CI: confidence interval

CIE: cranial ischaemic events

CRAO: central retinal artery occlusion

CRP: c-reactive protein

CsA=cyclosporine

csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs

CT: computed tomography

CTA: computed tomography angiography

CTD: connective tissue disease

CV: cardiovascular

CYC: Cyclophosphamide

DMARD: disease-modifying anti-rheumatic drugs

ECG: electrocardiography

ELISA: enzyme-linked immunosorbent assay

ESR: erythrocyte sedimentation rate

ESR: erythrocyte sedimentation rate

ETA: etanercept

FDG: fluorodeoxyglucose

FDG-PET: fluorodeoxyglucose positron emission tomography

Fig.: figure

FTP: fast-track pathway

fu: follow-up

GC: glucocorticoid (prednisone if not otherwise specified)

GCA: giant cell arteritis

GFR: glomerular filtration rate

HAQ: health assessment questionnaire

HBV: hepatitis B virus

HC: healthy controls

HCQ: Hydroxychloroquine

HCV: hepatitis C virus

HLA: human leukocyte antigen

HR: hazard ratio

HRCT: high-resolution computed tomography

HRQoL: health-related Quality of Life

hsCRP: high-sensitivity c-reactive protein

IA: Isolated aortitis

ICIE: irreversible cranial ischaemic events

ID: identification

IFX: Infliximab

IGRA: interferon gamma release assay

ILA: inflammation limited to the adventitia

ILD: interstitial lung disease

IL6: interleukin 6

i.m.: intramuscular

IQR: interquartile range

ITAS: Indian Takayasu's Arteritis Activity Score

ITU: intensive therapy unit

i.v.=intravenous

Lab: laboratory abnormalities

LEF: leflunomide

LV: large vessel

LV-GCA: large vessel giant cell arteritis

LVV: large vessel vasculitis

LoE: level of evidence according to Oxford centre for evidence-based Medicine – Levels of evidence (Match 2009)

MI: myocardial infarction

MMF: mycophenolate mofetil

MMP-3: metalloproteinasis-3

Mo: month(s)

MRI: magnetic resonance imaging

MRA: magnetic resonance angiography
MTX: methotrexate
N: number
NA or na: not applicable
NOC: neuro-ophthalmic complications
Nsp: not specified
Ns or ns: non-significant statistical result
OR: odds ratio
PET: positron emission tomography
PET-CT: Positron emission tomography-computed tomography
PI: principal investigator
PMR: polymyalgia rheumatica
PN: polyarteritis nodosa
p.o.: per os
PRED: prednisone
Pt: patient
Pts: Patients
PVL: permanent visual loss
QoL: quality of life
RoB: risk of bias
RR: relative risk
RTX: Rituximab
SAA= serum amyloid A
s.c.=subcutaneous
SD: standard deviation
SF-36: short-form 36
Subclav: subclavian
SVV: small vessel vasculitis
TA: temporal arteritis
TAB: temporal artery biopsy
TAK: Takayasu's arteritis
TB: tuberculosis
TCZ: tocilizumab
TIA: transient ischaemic attack
TNF: tumor necrosis factor
TNFi: tumour necrosis factor inhibitors
TMI: transmural inflammation
US: ultrasound
UST: ustekinumab
VEGF: vascular endothelial growth factor
VVV: vasa vasorum vasculitis
PDGF: platelet-derived growth factor
Wk: week
Yrs: year

1. DISEASE PATTERNS

1.1 OBSERVATIONAL STUDIES (Disease patterns)

1.1.1 Supplementary Table 1. Evidence retrieved for disease patterns in giant cell arteritis. Overview of included studies

Study ID	Study design	LoE	Overview	Inclusion criteria	Exclusion criteria	End of follow-up for analysis
GCA						
Disease patterns						
Prospective						
Liozon et al 2003 (1)	Prospective cohort Single center	2b	Prospective comparison of the main characteristics and short-term outcome of patients with typical cranial manifestations vs patients with silent presentation to identify the pretreatment characteristics associated with silent pattern	GCA diagnosis + performed TAB	Negative TAB Permanent visual loss (for the silent pattern group)	Jan 1977 - April 2002
Retrospective						
Daumas et al. 2014(2)	Retrospective cohort Single center	3b	Retrospective comparison of presentation and evolutive characteristics of GCA patients with and without aortitis at diagnosis	GCA (ACR criteria 1990) + Angio-CT at diagnosis or within 4 weeks from diagnosis + minimum follow up of 3 months Note (CRP ≥ 20 considered equivalent to ESR ≥ 50)	Absence of Angio-CT, not complying with ACR criteria, interruption of follow-up	Jan 1st, 2005 to September 30th 2011
Espitia et al. 2012(3)	Retrospective cohort Single center	3b	Description of long-term outcome of GCA patients with and without aortitis at diagnosis	GCA (ACR criteria 1990), all TAB positive + CT scan performed within 4 weeks from diagnosis	allergy to iodine, renal failure and infectious vasculitis or systemic vasculitis (other than GCA)	2008-2012

Espitia et al. 2016(4)	Retrospective cohort Multicentric	3b	Comparison of clinical/imaging findings and outcome in patients with idiopathic isolated aortitis (IA) and with GCA-related aortitis.	GCA diagnosis (3 ACR 1990 criteria including age over 50) Isolated aortitis diagnosis (aortitis with associated inflammatory syndrome, without any other ACR criteria for GCA, except age, and without any diagnosis criteria for any other causes of aortitis)	Patients with other causes of aortitis	Jan 2000 – Dec 2014
de Boysson et al. 2016(5)	Retrospective cohort Multicentric	3b	Description of clinical presentation, diagnostic process, and disease course of GCA patients without cranial symptoms vs typical cranial presentation.	GCA (3/5 ACR criteria 1990) OR GCA (2/5 ACR criteria 1990) and vascular biopsy other than temporal, displaying Giant cell arteritis OR GCA (2/5 ACR criteria 1990) and LV imaging, provided that no other condition appeared during follow-up. LV imaging by CT Scan, FDG PET/CT or cardiac echography + LV Doppler scan	nsp	1995-2015
Muratore et al. 2015(6)	Retrospective cohort Single center	3b	Comparison of baseline variables, treatment and outcomes in patients with large-vessel GCA (LV-GCA), primarily of the upper extremities, with those with cranial disease (C-GCA).	GCA diagnosis identified on records (ACR criteria were not necessary with exception to age > 50 years) For LV-GCA, radiographic evidence of subclavian artery vasculitis attributed to GCA (on CTA, CDS or FDG-PET) For C-GCA, positive TAB	For LV-GCA: Other inflammatory diseases (Behcet's disease, Takayasu arteritis, sarcoidosis or other autoimmune CTD); imaging showing only evidence of atherosclerosis or fibromuscular dysplasia For C-GCA: evidence of vasculitis involving the primary branches of the aorta	Jan 1999 to 31st Dec 2008
Schmidt et al. 2008(7)	Retrospective cohort Single center	2b	Comparison of patients with GCA with vs without proximal arm involvement, regarding comorbidities/complications of disease and GC use	LV-GCA: diagnosis of GCA + vasculitis of proximal arm vasculitis by CDS GCA controls: diagnosis of GCA without evidence of arm vasculitis	nsp	1997-2006

Ghinoi et al. 2012(8)	Retrospective cohort Single center	2b	Comparison of laboratory and clinical findings of GCA patients with and without LVV	GCA diagnosed according to ACR criteria and/or positive TAB OR other imaging proving disease + compatible symptoms + raised inflammatory parameters	Insufficient documentation	2003-2008
Hamidou et al. 2005(9)	Retrospective cohort Single center	3b	Retrospective comparison of initial presentation and outcomes of patients with typical cranial manifestations vs patients with silent presentation	Biopsy proven GCA (fulfilling ACR criteria)	nsp	Jan 1995 to Dec 1999
Gonzalez-Gay et al. 2005(10)	Retrospective cohort Single center	3b	Description and comparison of disease patterns of GCA presentation and differences in outcomes	Biopsy proven GCA (fulfilling ACR criteria)	nsp	1st Jan 1981 to 15th June 2004

1.1.2 Supplementary Table 2. Disease Patterns: outcome definition and statistical analysis

Study ID	Outcome/endpoint	Definition of outcome	Validation of outcome	Notes on analysis	Censoring at event
Liozon et al 2003 (1)	Clinical and laboratory features Delay to diagnosis Permanent ischaemic events	**Typical TA**: presence of 2 or more among the major cephalic symptoms/signs (i.e., recent headache, scalp tenderness, jaw claudication and abnormal temporal artery on examination) **Silent TA**: constitutional symptoms and raised erythrocyte sedimentation rate (ESR) but no evidence of cranial arteritis, polymyalgia rheumatica, or large artery involvement during the pretreatment course of disease or at least for an observational period of 2 months or more. **Laboratory** features: ESR, CRP, fibrinogen, haptoglobin, haemoglobin, platelet count, albumin and liver function tests. **Permanent ischaemic events**: stroke, hearing loss, myocardial infarction	Physician	Standard statistics, Mann Whitney rank-sum test, Chi-square and fisher's exact test, correlation coefficients	Patients with mixed clinical pattern were excluded from the main analysis.

Daumas et al. 2014(2)	Differences in clinical, and laboratorial features Complications (aneurysm, ectasia) Relapse Recurrence	**Clinical features** at diagnosis: fever, anorexia, weight loss, asthenia, PMR, headache, scalp hyperesthesia, jaw claudication, abnormal temporal arteries, tongue/skin necrosis, eye damage, cough, aortic insufficiency bruit, back ache, vascular involvement of upper and lower limbs **Laboratorial features**: ESR, CRP, Fibrinogen, platelet count, haemoglobin count, lipid profile, liver function. **Aneurysm**: saccular or fusiform dilation with loss of parallelism of vessel wall. **Ectasia**: vessel dilation by radiologist criteria with no loss of wall parallelism **Relapse**: reappearance of clinical symptoms with increased inflammatory markers and requiring increase in GC. **Recurrence**: reappearance of disease after stopping GC.	Physician Radiologist	Descriptive statistics, Qui-square, Fisher exact test, T-student or Mann-Whitney test, Kappa test	Nsp
Espitia et al. 2012(3)	Relapse GC discontinuation Vascular events Mortality	**Relapse**: recurrence of unexplained elevation of inflammatory markers (CRP > 20 mg/l) with symptoms and physical examination signs of GCA, leading a physician to increase or resume GC therapy. **Vascular events**: aortic dissection, aortic aneurysm, stage III/VI obliterating arteriopathy, stroke, coronary artery disease **GC discontinuation**: GC discontinuation without any new GC requirement for 6 years (72 months), or (in the case of death) GC discontinuation without any new GC requirement in the 3 months preceding death.	Two examiners	Descriptive statistics, chi-squared or Fisher's exact tests, Mann-Whitney U test, Kaplan-Meier method and log-rank test.	Nsp
Espitia et al. 2016(4)	Aortic events Aortic event free survival	**Aortic event**: aortic aneurysm, ectasia, dissection, or stenosis, on CT-scan or on Doppler ultrasonography **Aortic event free survival**: Free of aortic aneurism survival; Free of aortic surgery survival; Free of aortic dissection survival.	Two physicians	Descriptive statistics, chi-square tests or Fisher's exact tests, Student's t-test, Kaplan–Meier curves and a log-rank test (to compare aortic-event-free survivals).	Patients with aortic events at diagnosis were excluded from analysis and only new events were considered

de Boysson et al. 2016(5)	GC dependent disease Relapse Mortality	**GC dependent disease**: prednisone dose levels>20 mg/day for 6 months or> 10 mg/day for 1 year in order to prevent recurrence. **Relapse**: recurrence of symptoms and/or inflammatory parameters on laboratory findings, attributable to GCA, which required a sustained increase in treatment. Observation of aortitis on imaging was deemed to be a relapse only if the GCA symptoms and CRP levels increased.	One investigator	Descriptive statistics, Chi-square or Fisher exact test, Wilcoxon rank-sum test, Kruskal–Wallis test, Chi-square for trend	Nsp
Muratore et al. 2015(6)	GC and immunosuppressive requirements Relapse Complications	**Relapse**: reappearance of symptoms of GCA and/or PMR + increase in ESR and/or CRP. Isolated increase in inflammatory markers in the absence of other cause were considered relapses only if the treating rheumatologist increased the GC/immunosuppressive therapy with subsequent improvement **Sustained discontinuation of GC therapy**: at least 6 months	Nsp	Descriptive statistics, Wilcoxon rank sum test, chi-squared, Kaplan Meier and log-rank tests	Nsp
Schmidt et al. 2008(7)	eye complications mean GC dose duration of GC therapy Comorbidities/complications	**Eye complications**: amaurosis fugax and AION **Comorbidities/complications**: hypertension, peripheral arterial occlusive disease, stroke, myocardial infarction, aortic aneurysm, malignancy, osteoporosis, osteoporotic fractures)	Physician	Descriptive statistics, t-test, Mann–Whitney U-test, two-sided Fisher's exact test or the chi-square test, Logistic regression analysis	Nsp
Ghinoi et al. 2012(8)	Differences in clinical and laboratory profiles LVV prevalence	-	Nsp	Descriptive statistics, Fisher's exact test.	Nsp
Hamidou et al. 2005(9)	Laboratory and histopathological features Flare (primary and secondary) GC requirements Mortality Development of comorbid conditions	**Flare**: recurrence or worsening of symptoms associated with increasing inflammatory parameters attributed to GCA and requiring a change in the treatment. **Primary flares** were defined as flares under current GC therapy. **Secondary flares** occurred after treatment withdrawal	1 fellow	Descriptive statistics, Whitney rank test, chi-squared and Fisher's Exact Tests	Patients with Incomplete medical records, absence of medical follow up, absence of inflammatory cells in the arterial wall or with other diagnosis were excluded from analysis

Gonzalez-Gay et al. 2005(10)	Clinical features Delay to diagnosis Severe ischaemic manifestations Predictors of ischaemic complications	**Severe ischaemic manifestations**: - visual manifestations (transient visual loss including amaurosis fugax, permanent visual loss, or diplopia) - cerebrovascular accidents (stroke and/or transient ischaemic attacks) - jaw claudication - large-artery stenosis of the extremities that caused signs of occlusive manifestations (limb claudication) of recent onset	Nsp	Descriptive statistics, chi-square test, Fisher exact test, Student t test. Forward stepwise logistic regression with an entry p value of 0.20 (to obtain a predictive model of ischaemic complications)	Nsp

1.1.3 Supplementary Table 3. Disease patterns: intervention/treatments used

Study ID	Follow-up duration	Overall n	Intervention	Group 1	n	Group 2	n	Notes on treatment
Liozon et al 2003(1)	At least 2 months	151 (175* see comments in table D bellow)	Symptom assessment Laboratory workup	Cranial pattern	130	Silent GCA	21	Preestablished GC treatment protocol uniformly applied
Daumas et al. 2014(2)	Aortitis median 28 months [3-126] Without aortitis median 47 months [3-134]	63	Symptom assessment Laboratory workup Diagnostic imaging (CTA, FDG-PET)	With aortitis	26	Without aortitis	37	Mean GC dose at diagnosis on both groups 0,9 mg/kg/day (prednisone) Methylprednisolone pulses in 3 patients (2-3 days) due to AION Adjunctive treatment: Aspirin 75-160 mg/day, Clopidogrel

Espitia et al. 2012(3)	With aortitis Without aortitis Overall 94 months [7-83 years]	22	Symptom assessment CT scanning Treatment monitoring	With aortitis	10	With aortitis	12	Prednisone 0.7-1 mg/kg/day 3 daily IV methylprednisolone pulses (1 patient in each group)
Espitia et al. 2016(4)	GCA aortitis 34 months Isolated aortitis 34.5 months	326>117	Symptom assessment Diagnostic imaging (CT Scan or CDS)	GCA aortitis	73	Isolated Aortitis	44	Prednisone starting dose of 0.8 ± 0.2 mg/kg for GCA aortitis and 0.82 ± 0.2 mg/kg. 4 patients with IA did not receive therapy due to well controlled inflammation Adjunctive treatment: oral platelet aggregation inhibitors in 71.2% of GCA and 61.4% of IA. Statins in 23.3% of GCA and 34.1% of IA. MTX (13 GCA, 7 IA), AZA (7 GCA, 3 IA), IV CYC (5 GCA, 4 IA), TCZ (1 GCA, 2 IA), and anakinra (1 IA).
de Boysson et al. 2016(5)	No cranial pattern 30 [6–94] months Cranial pattern Missing data The same for both?	143	Symptom assessment Vascular biopsy FDG-PET/CT, CT-Angiography echocardiography+ LV CDS Treatment monitoring	No cranial pattern	31	Cranial pattern	112	Prednisone Adjunctive treatment: MTX, dapsone, CYC, AZA, anti-TNF-alfa
Muratore et al. 2015(6)	C-GCA 4.6 years LV- GCA 3.6 years	232	Symptom assessment Laboratory workup Diagnostic imaging using CTA, MRA, FDG-PET	C-GCA	212	LV-GCA	120	Prednisone Adjunctive treatment: MTX, AZA, Anti-TNF, MMF, CYC
Schmidt et al. 2008(7)	GCA without LV 59±33 months LV-GCA 40±25 months	106	Symptom assessment CDS Treatment monitoring	LV-GCA	53	GCA without LV	53	70 mg/day of prednisone in the first week with weekly dose reduction of 10 mg in the first 5 weeks. Only patients with eye involvement received doses of 250–1000 mg methylprednisolone I.V. for the first 3 days.
Ghinoi et al. 2012(8)	With LV-GCA Without LV GCA	62>35	Symptom assessment Laboratory workup	With LV-GCA	15	Without LV GCA	30	Glucocorticoid - Dosage missing

	Minimum ≥ 6 months for both		CDS evaluation (carotid, subclavian, axillary and proximal humeral arteries as well as the aortic arch, the abdominal aorta and its main branches (superior mesenteric artery, celiac tripod, proximal renal arteries and iliac arteries).					
Hamidou et al. 2005(9)	Cranial pattern Silent GCA Overall 54±15 [28–79 months]	58>50	Symptom assessment Laboratory workup TAB Treatment monitoring	Cranial pattern	27	Silent GCA	23	41% of the patients in the cephalic group and 39% in the silent group received 250–500 mg of intravenous methylprednisolone for 1–3 days at the beginning of the treatment, with initial daily doses of prednisone of 0.8±0.2 mg/kg per day and 0.8±0.1 mg/kg per day Adjunctive treatment: MTX, CYC, HCQ
Gonzalez-Gay et al. 2005(10)	With headache Without headache With PMR Without PMR At least 6 months	240	Symptom assessment Laboratory workup	With headache With PMR	203 96	Without headache Without PMR	37 144	initial prednisone dose 40–60 mg/day for 3–4 weeks or intravenous methylprednisolone [1 g daily for 3 days] followed by 60 mg/day for 3–4 weeks in most patients who had visual manifestations

1.1.4 Supplementary Table 4. Disease patterns: population characteristics and control and comparison (results of outcome assessment and other results of interest)

Study ID	Age	% females	Outcomes/results of interest	Results in group 1	Results in group 2	p-value
Liozon et al 2003(1)	Cranial pattern 75.6 ± 6.9 Silent GCA 74.3 ± 7.9	Cranial pattern 63.8 Silent GCA 66.7		<u>Cranial pattern</u>	<u>Silent GCA</u>	
			Delay in diagnosis, days, mean (range)	70 (4–350)	123 (30–360)	0.003
			Permanent visual loss	20 (15.4)	0	ns
			Other permanent ischaemic accidents	6 (4.6)	1 (5.6)	ns
			ESR, mm/h	89.3 ± 28.4	108.7 ± 23.8	0.002

			CRP, mg/l, (mean ± SD)	93.1 ± 59.2	136.5 ± 54.8	0.002
			Haptoglobin, mg/l, (mean ± SD)	4822 ± 1648	5267 ± 1556	ns
			Fibrinogen, mg/l, (mean ± SD)	6093 ± 1676	6939 ± 1982	ns
			Haemoglobin, g/dl, (mean ± SD)	11.46 ± 1.8	9.92 ± 1.25	<0.0001
			Platelet count, mm^3, (mean ± SD)	428 ± 135	440 ± 166	Nsp
			Albumin, mean ± SD	34.8 ± 5.8	30.7 ± 5.1	0.008
			Liver enzyme abnormalities	47 (45.2)	10 (47.6)	Nsp
Note: data was uniformly collected through a standardized survey applied since 1977. A third group (n=24) of patients with other clinical pictures, i.e., those with less than 2 cranial symptoms/signs and those with isolated polymyalgia rheumatica or upper limb artery involvement was created but excluded from the main outcome analysis. **Overall conclusions:** Patients with silent pattern have higher delay to diagnosis, more prominent inflammatory response with higher levels of CRP and ESR and lower levels of haemoglobin and albumin. There was an inverse correlation between CRP and haemoglobin, albumin and platelet count (respectively p=0.01, p<0.001, p=0.006). Ischaemic events where more frequent in the cranial group.						
Daumas et al. 2014(2)	Aortitis 66,8 [50–86] Without aortitis 73,8 [53–85]	Aortitis 76.9 Without aortitis 56.8		Aortitis	Without aortitis	
			Age	66.8 (50–86)	73.8 (53–85)	0.002
			Clinical features (definition in previous table)	-	-	ns
			Back ache (dorsal and lumbar)	3 (11.5)	0 (0)	0.002
			Vascular involvement of upper limbs	5 (19.2)	0 (0)	0.009
			ESR mm/h	95 (25–134)	80 (16–131)	0.034
			CRP mg/L	83.5 (19–200)	78.5 (8–360)	ns
			Fibrinogen, g/L	7.5 (4.7–10.5)	6,2 (2.08–12)	0.011
			Haemoglobin g/L	11.1 (7.9–14.3)	11.8 (9.2–16.2)	ns
			Platelets, G/L	426.8 (121–843)	395.6 (164–792)	0.002
			Lipid profile	-	-	ns
			Thoracic ectasia	2 (7.7)	na	na
			Abdominal ectasia	0(0)	na	na
			Thoracic aneurysm	2 (7.7)	na	na
			Abdominal aneurysm	0 (0)	na	na

			Relapse (n)	13	21	nsp
			Recurrence (n)	2	4	nsp
Note: additional imaging with FDG-PET-scan was performed in 20 patients (3 without aortitis and 17 with aortitis). Concerning the thoracic aorta, there was a good concordance between Angio-CT and PET, kappa ranging from 0.63 to 0.88, and 0.58 for abdominal aorta. For subclavian, carotid and iliac arteries kappa was 0.21, 0.34 and 0.34. When angio-CT was normal, PET did not add to the diagnosis. **Overall conclusions:** patients with aortitis were significantly younger, presented higher inflammatory markers, more dorsal/lumbar pain and upper limb involvement. Under GC, aortitis (angio-CT) regression was noted within 6 months in all patients though 80% still showed uptake on PET (without influencing treatment). Aortitis at diagnosis seems to associate with vascular complications as highlighted by the frequency of aortic aneurysm. Follow-up conclusions are limited due to different follow-up intervals between groups.						
Espitia et al. 2012(3)	With aortitis 76 ± 5.26 Without aortitis 72 ± 8.37	With aortitis 80 Without aortitis 75	N (%)	With aortitis	Without aortitis	
			Relapse (at least 1)	6 (60)	3 (27)	ns
			Multiple relapses	5 (50)	0 (0)	0.012
			Aortic complications	3 (30)	1 (9)	ns
			Thoracic aortic dissection	1 (10)	0 (0)	ns
			Ruptured abdominal aortic aneurysm	1 (10)	0 (0)	ns
			Uncomplicated abdominal aortic aneurysm	1 (10)	1 (9)	ns
			Stage III/VI obliterating arteriopathy	4 (40)	1 (9)	ns
			Stroke	4 (40)	0 (0)	0.03
			Coronary artery disease	2 (20)	1 (9)	ns
			GC discontinuation	2 (20)	8 (66)	0.04
			Mortality	7	5	ns
			Vascular cause of death	5*	0	0.027
*Causes of death where rupture of abdominal aortic aneurysm, dissection of thoracic aortic aneurysm, stroke, stage IV obliterating arteriopathy, coronary artery disease with congestive heart failure **Overall conclusion:** patients with initial aortitis were more susceptible to relapses and received more prolonged GC treatment. There were no differences regarding mortality nor survival rates (log rank: p=0.82) but significant differences were found for vascular cause of death (limited n).						
Espitia et al. 2016(4)	GCA aortitis 70 [52–83]	GCA aortitis	Age	GCA aortitis 70 [52–83]	Isolated aortitis 65.0 [37–87]	

	Isolated aortitis 65.0 [37–87]	57 (78.1) Isolated aortitis 28 (63.6)				0.0003
			Ever smoker	11 (15.1)	19 (43.2)	0.0007
			Aortic events n (%)			
			Aneurysm	19 (26.0)	22 (50.0)	0.008
			Ectasia	3 (4.1)	2 (4.5)	ns
			Dissection	6 (8.2)	6 (13.1)	ns
			Stenosis	0 (0)	1 (2.3)	ns
			Surgery	10 (13.7)	16 (36.4)	0.004
			Aortic event free survival			
			Free of aortic aneurism survival (58 GCA, 27 IA)	-	-	0.009
				-	-	0.02
			Free of aortic surgery survival (65 GCA, 36 IA)	-	-	ns
			Free of aortic dissection survival (68 GCA, 41 IA)			
Overall conclusions: No differences in between groups regarding biological parameters (mean CRP, ESR, fibrinogen, albumin, haemoglobulin, platelets), location of aortic involvement nor CV risk factors, exception to ever smoker – see above. Aortic aneurysms where significantly more frequent in patients with isolated aortitis as well as aortic surgery. Survival free of aortic events (not present at diagnosis) was better in GCA. Overall outcome was better in GCA than IA. Sub analysis: As IA ≥ 60 years old may overlap with GCA-related aortitis, these groups where compared for the same variables. No significant differences were found with exception to aortic involvement in aneurysm form, 15 (20.5) in GCA and 14 (48.3) in IA p=0.005						
de Boysson et al. 2016(5)	No cranial pattern 69 [50–85] Cranial pattern 71 [53–86]	No cranial pattern 21 (68) Cranial pattern 73 (65)		No cranial pattern	Cranial pattern	
			Vascular biopsy (positive TAB – other biopsy)	20/28 (71) - 3/3	64 (57) - /-	ns - /-
			LVV on imaging	19 (61)	42 (38)	0.02
			FDG-PET/CT	16/19 (84)	26/49 (53)	0.03
			CT-Angiography	10/23 (43)	14/66 (21)	0.04
			Echocardiography + LV Doppler	4/16 (25)	7/43 (16)	ns
			GC dependent disease	Missing data on text	41 (37)	ns

			Relapse	12 (39)	67(60)	0.04
			Mortality (n)	12	12	ns
Note: Cranial manifestations where present only in the cranial group and helped define the study groups. Extracranial manifestations (PMR, vascular bruits and limb claudication) where present in both groups with no significant differences in between them. **Overall conclusions:** patients without cranial symptoms display lower CRP (68 [9–250] vs 120 [3–120] p=0.0054), Higher rates of large vessel involvement on imaging and lower relapse rates. No differences in mortality. Sub analysis: using clinical and imaging the authors further divided the patients in 4 subgroups (1 Isolated cranial manifestations, 2 isolated LV, 3 cranial and LV, 4 No cranial symptoms and no LV involvement): lower CRP in isolated LV and more fever in Isolated cranial. No other differences were found, namely concerning relapse rates.						
Muratore et al. 2015(6)	C-GCA 75.7 ± 7.4 LV-GCA 68.2 ±7.5	C-GCA 153 (72) LV-GCA 96 (80)		C-GCA	LV-GCA	
			Age	75.7 (SD. 7.4)	68.2 (SD: 7.5)	<0.001
			Time from symptom onset to diagnosis, median (IQR) months	2.2 (1.2, 3.7)	3.5 (2.0, 7.2)	<0.001
			History of PMR prior to GCA diagnosis, n (%)	31 (15)	31 (26)	0.012
			Relapse rate per 10 person-years, median (95% CI)	3.0 (2.6-3.4)	4.9 (4.2-5.6)	<0.001
			Time to first relapse, median (95% CI)	1.2 (1.0-1.7)	0.8 (0.6-1.1)	0.006
			Cumulative GC dose at 1 year, mean (SD), g	9.1 (3.7)	11.4 (5.9)	<0.001
			Patients starting any immunosuppressive drug 1, 2 and 5 years, median (95% CI)	8 (4-12), 14 (8-20), 16 (10-22)	32 (22-42), 46 (36-56), 57 (45-69)	<0.001
			Rate of development of aortic aneurysm after GCA diagnosis, KM method, median (95% CI), % at 1, 2 and 5 years	2 (0-4), 2 (0-4), 3 (0-7)	8 (2-14), 9 (3-15), 15 (7-23)	0.005
Note: LV involvement was not exclusive, 52% of patients in LV-GCA cohort had positive TAB. Asymptomatic LV involvement may be present in C-GCA group since only 33% underwent imaging. **Overall conclusions:** Follow up duration was significantly (p=0.044) higher in C-GCA. LV- GCA patients were younger at diagnosis, had longer duration of symptoms prior to diagnosis and were more likely to have a previous (>6 months prior) diagnosis of PMR. C-GCA presented more cranial symptoms and LV-GCA presented more extracranial symptoms and physical examination abnormalities, with exception to abnormal temporal pulse, more frequent in C-GCA. LV-GCA was more likely and quicker to relapse than C-GCA and						

presented higher cumulative GC dose at 1 year and need for further immunosuppressive therapy. Median time to reach a daily dose of prednisone <10 mg (1.2 vs 0.9 years, log-rank P<0.001) and to discontinue GC therapy (4.5 vs 2.2 years, log-rank P<0.001) was significantly longer in LV-GCA. Prevalence of aortic aneurysm during follow-up was significantly higher in patients with LV-GCA.						
Schmidt et al. 2008(7)	GCA without LV 72 LV-GCA 66	GCA without LV 64 LV-GCA 83	Eye complications % AION Amaurosis fugax	<u>LV-GCA</u> 0 4	<u>GCA without LV</u> 0 6	 - ns *
			Comorbidities/complications %	-	-	ns *
			Mean GC dose (mg/day)	4.4	3.2	ns *
			Mean duration of GC therapy months	36	48	ns *
*p value adjusted for sex, age and duration of follow-up. **Overall conclusions:** No significant differences were found between groups, but there was a trend towards more peripheral occlusive disease in the LV group. Follow up was significantly longer in the GCA without proximal arm vasculitis. There were no differences in mean dosage nor duration of therapy with GC.						
Ghinoi et al. 2012(8)	With LV-GCA 71 Without LV GCA 72	With LV-GCA 100 Without LV GCA 73.3	PMR % Any cranial manifestations % Headache, visual loss, systemic manifestations % Jaw claudication % ESR mm/ first hour CRP mg/dl Diabetes mellitus, Hypercholesterolemia, Hypertension %	<u>With LV-GCA</u> 53 73 60, 13, 60 13 90 5.9 7, 13, 43	<u>Without LV GCA</u> 43 97 83, 20, 43 43 67 5.5 7, 36, 54	 ns 0.036 All ns 0.05 0.015 ns ns, ns, ns
Overall conclusions: Patients with LV-GCA where more frequently female, presented less cranial manifestations and jaw claudication and presented higher ESR. There were no differences in comorbidities nor complications, including visual loss. Prevalence of LV-GCA was 29%.						
Hamidou et al. 2005(9)	Cranial pattern 74.5±6.2	Cranial pattern 66.67	ESR (mm/h) CRP, mg/l (mean±SD)	<u>Cranial pattern</u> 70±33 (21) 86±61 (24)	<u>Silent GCA</u> 87±25 (16) 133±95 (23)	 ns <0.05

	Silent GCA 74.8±7.9	Silent GCA 82.6	Fibrinogen, Haptoglobin, Orosomucoid, Elevated liver enzymes	-	-	All ns
			Haemoglobin, g/dl (mean±SD)	11.2±1.8 (19)	10.3±1.3 (17)	ns
			Platelet count, mm3 (mean±SD)	373±148 (24)	474±170 (23)	<0.05
			Albumin, g/L	32.1±5.6 (20)	28.5±5.2 (16)	<0.05
			Mortality %	11	17	ns
			Free of GC %	44	57	ns
			Duration of GC treatment, months	51±15	49±14	ns
			Need for other immunosuppressant, n	4	0	-
			Primary flare (n=38), %	35	6	ns
			Secondary flare (n=34), %	41	18	ns
Overall conclusions: Patients with silent GCA had higher levels of CRP and platelet counts and lower levels of and albumin. There were no differences in the frequency of flares nor GC requirements nor mortality rates. In the cranial group, 4 patients needed further immunosuppressant therapy vs none in the silent GCA.						
Gonzalez-Gay et al. 2005(10)	With headache 74.7 ± 6.7 Without headache 75.2 ± 6.9	With headache 53.2 Without headache 59.5		With headache	Without headache	
			Delay to diagnosis (mean ± SD), weeks	9.2 ± 9.9	16.6 ± 15.0	<0.001
			Scalp tenderness	79 (38.9)	2 (5.4)	<0.001
			Constitutional Syndrome	123 (60.6)	23 (62.2)	ns
			Abnormal temporal arteries	162 (79.8)	13 (35.1)	<0.001
			Jaw claudication	88 (43.3)	10 (27.0)	ns
			Visual manifestations	49 (24.1)	7 (18.9)	ns
			Permanent visual loss	26 (12.8)	5 (13.5)	ns
			Cerebrovascular accidents	3 (1.5)	3 (8.1)	0.049
			Limb claudication of recent onset	5 (2.5)	1 (2.7)	ns

1.1.5 Disease patterns: Risk of bias assessment (Newcastle-Ottawa scale for cohort studies)

	With PMR 73.4 ± 6.3 Without PMR 75.6 ± 6.9	With PMR 60.4 Without PMR 50	Delay to diagnosis (mean ± SD), weeks	With PMR 13.4 ± 12.2	Without PMR 8.3 ± 10.0	<0.001
			Scalp tenderness	32 (33.3)	49 (34.0)	ns
			Constitutional Syndrome	58 (60.4)	88 (61.1)	ns
			Abnormal temporal arteries	65 (67.7)	110 (76.4)	ns
			Jaw claudication	40 (41.7)	58 (40.3)	ns
			Visual manifestations	15 (15.6)	41 (28.5)	0.021
			Permanent visual loss	10 (10.4)	21 (14.6)	ns
			Cerebrovascular accidents	4 (4.2)	2 (1.4)	ns
			Limb claudication of recent onset	3 (3.1)	3 (2.1)	ns
			Predictors of severe ischaemic disease OR, 95% CI			
			Abnormal temporal artery	2.25, 1.23–4.12		0.009
			Anaemia (haemoglobin <12 g/dL	0.53, 0.30–0.94		0.030
Overall conclusions: comparison of pts with headache vs no headache at presentation: no differences in age and sex. Patients without headache had significantly higher delay to diagnosis, less scalp tenderness and abnormal temporal arteries, presented more frequently with PMR and had more cerebrovascular accidents. With PMR vs without PMR: patients with PMR were significantly younger, had higher delay to diagnosis, less headache and visual manifestations. Abnormal temporal artery was the best positive predictor of severe ischaemic manifestations and anaemia was a negative (protective) predictor. Other notes: differences between 18 patients with subclinical GCA and the remaining 222. Subclinical GCA patients had higher delay to diagnosis (16.3 ± 15.0 vs 9.9 ± 10.7 p=0.018) and lower haemoglobin levels (11.0 ± 1.5 vs 11.8 ± 1.6 P= 0.030). Patients younger than 70 years had higher delay to diagnosis (p=0.035), more PMR (p=0.009) and higher phosphatase alkaline levels (p=0.002)									

Study ID	**Selection** 1)Representativeness of exposed cohort	**Selection** 2)Selection of the non exposed cohort	**Selection** 3)Ascertainment of exposure	**Selection** 4)Demonstration that outcome of interest was not present at start of study	**Comparability** 1)Comparability of cohorts on the basis of the design or analysis	**Outcome** 1)assessment of outcome	**Outcome** 2)Was follow-up long enough for outcomes to occur	**Outcome** 3)Adequacy of follow up of cohorts	**Total n of stars** (only comparability can have two *)

Daumas et al. 2014(2)	*	*	*	Nsp	Nsp	Not blinded	*	No statement	4
Espitia et al. 2012(3)	*	*	* data collected using standardized form and interviews	Nsp	Nsp	Not blinded	*	*	5
Espitia et al. 2016(4)	*	*	Na	*	Nsp	Not blinded	*	No statement	4
de Boysson et al. 2016(5)	*	*	* computerized patient record	*	Nsp	Not blinded	*	No statement	5
Muratore et al. 2015(6)	nsp	No description	*used an electronic clinical notes search tool	No	Nsp	Not blinded	*	No statement	2
Schmidt et al. 2008(7)	*	*	* charts reviewed using a predefined protocol and completed with interviews	*	**	Not blinded	*	Imaging follow up less than 80% in the GCA without LV	8
Ghinoi et al. 2012(8)	*	*	Nsp	No	Nsp	Only US evaluation was blinded	*	No statement	3
Liozon et al 2003(1)	*	*	* predefined questionnaire	No	Nsp	Not blinded	Not clear	No statement	3
Hamidou et al. 2005(9)	*	*	* charts reviewed using a predefined protocol	*	Nsp	Not blinded	*	*	6
Gonzalez-Gay et al. 2005(10)	*	*	other	No	*adjusts for CV factors	Not blinded	Not clear	No statement	3

2. FAST-TRACK CLINICS/PATHWAY

2.1 OBSERVATIONAL STUDIES (fast-track clinics)

2.1.1 Supplementary Table 6. Evidence retrieved for fast-track clinics/pathway for giant cell arteritis: overview of included studies

Study ID	Study design	LoE	Overview	Inclusion criteria	Exclusion criteria	End of follow-up for analysis
Suspected GCA						
Fast track pathway						
Patil et al. 2015(11)	Retrospective longitudinal cohort Single center	2b	Fast track pathway (FTP) approach influence on reducing permanent sight loss	Suspected GCA	nsp	FTP – January 2012 to December 2013 Conventional pathway – from January 2009 to December 2011
Diamantopoulos et al. 2016(12)	Retrospective longitudinal cohort Single center	2b	Fast track clinic (FTC) implementation influence on reducing permanent visual impairment, and its cost-effectiveness	Patients with ≥ 50 years + new-onset GCA (diagnosed based on positive US examination of temporal arteries and/or large vessels and/or a positive biopsy of the temporal artery and clinical signs of GCA)	nsp	April 2010 and October 2014 FTC was implemented in March 2012

2.1.2 Supplementary Table 7. Fast-track clinics/pathway: outcome definition and statistical analysis

Study ID	Outcome/endpoint	Definition of outcome	Validation of outcome	Notes on analysis	Censoring at event
Patil et al. 2015(11)	Permanent visual impairment – sight loss Time from symptom to diagnosis	Nsp	Rheumatologist	Descriptive statistics, Student's *t*-tests, Mann-Whitney U-test, chi-square test or Fisher's exact test, Multivariate backward logistic regression analysis	Nsp

Diamantopoulos et al. 2016(12)	Transient visual loss Permanent visual loss Inpatient days Cost reduction	Permanent visual impairment was defined as total visual loss in one or both eyes Cost of an inpatient day was calculated according to the cost reported by the Norwegian Ministry of Finance in 2013	Nsp	Descriptive statistics, t-test chi-square test or Fisher's exact test, Wilcoxon signed-rank test	Nsp

2.1.3 Supplementary Table 8. Fast-track clinics/pathway: intervention/treatments used

Study ID	Follow-up duration	Overall n	Intervention	Group 1	n	Group 2	n	Notes on Treatment
Patil et al. 2015(11)	-	113	Referral pathway Symptom assessment Temporal, axillary CDS TAB	GCA Conventional	46	GCA FTP	67	Pre-defined referral and treatment protocols
Diamantopoulos et al. 2016(12)	-	75	Symptom assessment Laboratory workup Temporal, axillary and common carotid arteries CDS TAB	GCA conventional	32	GCA FTC	43	Pre-defined referral and treatment protocols

2.1.4 Supplementary Table 9. Fast-track clinics/pathway: population characteristics and control and comparison (results of outcome assessment and other results of interest)

Study ID	Age	% females	Outcomes/results of interest	Group 1	Group 2	p-value
Patil et al. 2015(11)	GCA conventional 75.4 (±7.6) GCA FTP	GCA conventional 71.7 GCA FTP	Time from symptoms to diagnosis (days, range)	GCA conventional 21 (1-196)	GCA FTP 17.5 (0–206)	ns

	74.1 (±7.6)	77.6	Permanent visual impairment n (%), OR, CI*	17 (37.0)	6 (9.0)	OR 17 (0.06-0.47) p=0.001
			Variables associated with visual impairment OR, CI	Multivariate analysis		
			Age	OR 1.16, (95%CI 1.04-1.27)		0.005**
			Male sex	OR 3.49 (95%CI 0.82-14.8)		0.09**
			Scalp tenderness	0.13 (95%CI 0.03-0.54)		0.005**
			Haemoglobin	0.64 (95%CI 0.4–1.01)		0.053**
*Visual impairment was caused by central artery occlusion in 2 patients, in all other patients AION was the cause of sight loss. **none of these factors altered the association between FTP and sight loss [OR 0.08 (95% CI 0.02–0.34), *p*=0.001]. Sensitivity analyses also did not change the primary result. **Overall results:** FTP implementation led to a significant reduction in permanent visual impairment and reduction of time from symptoms to diagnosis.						
Diamantopoulos et al. 2016(12)	GCA conventional 74 (71-78) GCA FTC 72 (70-75)	GCA conventional 75 GCA FTC 58.1	Transient visual disturbances (n)	GCA conventional 9	GCA FTC 9	RR (95% CI), p-value 0.74 (0.33,1.66), Nsp
			Permanent visual impairment (n)	6	1	0.12 (0.01,0.97), 0.01
			Inpatient days of care	3.6	0.60	NA, <0.0005
			Cost reduction - Daily inpatient cost in the Norwegian Hospitals was calculated to be 12 433, implementation of the FTC reduced the cost of inpatient care by ~37 300 NOK per patient (total reduction for 42 GCA FTC was 1 566 558 NOK (~185 000 Euros).			
Note: all patients suffered from visual disturbances before GC introduction **Overall results:** Number of patients with visual disturbances was equal in both groups but permanent impairment was more frequent in conventional group. FTC helped reduce permanent visual impairment and seems to be cost effective.						

2.1.5 Supplementary Table 10. Fast-track clinics/pathway: risk of bias assessment (Newcastle-Ottawa scale for cohort studies)

Study ID	Selection 1)Representativeness of exposed cohort	Selection 2)Selection of the non exposed cohort	Selection 3)Ascertainment of exposure	Selection 4)Demonstration that outcome of interest was not present at start of study	Comparability 1)Comparability of cohorts on the basis of the design or analysis	Outcome 1)assessment of outcome	Outcome 2)Was follow-up long enough for outcomes to occur	Outcome 3)Adequacy of follow up of cohorts	Total n of stars (only comparability can have two *)
Patil et al. 2015(11)	*	*	Case records	No→ visual loss?	Nsp	Not blinded	Nsp	No statement	2
Diamantopoulos et al. 2016(12)	*	*	Clinical records	No → visual loss?	Nsp	Not blinded	Nsp	No statement	2

3. ROLE OF BIOPSY

3.1 OBSERVATIONAL/INTERVENTIONAL* STUDIES (Role of biopsy)

3.1.1 Supplementary Table 11. Evidence retrieved for the role of biopsy for giant cell arteritis: overview of included studies

Study ID	Study design	Level of evidence	Overview	Inclusion criteria	Exclusion criteria	End of follow-up for analysis
GCA						
Histology						
Prospective						
Hernandez-Rodrigue	Prospective cohort Single center	2b	Validation of histological scoring system and clinical-histological correlation	biopsy-proven GCA fulfilling ACR criteria	Patients with biopsies with inflammation limited to	1992 to 2012

z et al. 2016(13)					small vessels surrounding a spared temporal artery Note: GC therapy prior to TAB was not as exclusion factor, in fact 25 patients had 1mg/kg/day for 7-28 days prior to TAB	
Maleszewski et al. 2017(14)	Prospective Cohort Single center (*)	2b	Histological features changes over time, under GC therapy	GCA diagnosis made at enrolling center	nsp	2004-2010
Luqmani et al. 2016 (15)	Prospective cohort Multicentric (*)	1b	Evaluation of diagnostic accuracy and cost-effectiveness of US compared to TAB or US combined with TAB for the diagnosis of GCA	Newly suspected GCA	Previous GCA diagnosis High dose GC for more than 1 month within the previous 3 months	June 2010 to December 2013
Retrospective						
Armstrong et al. 2008(16)	Retrospective cohort Single center	2b	Investigated the prognostic role of giant cells on biopsy.	biopsy proven GCA	nsp	1994 to 2004
Breuer et al. 2013(17)	Retrospective cohort Single center	3b	Correlation between histopathological parameters and clinical features and disease outcomes	GCA (1990 ACR criteria) + favorable rapid response (within 3 days) to GC therapy + absence of any medical condition explaining their symptoms during a follow-up of 6 months.	Follow up inferior to 12 months GC therapy prior to TAB	Nsp
Cavazza et al. 2014(18)	Retrospective Cohort Single center	3b	Correlation between histopathological parameters and clinical and laboratorial features	Biopsy proven GCA	nsp	January 1st 1986 to December 31st 2013
Chatelain et al. 2009(19)	Retrospective Cohort Multicentric	3b	Analysis of histological features predictive of permanent visual loss (PLV)	All patients had to fulfil criteria 1, 2 and 3. Patients included in the positive biopsy GCA group had to have criterion 4. Patients included in the negative biopsy group had to fulfil two	Pure PMR, current malignant diseases, current infectious diseases, other inflammatory or vasculitis disease, rheumatoid	January 1991 to ?

				criteria from criteria 5, 6,7, 8 and 9. Criterion 10 could be present, or not Criterion 1: age over 50. Criterion 2: erythrocyte sedimentation rate (Westergren method) above 40 mm (except for a few cases with typical symptoms, for whom TAB was positive on microscopic examination). Criterion 3: clinical response to GC therapy within 72 h (disappearance of fever and pain). Criterion 4: positive TAB. Criterion 5: clinically abnormal temporal artery Criterion 6: visual disturbances including those occurring during the first week of treatment. Criterion 7: jaw claudication. Criterion 8: headache, temporal headache, facial pain or sensation of facial swelling. Criterion 9: systemic symptoms Criterion 10: polymyalgia rheumatica.	arthritis, systemic lupus erythematosus and polyarteritis nodosa	
Kaiser et al. 1998(20)	Retrospective case control	4	Evaluates the relation between intima hyperplasia and in situ production of platelet derived growth factor (PDGF) and ischaemic complications	GCA fulfilling ACR criteria + positive biopsy Control specimens: from patients who did not have clinical evidence of PMR.	nsp	Nsp
Makkuni et al. 2008(21)	Retrospective series Single center	4	Evaluation of intimal hyperplasia degree with neuro-ophthalmic complications	Biopsy proven GCA	nsp	2000-2006
Muratore et al. 2016(22)	Retrospective population based cohort Single center	2b	Evaluated correlations of histopathological features of positive TAB with clinical manifestations/complications and evaluated possible complications predictors	Positive histological findings + GCA diagnosis No mention to ACR criteria	Incomplete medical records	January 1st 1986 to December 31st 2013

Quinn et al. 2012(23)	Retrospective Cohort Single center	3b	Evaluated whether a TAB is required in all cases of suspected GCA, and in which cases may be omitted	Suspected GCA patients + TAB	nsp	January 1990 to December 2010
Ter Borg et al. 2007(24)	Retrospective cohort Single center	3b	Evaluates the relation between histological defined features, clinical features and outcomes	Biopsy proven GCA fulfilling ACR criteria	nsp	1st June 1991 to 1st November 1998
Schmidt and Loffler 1994(25)	Retrospective cohort Single center	3b	Evaluates relation of the presence of giant cells with visual disturbances	Not clearly stated GCA diagnosis	nsp	January 1st 1982 to December 31st, 1991
Ypsilantis et al. 2011(26)	Retrospective cohort Multicentric	3b	Association between specimen length and diagnostic sensitivity of TAB	Not clearly stated GCA diagnosis	nsp	2004-2009
Muratore et al. 2016(27)	Retrospective Cohort Single center	2b	Role of histopathological features of negative TAB in differentiating GCA from non-GCA patients	Suspected GCA who underwent TAB	nsp	January 2009 to June 2014
Achkar et al 1994 (28)	Retrospective Case series Single center	4	Evaluates how previous GC influences TAB results	Patient with suspected arteritis with biopsy done Only 73% fulfilled ACR criteria	Unavailable records, unavailable slides, systemic non-giant cell arteritis, juvenile age, temporal arteritis with dissection and first temporal artery biopsy done at the Mayo Clinic before 1st January 1988	1st January 1988 to 31st December 1991

3.1.2 Supplementary Table 12. Role of biopsy: outcome definition and statistical analysis

Study ID	Outcome/endpoint	Definition of outcome	Validation of outcome	Notes on analysis	Censoring at event

Hernandez-Rodriguez et al. 2016(13)	Histological pattern validation and correlation with clinical features	**Histological scoring as follows:** (1) Adventitial pattern: inflammatory cells restricted to the adventitia, with preservation of media and intima (2) Adventitial invasive pattern: adventitial infiltration was followed by local invasion of the muscular layer, with integrity of the intima (3) Concentric bilayer pattern: inflammatory cells infiltrating the adventitia and the intima (or the intima/media junction), with a preserved media (4) Panarteritic pattern: inflammatory infiltrates were distributed through the 3 arterial layers (1) and (2) = Mild infiltrative pattern (3) and (4) = Extensive infiltrative pattern Other findings: giant cells, granuloma, intimal hyperplasia, overlap with other patterns	4 investigators blinded to clinical data and 2 external investigators	Descriptive statistics, chi-square or Fisher exact tests, Student's unpaired t-test	Nsp
Maleszewski et al. 2017(14)	Histological changes at 3,6,9 and 12 months from diagnosis	**Histological features** monitored included (1) medial inflammation; (2) vascular remodeling; (3) adventitial/peri-vasa vasorum inflammation; (4) intimal inflammation.	Pathologist	Descriptive statistics, Fisher exact tests, Kruskall-wallis	Nsp
Luqmani et al. 2016 (15)	Sensitivity and specificity of US and TAB Cost-effectiveness analysis	Sensitivity analysis Specificity analysis Cost-effectiveness analysis took into account: the different costs of the tests or strategies; different proportions of false negatives and false positives; cost and health-related quality-of-life impact of a false negative; cost and health-related quality-of-life impact of a false positive.	Pathologist Sonographer	Sensitivities and specificities calculated for TAB and US in comparison with the gold standard reference diagnosis (to be confirmed at follow-up based on ACR classification criteria), kappa statistic, McNemar's test, two-way random-effects analysis of variance to estimate the intraclass correlation coefficients for agreement with 95% Cis. Ultrasonographer and pathologist blinded for reference diagnosis	Impossibility to perform US and TAB within 7 days of GC start
Armstrong et al. 2008(16)	Clinical course Blindness	**Relapse** was considered to include those events where GC therapy was reinstituted due to return of clinical symptoms or increased sedimentation rate	pathologist	Descriptive statistics, t-test, Wilcoxon rank-sum test, qui-square, Fisher's exact test	Nsp

	GC requirements Relapse				
Breuer et al. 2013(17)	Clinical features correlation Complications GC requirements Flares	**Complications**: ischaemic manifestations included vision loss, transient vision loss and stroke. **Flares**: signs or symptoms related to GCA, occurring during therapy or following cessation of therapy, and resulting in a dose increment of prednisone or resumption of GC therapy	pathologist	Descriptive statistics, linear regression, Fisher exact test, survival curves	Nsp
Cavazza et al. 2014(18)	Clinical features correlation GC requirements	nsp	pathologist	Descriptive statistics, Kruskal-Wallis or Mann-Whitney U tests and chi square tests or Fisher exact test	Samples deemed inadequate or negative histological findings were recut and reanalyzed and included in analysis only if positive. Some patients were later excluded given a diagnosis reclassification (5 ANCA associated vasculitis, PN, amyloidosis)
Chatelain et al. 2009(19)	Permanent visual loss	nsp	Two senior pathologists	Descriptive statistics, chi square test or Fisher exact test, Wilcoxon rank sum test, logistic regression	Nsp
Kaiser et al. 1998(20)	Ischaemic complications PDGF relation to intimal hyperplasia	**Ischaemic complications**: ocular symptoms, jaw claudication, stroke, transit cerebral ischaemia, aortic arch syndrome	Nsp	Nsp	Nsp
Makkuni et al. 2008(21)	Neuro-ophthalmic complications (NOC)	**NOC**: decrease in visual acuity, complete/ sectoral visual loss, anterior ischaemic neuropathy (AION), constriction of visual fields and cerebral infarcts	2 micropathologists	Descriptive statistics, Mantel–Haenszel test stratified for sex.	Nsp
Muratore et al. 2016(22)	Clinical features relation to histology Cranial ischaemic events	**Cranial ischaemic events (CIEs):** jaw claudication, visual manifestations (amaurosis fugax, permanent visual loss and diplopia) and CVAs (stroke and transient ischaemic attacks);	Pathologist	Descriptive statistics, t-test or Mann- Whitney test, chi-square or Fischer's exact test, logistic regression model	Patients without comprehensive information about clinical and laboratory

					manifestations were not analyzed
Quinn et al. 2012(23)	Complications Sensitivity and specificity	Nsp	Nsp	Descriptive statistics, Chi square, Student t test, multivariate analysis	Nsp
Ter Borg et al. 2007(24)	Clinical and laboratorial features relation to histology GC requirements Reactivation of disease Recurrence	**Reactivation**: recurrence of clinical symptoms and/or an increase in inflammatory parameters (ESR/CRP) during treatment with GC, which required an increase in its dosage of ≥25%, with a minimum of ≥5 mg a day **Recurrence**: new onset of clinical symptoms and/or increase in inflammatory parameters, which required retreatment with GC (≥5 mg/ day) after this agent was stopped previously.	pathologist	Descriptive statistics, Mann–Whitney U test	Nsp
Schmidt and Loffler 1994(25)	Visual disturbances	**Visual disturbances:** anterior ischaemic optic neuropathy, central retinal artery occlusion, third cranial nerve involvement	nsp	Fisher's exact test	Nsp
Ypsilantis et al. 2011(26)	TAB sensitivity in relation to specimen length	nsp	nsp	Descriptive statistics, multivariate analysis, ROC analysis, Kruskal-Wallis test	Nsp
Muratore et al. 2016(27)	Histopathological features of negative TAB GCA patients	Positive TAB was considered when features of transmural inflammation as well as inflammation restricted to the adventitial or periadventitial tissue was identified. Histopathologic features evaluated included: presence of a mediointimal scar (with focal disappearance of the internal elastic lamina, medial attenuation (localized medial scar with focal disappearance of the media, but with preservation of the IEL), intimal hyperplasia, fragmentation of internal elastic lamina, calcification, adventitial fibrosis, and neoangiogenesis.	Rheumatologist Pathologist	Descriptive statistics, Mann-Whitney U chi-square test or Fisher's exact test	Inadequate samples and positive biopsy patients were not included in the analysis
Achkar et al 1994 (28)	TAB results in relation to GC treatment	Negative TAB: no evidence of arteritis Positive TAB: histologic evidence of arteritis. Within positive results: typical temporal arteritis (granulomatous arteritis with one or more giant cells present in a cross section of the artery and inflammatory infiltrate is a mixed cell type with mononuclear cells) OR atypical temporal arteritis (presence of	Pathologist blinded to clinical a laboratory and histology data	Descriptive statistics, Kappa statistics for reliability, chi-square or fisher exact test, logistic regression analysis, stepwise method to develop a logistic model with a $p<0.05$ entry value	Nsp

		inflammation consistent with giant cell arteritis, but with atypical features such as the absence of giant cells or the occurrence of the inflammatory infiltrate mainly in the adventitia rather than in the media).	reviewed all slides		

3.1.3 Supplementary Table 13. Role of biopsy: intervention/treatments used

Study ID	Follow-up duration	Overall n	Intervention	Group 1	n	Group 2	n	Note on Treatment
Hernandez-Rodriguez et al. 2016(13)	Nsp	285	Symptom assessment TAB	Mild infiltrative pattern	37	Extensive infiltrative pattern	248	Prednisone at physician discretion
Maleszewski et al. 2017(14)	3-12 months minimum	40	Histology review	GCA patients with 1st positive biopsy that accepted to undergo 2nd biopsy			40	Standardized initial GC dosage, weaning at physician's discretion
Luqmani et al. 2016 (15)	Minimum 6 months	430>381	TAB US	Suspected GCA included for primary analysis			381	Nsp
Armstrong et al. 2008(16)	Nsp	92	Symptom assessment Histology review	With giant cells	76	Without giant cells	16	Treatment based on GC, no mention to adjunctive treatment.
Breuer et al. 2013(17)	Minimum 12 months	70	Symptom assessment Laboratory workup Histology review	Biopsy positive	65	Biopsy negative	5	Treatment scheme Nsp
		65		With ischaemic manifestations	19	Without ischaemic manifestations	46	

Cavazza et al. 2014(18)	Nsp	871 screened 317 analyzed	Symptom assessment Laboratory workup Histology review	For this analysis 4 groups were created Small Vessel Vasculitis (SVV) n= 27 Vasa Vasorum Vasculitis (VVV) n=19 Inflammation Limited to Adventitia (ILA) n=18 Transmural Inflammation (TMI) n=253				Treatment scheme Nsp. Note that patients were on prednisone for a mean of 12 ± 6.45 days before TAB
Chatelain et al. 2009(19)	Mean 4 years of follow-up	391	Symptom assessment Laboratory workup Histology review	With PVL	29	Without PVL	362	Nsp
Kaiser et al. 1998(20)	Nsp	40	Symptom assessment Histology review Immunochemistry analysis	Moderate to severe intimal hyperplasia	20	Minimal or no intimal hyperplasia	20	Nsp
Makkuni et al. 2008(21)	Nsp	30	Symptom assessment Histology review	With NOC	12	Without NOC	18	Nsp
Muratore et al. 2016(22)	Nsp	299screened 274 analyzed	Symptom assessment Histology review	Patients with Transmural Inflammation or Inflammation Limited to Adventitia			274	Nsp
Quinn et al. 2012(23)	Nsp	176 patients 182 biopsies	Symptom assessment Histology review	Positive biopsy	58	Negative biopsy	124	Nsp
Ter Borg et al. 2007(24)	Not clear most patients had at least 2 years	44	Symptom assessment Histology review	Group 1: classical giant-cell arteritis n=23 Group 2: atypical giant-cell arteritis n=14 Group 3: healed arteritis n=7 Group definition (1) classical giant-cell arteritis (dense chronic inflammation with giant cells; (2) atypical giant-cell arteritis (less dense chronic inflammation, occasional giant cells; (3) healed arteritis (focal areas of chronic inflammation, no giant cells;				Standardized treatment protocol

Schmidt and Loffler 1994(25)	10 years	85	Symptom assessment Histology review	Without giant cells	42	With giant cells	43	Standardized treatment protocol
Ypsilantis et al. 2011(26)	Not clear	966 screened 956 analyzed	Symptom assessment Histology review	Number of patients with adequate biopsy Positive biopsies			956 207	Nsp
Muratore et al. 2016(27)	GCA 19.0 [9.2-31.2] months Non-GCA 26.3 [4.9–36.7] months	112 screened 69 analyzed	Symptom assessment Histology review	GCA	38	Non-GCA	31	Nsp
Ackhar et al. 1994 (28)	Nsp	545 screened 535 analyzed	Histology review	Untreated	286	GC Treated	249	Some patients were already treated with GC (prednisone or equivalent) before referral, so there is no standardized GC scheme, but GC dosage was recorded

3.1.4 Supplementary Table 14. Role of biopsy: population characteristics and control and comparison (results of outcome assessment and other results of interest)

Study ID	Age	% females	Outcomes/results of interest	Group 1	Group 2	p-value
Hernandez-Rodriguez et al. 2016(13)	Mild infiltrative pattern 78 (57–96) Extensive infiltrative pattern 77 (57–91)	Mild infiltrative pattern 64.86 Extensive infiltrative pattern 70.97		Mild infiltrative pattern	Extensive infiltrative pattern	
			Ischaemic events (included Permanent visual loss, established diplopia, Stroke, Ischaemia of other territories)	9 (24.3)	86 (34.7)	ns
			Reversible ischaemic complications (included Amaurosis fugax, Transient diplopia, Transient ischaemic attack, Transient ischaemia of other areas)	4 (10.8)	31 (12.5)	ns
			Other findings %			
			Granulomas	5.4	81.9	<0.001
			multinucleated giant cells	2.7	70.4	<0.001
			Sectoral involvement of the arterial wall	89.2	38.1	<0.001

			Presence of a different histological pattern	78.4	37.4	<0.001
			Presence of a normal artery section	45.9	4.5	<0.001
			Severe intimal hyperplasia	8.1	81.9	<0.001
Overall conclusions: Validation of the proposed histological scoring system was achieved by demonstration of reliability and reproducibility. Raw agreement of each external scorer with the gold-standard was 82% and 77% (55% and 46% agreement expected from chance); kappa¼ 0.82 (95% confidence interval [CI] 0.70–0.95) and 0.79 (95% CI 0.68–0.91). There were no significant differences between groups regarding sex and age, presence of any cranial symptoms (p=0.34), abnormal temporal artery on palpation (p=0.15), systemic manifestations, laboratory parameters and ischaemic complications. However, some trends were noted. Even if non-significant, patients with the extensive pattern tended to present more often with jaw claudication and scalp tenderness, more abnormalities on temporal artery palpation, mainly temporal artery thickening, and into a lesser extent, decreased pulse. Severe intimal hyperplasia, granulomas and giant cells were significantly more common in the extensive pattern. No significant differences in the proportion of the different infiltrative patterns were found between patients treated with GC and untreated.						
Maleszewski et al. 2017(14)	77 [57-89] years	70		3 months n=10	6 months n=12	9 months n=9	12months n=9	
			Prednisone dose (mg/day) median (range)	25 (15-50)	9 (5-40)	10 (2.5-25)	5 (0-20)	
			Arteritis present n (%)	7 (70)	9 (75)	4 (44)	4 (44)	
				Initial biopsy		Second biopsy		
			Inflammatory pattern n (%)					
			Granulomatous	37 (93)		14 (58)		
			Non-granulomatous	3 (7)		10 (42)		
			Inflammatory cell type n (%)					
			Lymphocytes	40 (100)		24 (100)		
			Plasma cells	33 (83)		10 (40)		
			Giant cells	22 (55)		11 (45)		
			Eosinophils	7 (18)		1 (4)		
			Neutrophils	1 (3)		0		
			Medial fibrosis n (%)	13 (33)		24 (60)		
			Calcification n (%)					
			Limited to the IEM	9 (23)		7 (18)		
			Medial	1 (3)		1 (3)		
			Disruption of IEM n (%)	40 (100)		39 (98)		

			Intimal fibroplasia n (%)			
			Absent/mild	37 (92)	33(82)	
			Moderate/severe	3 (8)	7 (18)	
Overall results: Clinical manifestations were readily suppressed, however features of arteritis could still be found after 12 months. Lymphocytes were present in all initial biopsies and were still the dominant cell type at second biopsies. Granulomatous inflammation decreased over time whereas medial fibrosis increased and may represent a chronic finding.						
Luqmani et al. 2016 (15)	71.1 years	72	Versus reference diagnosis	Sensitivity	Specificity	
			Biopsy (%)	39	100	
			US (%)	54	81	
			Biopsy in ≤ 3 days from GC start (%)	48	100	
			Biopsy in 4-6 from GC start (%)	37	100	
			Biopsy in ≥ 7 days from GC start (%)	33	100	
			US in ≤ 1 days from GC start (%)	64	81	
			US in ≥ 2 days from GC start (%)	47	82	
Overall conclusions: From the 381 patients included for primary analysis, 257 were diagnosed as GCA. Biopsy and US results were concordant in 70% of patients (kappa 0.35). Comparing strategies of clinical judgment plus biopsy vs performing US in all suspected GCA, the latter was more sensitive (93% vs 91%) although less specific (77% vs 81%) and more cost effective (benefit of £485 per patient). Sensitivity decreases rapidly for biopsy and US after GC start.						
Armstrong et al. 2008(16)	With giant cells 74.6 (7.9) Without giant cells 75.8 (4.8)	With giant cells 61.8 Without giant cells 68.8	Presenting symptoms (headache, visual trouble, scalp tenderness, jaw claudication, fever, fatigue, muscle /joint problems)	Giant cells -	No Giant cells -	 ns
			PMR	28 (36.8%)	2 (12.5%)	0.059
			Blindness	12 (16.2%)	1 (6.3%)	ns
			Relapses needing treatment	29 (50.9%)	6 (54.6%)	ns
			Starting GC dose, Median (range)	60.0 (20.0–1250.0)	80.0 (60.0–1250.0)	ns
			Length of GC treatment	22.3 (9.2)	22.9 (8.1)	ns
Overall results: no significant differences in the presenting symptoms, relapses, starting GC dose nor length of GC between the two groups. Patients with giant cells presented almost with three times more blindness, but still non-significant (p= 0.45)						
Breuer et al. 2013(17)	Nsp	Nsp		Biopsy positive	Biopsy negative	

			Flare	17	2		-
				With ischaemic manifestations	Without ischaemic manifestations		
			Transmural inflammation	9 (47%)	36 (78%)		0.02
			Intense inflammation, Giant cells, Neutrophils, Eosinophils, Histiocytes, Plasma cells, Severe intimal thickening, Luminal thrombus, Vessel-wall calcifications, Severe fragmentation of internal elastic lamina	-	-		ns
			Positive biopsy group > Correlation between Intensity of inflammatory reaction (ISIR) and:	r value			p value
			Extent of tissue inflammation	0.30			0.02
			Intensity of tissue inflammation	0.05			0.66 ns
			Presence of giant cells	0.02			0.8 ns
			Severity of internal elastic lamina fragmentation	0.1			0.4 ns
			Degree of intimal thickening	0.1			0.4 ns
Overall results: there was no significant association between flares and histological features. Transmural inflammatory infiltrates were associated with strong ISIR and with lower rate of cerebral-ophthalmic ischaemic manifestations. This was also demonstrated by the positive, although weak, correlation found between ISIR and extension of inflammation. Even though duration of therapy is not specified in the text, the authors do refer that there was no statistically significant association between duration of GC therapy and any histological feature.							
Cavazza et al. 2014(18)	Age at disease onset TMI 74.2±7.4 ILA 71.2±5.8 VVV 74.4±7.3 SVV 73.7±8.7	TMI 77.9 ILA 88.9 VVV 57.9 SVV 37		TMI	ILA	VVV	SVV	
			Gender %	77.9	88.9	57.9	37	<0.0001
			Any cranial symptoms %	86.2	61.1	57.9	55.6	<0.0001
			Headache	77.9	55.6	57.9	55.6	0.006
			Scalp tenderness	36.1	11.8	21.1	18.5	0.041
			Abnormalities of temporal arteries	71.3	40	47.1	33.3	<0.0001
			Jaw claudication%	44.7	33.3	15.8	7.4	<0.0001
			Visual loss, visual symptoms, Systemic signs, PMR%	-	-	-	-	-
			Peripheral synovitis %	6	11.1	10.5	22.2	0.025
			Halo on CDS of temporal arteries%	72.4	14.3	16.7	27.3	<0.0001
			ESR (mean ± SD) (mm/h)	86.5±30.1	96.1±22.2	64.9±34.7	70.4±30.9	0.002

			ESR>40 mm/h	92.5	94.4	78.9	88.9	ns
			CRP (mean ± SD) (mg/dL)	8.9±6.1	7.1±4.3	3.5±3.7	7.4±8.4	<0.0001
			CRP>0.5 mg/dL	99.5	100	66.7	88.5	<0.0001
			Haemoglobin (mean ± SD) (g/dL)	11.3±1.5	10.9±1.2	11.9±1.2	12.0±1.6	0.004
			Patients taking prednisone at the time of TAB	48	52.9	17.6	26.9	0.020
			Prednisone dose at the time of TAB (mean ± SD) (mg/d)	35.7±24.1	36.7±29.6	11.0±9.7	40.0±19.0	ns
Notes: bilateral biopsies have been performed in only 2% of the patients. However, the second biopsy showed TMI in 4 of 9 patients in whom the first biopsy was negative, suggesting that bilateral TAB may be useful in selected cases. **Overall conclusions:** In comparison with patients with TMI, those with SVV and VVV had a significantly lower frequency of cranial manifestations (including headache, jaw claudication, and abnormalities of temporal arteries at physical examination), lower serum levels of acute-phase reactants, and a lower frequency of GC therapy at the time of TAB, of a positive "halo sign" at CDS of temporal arteries, and of systemic symptoms (for VVV). In these milder forms of histological inflammation, color duplex sonography may not be a reliable alternative to TAB.								
Chatelain et al. 2009(19)	With PVL 78.3 Without PVL 74.7	With PVL 90 Without PVL 71		With PVL	Without PVL			
			Age	78.3	74.7			0.01
			Gender	90	71			0.03
			Positive TAB	26 (89.6%)	248 (59.1%)			0.01
			OR for blindness associated with the presence of giant cells	2.6 CI 1.02 to 6.89				0.027
			OR for blindness associated with the numerous giant cells	7.03 CI 2.18 to 2				<0.001
			OR for blindness associated with presence of plasmocytes	3.17 CI 1.13 to 8.59				0.02
			OR for blindness associated with obstruction greater than 75% as compared to obstruction lower than 25%	5 CI 1.33 to 22.48				0.006
			OR for blindness associated with neoangiogenesis	3.84 CI 1.56 to 9.72				<0.001
Notes: Female gender (90% vs 71%, p=0.03), older age (p=0.01), shorter delay between the onset of the symptoms and the diagnosis (p=0.03), diplopia (14% vs 4%; p=0.02) and abnormal temporal artery with rigidity at clinical examination (69% vs 51%, p=0.02) were statistically significantly associated with PVL. All inflammatory markers, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and platelet counts were similar in both groups.								

Overall conclusions: The risk associated with blindness for a positive biopsy compared to a negative biopsy was estimated at 4 with a confidence interval excluding 1. Pathological features strongly predictive of PVL were the presence (p=0.003) and number of giant cells (p=0.001) in the arterial wall and aggregates of giant cells (p=0.001). Global obstruction seemed to be mostly related to intima thickening, which highly correlated with PVL (p=0.007) so did neoangiogenesis OR 3.84 (95% CI 1.56 to 9.72, p<.001). Pathological items significantly associated with PVL in univariate analysis were integrated into a logistic regression model. The only significant item was quantity of giant cells (p=0.001). None of the other items, including the positivity or negativity of the TAB, remained significant						
Kaiser et al. 1998(20)	Not specified	Not specified		Moderate to severe intimal hyperplasia	Minimal or no intimal hyperplasia	
			Ischaemic manifestations, %	65	10	0.001
			Ocular symptoms	40	5	0.01
			Jaw claudication	40	5	0.01
			Stroke, transient cerebral ischaemia	15	0	ns
			Aortic arch syndrome	10	0	ns
Overall results: Tissue expression of PDGF-A and PDGF-B strongly correlated with the presence of hyperplastic intima. Accumulation of PDGF-A- and PDGF-B- producing macrophages at the media-intima junction was the characteristic feature in patients in whom luminal narrowing developed. Ischaemic manifestations (ocular symptoms and jaw claudication) were significantly more frequent in patients with moderate to severe intimal hyperplasia.						
Makkuni et al. 2008(21)	Age means per intimal hyperplasia graded groups varied between 75.6 and 78.8 years	Female % per intimal hyperplasia graded groups varied between and 50% and 81.8%		With NOC (n)		
			Complete visual loss, AION, visual field defects	10		-
			Cerebral infarcts	1		
			Cerebral infarcts + visual loss	1		
			Intimal hyperplasia grade, n			-
			1	0		
			2	3		
			3	6		
			4	3		
Note: intimal hyperplasia grades: grade 1 <50% luminal occlusion, grade 2 is 50–75%, grade 3 is >75% and grade 4 is complete luminal occlusion **Overall results:** There was evidence for association between NOC and higher intimal hyperplasia scores (P=0.001).						
Muratore et al. 2016(22)	Age at disease onset 74 ± 7.4 years	78.5	Significant predictors of cranial ischaemic events	Univariate analysis OR (95% CI)		
			Age at disease onset	1.060 (1.025-1.097)		0.001*
			ESR	0.990 (0.981-0.998)		0.016*

			Severe inflammation	2.282 (1.256-4.149)				0.007
			Giant cells	2.059 (1.214-3.491)				0.007*
			Calcifications	2.416 (1.246-4.686)				0.009
			Laminar necrosis	2.652 (1.418-4.962)				0.002*
			Predictors for the development of PVL					
			CRP	0.906 (0.827-0.992)				0.033**
			Calcifications	3.672 (1.479-9.121)				0.005**
			Age	1.069 (0.996-1.146)				0.064**
*remained significant on multivariate analysis. ** multivariate analysis. cranial ischaemic events (CIEs). **Overall results:** Older age, lower ESR values and the presence of giant cells and laminar necrosis at TAB were predictors of CIE's at multivariate analysis. Patients with permanent visual loss as opposed to those without, were significantly older (78.3 ± 5.0 vs 73.0 ± 7.5 years, p < 0.0001), had lower ESR and CRP values (78.4 ± 27.2 vs 89.1 ± 30.3 mm/h, p = 0.012 and 6.2 ± 4.8 vs 9.1 ± 6.0 mg/dl, p = 0.010, respectively) and more frequent evidence of calcifications at TAB (19/51 (37.3%) vs 36/223 (16.1%), p = 0.001). Independent predictors for the development of permanent visual loss were lower CRP values and the presence of calcifications. There was a trend for older age, but it did not reach statistical significance								
Quinn et al. 2012(23)	71[37-89]	70.8		Biopsy positive		Biopsy negative		
			Jaw claudication yes/no (n)	17/16		16/74		0.001
			Temporal artery pulse absent/present (n)	17/18		51/4		0.014
			Visual acuity normal/abnormal (n)	20/14		78/12		0.002
			Visual fields normal/abnormal (n)	20/11		73/13		0.048
			Fundoscopy normal/abnormal (n)	16/18		62/15		0.001
			Symptom duration (days, mean)	43.7 (±19.3)		105.4 (±18.4)		0.023
			ACR prebiopsy score (maximum = 4)	Sens	Spec	PPV	NPV	
			2	100%	20%	35%	100%	
			3	73%	67%	49%	85%	
			4	20%	100%	100%	74%	
			ACR prebiopsy score + abnormal fundoscopy + jaw claudication (maximum = 6)					
			2	100%	24%	32%	100%	

			3	92.6%	55%	45%	95%	
			4	48.8%	91%	70%	80%	
			5	18.6%	99%	89%	74%	
			6	9.5%	100%	100%	73%	
Overall results: Prebiopsy ACR score correlated significantly with likelihood of positive biopsy (P < 0.001). Positive TAB results correlated with presence of jaw claudication, elevated ESR level, absent temporal artery pulsation, shorter duration of symptoms, abnormal visual acuity, abnormal fundoscopy and with lower haemoglobin level (P=0.025), and higher platelet count (P=0.002). There was no relation to prebiopsy GC treatment (P=0.699). A prebiopsy ACR score of <2 has 100% sensitivity for excluding GCA, whereas a score of >3 has 100% specificity for GCA. Incorporating scores for jaw claudication and abnormal fundoscopy to the prebiopsy ACR criteria score showed that a score of <2 of 6 had 100% sensitivity for excluding GCA. A score >4 of 6 had 99% specificity for GCA. The greatest benefit of TAB is seen in patients who do not meet ACR criteria for temporal arteritis without biopsy. Patients who score, less or equal to 1 on ACR criteria on admission do not require TAB.								
Ter Borg et al. 2007(24)	74.5 years (range 50–86)	81.8		Classical	Atypical	Healed		
			ESR (mm/first hour)	84.5±26.6	91.4±25.3	44.3±33.6	healed vs classical p=0.003 healed vs atypical p=0.002	
			Haemoglobin (mmol/l)	7.6±0.9	6.7±0.7	8.4±0.8	healed vs classical p=0.04 healed vs atypical p=0.002	
			With permanent blindness	6 (35)	6 (35)	0 (0)	ns	
			With reactivation (<3 years)	5 (29)	5 (29)	0 (0)	ns	
			With recurrence (<3 years)	4 (24)	4 (24)	0 (0)	ns	
Overall conclusions: Patients with classical and atypical GCA pattern on biopsy presented significantly higher ESR and lower haemoglobin levels. There were no differences concerning age, gender, CRP nor clinical manifestations (including jaw claudication and visual disturbances). Nearly all visual disturbances occurred in the classical and atypical GCA groups. The same for reactivation and recurrence. Prednisone dosage after 2 and 3 years was lower in the healed GCA group than in the others, but this was only statistically different when comparing atypical with healed GCA. At 3 years, 60% of the patients in the healed group were off prednisone, compared to 35% in the classical and 9% in the healed GCA groups. Additional immunosuppressive treatment was necessary only in the classical and atypical groups. Healed histological pattern patients appear to have a more benign course e less treatment requirements								
	73 years [48-87]	80%		Without Giant cells	With giant cells			

Schmidt and Loffler 1994(25)			Optic nerve involvement %	40.5	46.5	ns
			AION unilateral	23.8	37.2	ns
			AION bilateral	9.5	4.6	ns
			CRAO unilateral	4.8	2.3	ns
			CRAO bilateral	2.4	-	ns
			AION unilateral + CRAO contralateral	-	2.3	ns
			Cotton-wool spots	2.4	-	ns
			Episcleritis	4.8	-	ns
			Paresis of the third nerve or diplopia	-	2.3	ns
AION: anterior ischaemic optic neuropathy CRAO: central retinal artery occlusion **Overall conclusions:** this study found no correlation between histological presence of giant cells and visual disturbances.						
Ypsilantis et al. 2011(26)	74 years [20-99]	68.2	Median post-fixation biopsy specimen length (cm)	1 (range 0.1–8.5)		
			Predictors of positive biopsy (regression analysis coefficient)			
			Age	0.04		<0.001
			ESR	0.01		<0.001
			Specimen length	0.29		0.007
Overall results: Patient age, ESR and specimen length were independent predictors of a positive histopathological diagnosis of GCA. ROC analysis identified post fixation length of at least 0.7 cm as having the highest predictive value for a positive biopsy (area under the ROC curve 0,574).						
Muratore et al. 2016(27)	GCA	GCA	n (%)	GCA	Non-GCA	
	75±9	73.7	Medio intimal scar	0	0	ns
	Non-GCA	Non-GCA	Medial attenuation	4 (10.5)	4 (12.9)	ns
	72±9	77.4	Intimal hyperplasia	27 (71.1)	17 (54.8)	ns
			Fragmentation of inner elastic lamina	34 (89.5)	26 (83.9)	ns
			Adventitial fibrosis	3 (7.9)	1 (3.2)	ns
			Neoangiogenesis	2 (5.3)	2 (6.5)	ns
			Calcification	10 (26.3)	4 (12.9)	ns

3.1.5 Supplementary Table 15. Role of biopsy: risk of bias assessment (Newcastle-Ottawa scale for cohort studies)

Overall results: accompanying histopathological features did not aid in differentiating GCA from non-GCA patients.						
Achkar et al. 1994 (28)	71,7 Range 31-93	64	n (%)	Positive results	Positive with atypical features	
			Untreated (n=286)	89 (31)	40/89 (45)	
			Treated (n=249)	86 (35)	49/86 (57)	
			Remote treatment with GC within 6 months of TAB but no GC within 2 weeks of TAB (n = 46)*	11 (24)	7/11 (64)	
			≤15 mg/d (any duration) (n = 54)	17 (32)	9/17 (53)	
			>15 mg/day 1-7 days of treatment (n = 107)t	46 (43)$	23/46 (50)	$0.027 vs untreated
			>15 mg/day 8-14 days of treatment (n = 10)t	3(30)	2/3 (67)	
			>15 mg/day for >14 days of treatment (n = 32)t	9(28)	8/9 (89)§	
			Entire cohort (n = 535)	175 (33)	89/175 (51)	
Overall results: The reviewed histologic diagnosis correlated well with the original pathologist's interpretation in 94% of cases (estimated kappa = 0.87). Mean biopsy specimen length was similar in patients with positive (3.7 cm) and negative (3.6 cm) results. Patients with 1-7 days of prednisone >15 mg/day had positive TAB more often positive than untreated patients, however this subgroup also tended to have more frequent classic giant cell arteritis symptoms or signs (such as jaw claudication or tender or pulseless temporal artery) than did untreated patients. The odds of a positive TAB for this subgroup to the odds of a positive result for those who received no previous GC treatment was 1.67 (CI, 1.06 to 2.64), but became 1.23 (CI, 0.72 to 2.12) after adjusting for clinical and laboratory variables. Analysis of the other treatment subgroups was non-significant. There was a higher proportion of atypical histologic features among the 9 biopsy-positive patients who had > 15 mg/day of GC for > 14 days than in untreated patients (8 of 9 compared with 40 of 89; P = 0.012).							

Study ID	**Selection** 1)Representativeness of exposed cohort	**Selection** 2)Selection of the non-exposed cohort	**Selection** 3)Ascertainment of exposure	**Selection** 4)Demonstration that outcome of interest was not present at start of study	**Comparability** 1)Comparability of cohorts on the basis of the design or analysis	**Outcome** 1)assessment of outcome	**Outcome** 2)Was follow-up long enough for outcomes to occur	**Outcome** 3)Adequacy of follow up of cohorts	**Total n of stars** (only comparability can have two ∗)
Armstrong et al. 2008(16)	*	*	* secure reports	No	Nsp	Not blinded	NA	No statement	3
Breuer et al. 2013(17)	No description	No description	other	No	Nsp	Not blinded	*	No statement	1

Cavazza et al. 2014(18)	No description	No description	* secure record	No	Nsp	* blinded to clinical data	Not clear	No statement	2
Chatelain et al. 2009(19)	*	*	Other	No	Nsp	only TAB analysis was blinded to clinical data	*	No statement	3
Hernandez-Rodriguez et al. 2016(13)	* somewhat representative	*	* secure record	No	Nsp	* blinded to clinical data	Nsp	No statement	4
Maleszewski et al. 2017(14)	*	NA	other	No	Nsp	* blinded to clinical data	*	*	4
Makkuni et al. 2008(21)	*	*	Other	No	Nsp	only TAB analysis was blinded to clinical data	Nsp	No statement	2
Muratore et al. 2016(22)	*	*	Medical record	No	Nsp	only TAB analysis was blinded to clinical data	Nsp	No statement	2
Quinn et al. 2012(23)	* somewhat representative	*	Medical record	No	Nsp	Nsp	Nsp	No statement	2
Ter Borg et al. 2007(24)	* somewhat representative	*	Other	No	Nsp	Not blinded	*	No statement	3
Schmidt and Loffler 1994(25)	Nsp	Nsp	Nsp	No	Nsp	Nsp	*	No statement	1
Ypsilantis et al. 2011(26)	* somewhat representative	NA	Medical records	No	Nsp	unclear	NA	No statement	1
Muratore et al. 2016(27)	* somewhat representative	*	other	No	Nsp	only TAB analysis was blinded to clinical data	*	*	4
Achkar et al. 1994 (28)	* somewhat representative	*	Medical records	No	*	only TAB analysis was	*	No statement	4

						blinded to clinical data			

3.1.6 Supplementary Table 16. Role of biopsy: risk of bias assessment (Newcastle-Ottawa scale for case-control studies)

Study ID	Selection 1)Representativeness of exposed cohort	Selection 2) Representativeness of the cases	Selection of Controls 3) Selection of Controls	Selection 4) Definition of Controls	Comparability 1) Comparability of cases and controls on the basis of the design or analysis	Exposure 1) Ascertainment of exposure	Exposure 2) Same method of ascertainment for cases and controls	Exposure 3) Non-Response rate	Total n of stars
Kaiser et al. 1998(20)	No description	Not stated	Hospital controls	*	No adjusts made	Medical records	*	non-respondents described	**2**

3.1.7 Supplementary Table 17. Role of biopsy: risk of bias assessment (QUIPS tool) (low (☺), high (☹) or unclear (?) risk of bias)

Study ID	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall result
Armstrong et al. 2008(16)	?	☹	?	☺	☹	☺	High RoB
Chatelain et al. 2009(19)	☹	☹	☺	☺	?	☺	high RoB
Overall appraisal of risk of bias defined as: low, if 0 items are considered high RoB and only 1-2 unclear RoB or ≥4 low RoB; high, if ≥2 items are considered high RoB or ≥4 are considered unclear. The remaining will fall in the moderate RoB category.							

3.1.8 Supplementary Table 18. Role of biopsy: risk of bias assessment (QUADAS 2 Tool) low (☺), high (☹) or unclear (?) risk of bias

Study ID	Risk of Bias				Applicability concerns			RoB
	Patient selection	Index test	Reference standard	Flow and Timing	Patient selection	Index test	Reference standard	

	P1	P2	P3	IT1	IT2	R1	R2	FT1	FT2	FT3	APS	AIT	ARS	
Luqmani et al. 2016 (15)	☺	☺	☺	☺	☺	☺	☹	☺	☺	☺	☺	☹	☹	moderate
Overall appraisal of risk of bias and concerns about applicability were arbitrarily defined as: high, in the case of concern on ≥5/10 risk of bias items or concern on 3/3 applicability items out of the QUADAS-2 tool; moderate, in case of concern on 4/10 risk of bias items and/or concern on ≥1/3 applicability items out of the QUADAS-2 tool, low, in case of concern on ≤3/3 risk of bias items and no concern about applicability.														

4) BIOMARKERS

4.1 OBSERVATIONAL OR INTERVENTIONAL* STUDIES

4.1.1 Supplementary Table 19. Evidence retrieved regarding biomarkers for giant cell arteritis: overview of included studies

Study ID	Study design	LoE	Main molecule(s) investigated and overview	Inclusion criteria	Exclusion criteria	End of follow-up for analysis
GCA						
Multiple biomarkers						
Garcia-Martinez et al. 2010(29)	Cross sectional Case control Single center	4	TNF alpha and IL-6 relation to disease outcomes during follow-up	Biopsy proven GCA + regular follow up every 4-6 years + minimum 4 years of follow-up	Nsp	Nsp
Van der Geest et al. 2015(30)	Prospective Case control Single center	4	Multiple biomarkers with emphasis to BAFF and IL-6 and its ability to distinguish between patients and healthy controls. Relation to disease activity	GCA according to ACR criteria FDG PET was considered as equal to TAB as diagnostic criteria PMR according to Chuang/ Hunder criteria	Nsp	Nsp

Kyle et al. 1989(31)	Prospective cohort Single center	4	ESR and CRP before and during treatment, its relation to disease activity and its predictive role	Active and untreated PMR/GCA according to Jones and Hazleman criteria	Nsp	Nsp
Hernandez-Rodriguez et al. 2003(32)	Prospective cohort Single center	2b	IL-6, TNF-alpha and IL-1 beta. Determination of circulating levels and tissue expression (TAB) of these cytokines and relation to disease complications	Biopsy proven GCA patients, untreated or single GC dose at inclusion	Nsp	Nsp
Weyand et al. 2000(33)	Prospective series Single center	4	IL-6 and ESR > role as markers of disease activity > flares	Biopsy proven GCA, untreated	Nsp	April 1994 to October 1996
Gudmundsson et al. 1993(34)	Prospective cohort Single center	4	Emphasis on Plasma viscosity in relation to ESR, CRP and fibrinogen to monitor disease activity	Biopsy proven GCA. If TAB negative, patients needed to fulfill criteria according to Bengtsson and Malmvall	Heavy smoking clinical or laboratory evidence of infection, malignant disease, rheumatoid arthritis, lupus erythematosus, or periarteritis nodosa	Nsp
Retrospective						
Fukui et al. 2016(35)	Retrospective cohort Multicentric	3b	Mainly MMP-3 and its relation to other biomarkers like ESR and CRP and aid in distinction of isolated PMR from GCA with or without PMR	For PMR group: provisional diagnostic criterion by ACR/EULAR GCA: ACR criteria 1990	Patients that had already received GC at diagnosis were excluded (given its effect of raising MMP-3)	November 2004 and April 2013
Gonzalez-Gay et al. 2005(36)	Retrospective cohort Single center	2b	White blood cell count, platelet count, haemoglobin, ESR, CRP, ALP, albumin, alpha-2 globulin and gamma globulin. Correlations in between them and relation to ischaemic complications.	Biopsy proven GCA fulfilling ACR criteria	Nsp	January 1st, 1981 to June 15th 2004

Cid et al. 1998(37)	Retrospective Cohort Multicentric	3b	Evaluates possible clinical and laboratorial predictors of cranial ischaemic events	Biopsy proven GCA diagnoses at the including institutions	Nsp	Inclusion over a 16-year period
Lopez-Diaz et al. 2008(38)	Retrospective cohort Single center	3b	Mainly evaluates ESR and compares patients with ESR > and < to 50 mm/h regarding visual ischaemic complications	Biopsy proven GCA fulfilling ACR criteria	Nsp	January 1981 to December 2006
Main biomarker(s) studied: anti cardiolipin antibodies						
Prospective						
Duhaut et al. 1998(39)	Prospective Case control Multicenter	3b	Anti-cardiolipin association with disease complications	All patients had to fulfil criteria 1, 2 and 3. Patients included in the positive biopsy GCA group also needed criterion 4. Patients included in the negative biopsy GCA group needed Two criteria from 5, 6,7, 8 and 9. Patients in the biopsy positive PMR group needed criterion 4 and 10 Criterion 1: age over 50. Criterion 2: erythrocyte sedimentation rate (Westergren method) above 40 mm Criterion 3: clinical response to GC therapy within 72 h (disappearance of fever and pain). Criterion 4: positive TAB. Criterion 5: clinically abnormal temporal artery Criterion 6: visual disturbances including those occurring during the first week of treatment. Criterion 7: jaw claudication. Criterion 8: headache, temporal headache, facial pain or sensation of facial swelling. Criterion 9: systemic symptoms	any current malignant disease, any current infectious disease, rheumatoid arthritis, systemic lupus erythematosus, and/or periarteritis nodosa.	January 1991 to ? -

				Criterion 10: polymyalgia rheumatica.		
Liozon et al. 1995(40)	Prospective Case control	4	Anti-cardiolipin association with arterial ischeamic complications, flares and relapses	Biopsy proven GCA GC free at inclusion	Nsp	Nsp
Chakravarty et al. 1995(41)	Prospective Case control	4	Anti-cardiolipin association with major vascular complications and progression PMR >GCA	Referrals with presumed diagnosis of PMR or GCA. PMR according to Bird et al. criteria. No mention of criteria for GCA, all patients had TAB done.	history of inflammatory joint disease, connective tissue disease, recent stroke, or myocardial infarction (within last 6 months), malignancy	Nsp
Liozon et al. 2000(42)	Prospective series Single center	4	Anti-cardiolipin association with relapses and flares	Biopsy proven GCA	Nsp	1990 to ?
Main biomarker(s) studied: circulating soluble adhesion molecules						
Coll-Vinent et al. 1999(43)	1st part cross-sectional case-control 2nd part prospective evaluation of 13 patients. Single center	3b	soluble intercellular adhesion molecule-1 (sICAM-1), sICAM-3, vascular cell adhesion molecule-1 (sVCAM-1), E-selectin (sE-selectin), and L-selectin (sL-selectin) relation to disease activity	Biopsy proven GCA	Nsp	Nsp
Main biomarker(s) studied: ANCA antibodies						
Gil et al. 2008(44)	Retrospective cohort Single center	3b	ANCA > relation to disease course > relapses	Biopsy proven GCA fulfilling ACR criteria	Patients under pharmaceuticals that might induce ANCA (propylthiouracil, allopurinol, minocycline, hydralazine, penicillin)	Jan 1997 to Dec 2003

Main biomarker(s) studied: haemoglobin						
Martinez-Lado et al. 2011(45)	Retrospective cohort Single center	2b	Investigated possible clinical and laboratorial predictors of relapses and recurrences	Biopsy proven GCA diagnosed at the hospital promoting the study	Patients whose diagnosis was made elsewhere Incomplete medical records	1992-2006
Main biomarker(s) studied: genetic markers						
Cid et al. 2006(46)	Prospective cohort Single center	2b	Mainly CCL2 association with disease persistence	Biopsy proven GCA	Nsp	Nsp
Salvarani et al. 2007(47)	Retrospective Case control Single center	4	P1A1/A2 polymorphism > relation to susceptibility and complications of disease.	Biopsy proven GCA	Nsp	Nsp
Main biomarker(s) studied: serum osteopontin						
Prieto-Gonzalez et al. 2017(48)	Prospective Case control Single center	4	Serum osteopontin as a marker of disease activity in patients treated with GC and patients on Tocilizumab	Biopsy proven GCA	Nsp	Nsp
Main biomarker (s) studied: endothelin system						
Lozano et al. 2010(49)	Retrospective Case control Single center	4	Role of the endothelin system (expression and regulation in GCA lesions and endothelin production) in the development of ischaemic events	Biopsy proven GCA, untreated or single dose of GC at inclusion	Nsp	1997-2006

5.1.7 Supplementary Table 20. Biomarkers: outcome definition and statistical analysis

Study ID	Outcome/endpoint	Definition of outcome	Validation of	Notes on analysis	Censoring at event

			outcome		
Garcia-Martinez et al. 2010(29)	Biomarkers relation to: Relapse Disease related complications GC requirements GC related complications	**Relapse**: reappearance of disease-related symptoms, not attributable to other causes, that resolved with an increase in prednisone dose 10 mg above the previous dose able to maintain remission. **Disease-related complications**: aortic dilatation and visual deterioration due to anterior ischaemic optic neuritis during follow-up (confirmed by an ophthalmologist); other vascular events included clinically symptomatic cardiovascular (angina or myocardial infarction), cerebrovascular (transient ischaemic attack or stroke), or lower extremity arteriopathy (intermittent claudication or ischaemia). **GC related complications**: new or worsening hypertension, diabetes mellitus and hypercholesterolemia, symptomatic fractures, gastrointestinal bleeding, mild or serious (requiring hospitalization) infection, and symptomatic cataracts requiring intervention.	Nsp	Descriptive statistics, Mann-Whitney test or Student t-test, Spearmans or Pearsons test	Nsp
Van der Geest et al. 2015(30)	Disease activity	**Disease activity** in relation to CRP and ESR	Nsp	Descriptive statistics, Mann-Whitney U-test, Wilcoxon Signed Rank test, ROC analysis with AUC, Spearman's rho correlation coefficient	Nsp
Kyle et al. 1989(31)	Disease activity	To give an overall grading of **activity** in relation to the previous visit, the patients were classified as follows: grade 1-relapse, either as a new or persisting event; grade 2-improvement but still not normal; grade 3-well; symptoms minimal.	Nsp	Descriptive statistics, Chi square tests, Kruskal- Wallis tests, correlation testing, and analysis of variance.	Nsp
Hernandez-Rodriguez et al. 2003(32)	Ischaemic events	-	Nsp	Descriptive statistics, Mann-Whitney U test, Chi square and Fisher's exact test	Nsp
Weyand et al. 2000(33)	Flares > relapse/recurrence	**Flare** was indicated in the presence of any of the following criteria: 1) new headache, 2) scalp/arterial tenderness, 3) new jaw claudication, 4) fever in the absence of infection, 5) new visual deficit, 6) new arterial bruits (cervical, supraclavicular, or brachial), 7) symptoms of	Nsp	Descriptive statistics, Chi square test and Mann-Whitney rank sum test	Nsp

		polymyalgia rheumatica, or 8) increase in global disease activity as assessed by the physician			
Gudmundsson et al. 1993(34)	Flare	**Flare up** was defined as symptoms of the disease requiring an increase in the dose of prednisolone. **No flare up** was defined as the absence of symptoms of disease at two consecutive visits of the patients receiving a constant low glucocorticoid dose of prednisolone (≤10 mg daily).	Nsp	Descriptive statistics, Student T test, Pearson correlation coefficients, logistic regression analysis	Nsp
Fukui et al. 2016(35)	Biomarkers relation to clinical features Relapse	**Relapse**: aggravation or reappearance of clinical symptoms associated with an elevated ESR or CRP (ESR > 30 mm/h or CRP > 0.5 mg/dL), while the patients were being treated with a GC or after the discontinuation of a GC.	Nsp	Descriptive statistics, Student 's t - test, Chi-square test, Fisher 's exact, Pearson' s correlation; Logistic regression Analyses ROC curve analysis	Patients later reclassified has having other disease were excluded from analysis
Gonzalez-Gay et al. 2005(36)	Biomarkers relation to clinical features Severe Ischaemic complications	**Severe ischaemic manifestations**: visual manifestations (transient visual loss including amaurosis fugax, permanent visual loss, or diplopia), cerebrovascular accidents (stroke and/or transient ischaemic attacks), jaw claudication, or large-artery stenosis of the extremities that caused signs of occlusive manifestations (limb claudication) of recent onset.	Nsp	Descriptive statistics, Fisher exact test, Student t test, analysis of variance (ANOVA), Pearson linear correlation coefficients, logistic regression with adjusts for the presence of classic atherosclerosis risk factors at the time of disease diagnosis	Nsp
Cid et al. 1998(37)	Irreversible cranial ischaemic events (ICIE)	**Ischaemic event** was considered GCA-related if: development concomitant with disease manifestations and absence of significant vascular risk factors such as heavy smoking, hypertension, hypercholesterolemia, or diabetes. ICEI Included – visual loss, persistent ophthalmoplegia, stroke and scalp necrosis.	Nsp	Descriptive statistics, Mann-Whitney test 2-tailed Fisher's exact. Estimated odds ratios (OR) with 95% confidence intervals (95% CT	Nsp
Lopez-Diaz et al. 2008(38)	Visual ischaemic complications Predictors of visual loss	**Visual ischaemic manifestations:** transient visual loss, including amaurosis fugax, permanent (irreversible) visual loss, or diplopia.	Nsp	Descriptive statistics, Chi square test or Fisher exact test, Student's t-test or the Mann- Whitney U-test; Goodman-Kruskal γ test, multiple logistic regressions	Nsp
Duhaut et al. 1998(39)	Disease complications	**Disease complications:** visual disturbances general, blindness only, jaw claudication.	Nsp	Descriptive statistics, Chi-square test or Fisher's exact test Wilcoxon rank sum test Logistic regression	Nsp

Liozon et al. 1995(40)	Ischaemic complications	**Arterial ischaemic complications**: Ocular (amaurosis fugax, diplopia, blindness, Anterior ischaemic optic neuropathy (AION), central retinal artery thrombosis); Upper limbs (not specified); cardiac (myocardial infarct)	Nsp	Descriptive statistics, Mann-Whitney, Chi square test and eventually with yates correlation, Fisher's exact test	Nsp
Chakravarty et al. 1995(41)	Correlation between aCL at diagnosis and progression PMR > GCA aCL relation to major vascular complications	Nsp	Nsp	Descriptive statistics, Chi square test and eventually with yates correlation Fisher's exact test	Nsp
Liozon et al. 2000(42)	Flares Relapses	**Flares**: recurrence of clinical symptoms suggestive of temporal arteritis and/or PMR and/or unexplained elevation of ESR and CRP during therapy that disappeared upon increase of GC. **Relapse**: the same as above but in the absence of therapy	Nsp	Descriptive statistics, Qui-square test, Mann-Whitney U-test, spearman's correlation	Nsp
Coll-Vinent et al. 1999(43)	Disease activity	**Active GCA:** clinically symptomatic and evaluated before starting treatment (prednisone 1 mg/kg/day). **Remission**: if none of GCA related signs or symptoms present at the time of diagnosis were present anymore + no new signs or symptoms attributable to GCA + normal ESR Within **remission**: > patients treated for one month to two years in whom remission was maintained with GC treatment (recent remission) > and patients who, having been treated for at least two years, no longer were receiving GC (long term remission).	Nsp	Descriptive statistics, Kruskal-Wallis H test, Wilcoxon's rank sum test, Mann- Whitney U, Pearson's correlation coefficient	Nsp
Gil et al. 2008(44)	ANCA relation to disease course > relapse	**Absence of relapse** was defined as successful tapering of GC during the study period or remission > 36 months.	Nsp	Descriptive statistics, chi-square, Fisher's exact test, Kruskal-Wallis test, Kaplan-Meier curves, exact log rank test for comparison of survival curves.	Nsp
Martinez-Lado et al. 2011(45)	Flares (relapses and recurrences)	**Flare**: worsening symptoms + ESR ≥ 20 mm/1st h. Flares when patients were still taking prednisone or within the first month after prednisone discontinuation were defined as relapses. Flares that occurred at least 1 month after the prednisone dose had been discontinued were defined as recurrences.	Nsp	Descriptive statistics, Fisher exact test Student t test, forward stepwise logistic regression, Kaplan-Meier method	Uniform follow up and treatment approach

Cid et al. 2006(46)	Disease persistence	Nsp	Nsp	Descriptive statistics, Mann–Whitney U-test, Fisher's exact test, Pearson or Spearman's rank, Kaplan–Meier survival analysis method	Nsp
Salvarani et al. 2007(47)	Disease complications	**Disease complications:** ischaemic complications: visual loss, jaw claudication, cerebrovascular accidents (CVAs), and/or aortic arch syndrome Cranial ischaemic complications: Visual loss and CVAs	Nsp	Descriptive statistics, Student's t-test, chi-square test Odds ratios calculation at 95% confidence intervals	Nsp
Prieto-Gonzalez et al. 2017(48)	Disease activity Disease complications	**Relapse**: reappearance of GCA manifestations, usually accompanied by elevation of acute-phase reactants, that required treatment adjustment. **Remission**: absence of disease-related manifestations and the presence of ESR and CRP levels within the normal range **Cranial ischaemic manifestations**: amaurosis fugax, GCA-related visual loss, diplopia, transient ischaemic attacks or stroke	Nsp	Descriptive statistics, Mann-Whitney U test, Student's t-test, Spearman's correlation test ROC curves for sensitivity and specificity analysis Kaplan-Meier survival method and log-rank test	Nsp
Lozano et al. 2010(49)	Disease activity Disease related ischaemic complications	**Weak systemic inflammatory response** > two of the following > fever greater than 37ºC; weight loss greater than 3 kg; haemoglobin less than 110 g/l; erythrocyte sedimentation rate of 85 mm or greater. **Strong systemic inflammatory response** > three or four of the mentioned parameters	Nsp	Descriptive statistics, Mann-Whitney U test Spearman's rho correlation	-

4.1.3 Supplementary Table 21. Biomarkers: intervention/treatments used

Study ID	Follow-up duration	Overall n	Intervention	Group 1	n	Group 2	n	Notes on treatment
Garcia-Martinez et al. 2010(29)	At least 4 years	69	Symptom assessment Laboratory workup	GCA	54	Healthy controls	15	Prednisone according to a defined protocol
		24	Laboratory workup	New GCA	12	Healthy controls	13	Nsp

Van der Geest et al. 2015(30)	Minimum 3 months?			New PMR Follow up samples from GCA and PMR on remission	12 7 7			
Kyle et al. 1989(31)	4-177 weeks	74	Symptom assessment Laboratory workup	PMR	39	GCA 18 GCA/PMR	17	Standardized initial GC dosages
Hernandez-Rodriguez et al. 2003(32)	Nsp	106	Symptom assessment Laboratory workup TAB	With ischaemic complications	33	Without ischaemic complications	73	Nsp
Weyand et al. 2000(33)	550 days	25	Symptom assessment Laboratory workup	GCA patients			25	Standardized treatment protocol
Gudmundsson et al. 1993(34)	1 year	31	Symptom assessment Laboratory workup	Temporal arteritis Polymyalgia rheumatica TA and PMR General symptoms			6 20 4 1	Nsp
Fukui et al. 2016(35)	Minimum 6 months	144	Symptom assessment Laboratory workup	Isolated PMR	115	GCA	29	Used GC and immunosuppressants namely MTX
Gonzalez-Gay et al. 2005(36)	Not clearly stated, assumed minimum 4 weeks	240	Symptom assessment Laboratory workup	With altered biomarker	Variable	Without altered biomarker	Variable	Standardized initial treatment
Cid et al. 1998(37)	Not clearly stated	200	Symptom assessment Laboratory workup	With ICIE	32	Without ICIE	178	Nsp
Lopez-Diaz et al. 2008(38)	Not clearly stated	273	Symptom assessment Laboratory workup	ESR < 50	10	ESR ≥50	263	Standardized initial treatment
Duhaut et al. 1998(39)	Not clearly stated	494	Symptom assessment Laboratory workup	Case group	284	Healthy Controls	210	Nsp

Liozon et al. 1995(40)	6 months	136	Symptom assessment Laboratory workup	GCA	86	Healthy controls	50	Nsp
Chakravarty et al. 1995(41)	2 years	198	Symptom assessment Laboratory workup	GCA/PMR	98	Healthy controls	100	Nsp
				PMR	64			
				GCA	12			
				GCA&PMR	22			
				High aCL	20	Normal aCL	78	
Liozon et al. 2000(42)	Mean 34 months (10-78)	58	Symptom assessment Laboratory workup	aCL+	27	aCL-	31	Standardized initial treatment protocol
Coll-Vinent et al. 1999(43)	For the prospective part of the study, at least 2 years	99	Symptom assessment Laboratory workup	GCA	64	Healthy controls	35	Nsp
				Prospective GCA group	13			
Gil et al. 2008(44)	Nsp	50	Symptom assessment Laboratory workup	ANCA +	9	ANCA -	21	GC initial dosage of 0,7 mg/kg -1 mg/kg. A few patients also received MTX or azathioprine.
				No ANCA measurement			20	
Martinez-Lado et al. 2011(45)	Mean 104 (58-155) months.	174	Symptom assessment Laboratory workup	With flare	71	Without flare	103	Standardized scheme for initiation of GC therapy and for treatment of relapses and recurrences.
Cid et al. 2006(46)	Minimum 35 weeks	12	Symptom assessment Laboratory workup Genetic workup on TAB samples	Sustained remission	6	Relapsing course	6	Nsp
				Later, expression of CCL2 and its receptor CCR2 was analyzed by immunohistochemistry in TAB sections from 50 patients and in normal TAB from nine patients. Circulating levels of CCL2 were determined in 56 patients				
Salvarani et al. 2007(47)	GCA 26±21 months	381	Symptom assessment Laboratory workup Genetic workup (blood)	GCA	140	Healthy controls	241	Nsp

Prieto-Gonzalez et al. 2017(48)	Mean 187 weeks (114-360)	101	Symptom assessment Laboratory workup	Pooled cohort	76	Healthy Controls	25	Patients were uniformly treated
Lozano et al. 2010(49)	Nsp	77	Symptom assessment Laboratory workup	GCA	61	Healthy Controls	16	Nsp

4.1.4 Supplementary Table 22. Biomarkers: population characteristics and control and comparison (results of outcome assessment and other results of interest)

Study ID	Age	% females	Outcomes/results of interest	Group 1	Group 2	p-value
Garcia-Martinez et al. 2010(29)	GCA 79 (63-91) Healthy controls (HC) age matched	GCA 74.1 HC gender matched	 IL-6 TNFalpha	GCA Fig. (higher than HC) Fig. (higher than HC)	Healthy controls (HC) Fig. Fig.	 <0.001 <0.001
			At least 1 relapse (n=41) vs no relapse (n=13) IL-6 TNF-alpha	At least 1 relapse Fig. Fig.	No relapse Fig Fig	 0.04 0.042
			 IL-6 TNF-alpha	Still needing Pred. Fig. Fig	No need for pred. Fig fig	 0.008 0.47 ns
			Correlation between TNF and: ESR, CRP, haptoglobin, haemoglobin Disease complications Time to maintenance dose of prednisone < 10 mg Cumulative prednisone dose	r= no correlation no correlation 0.235 0.292		 ns ns 0.09 ns 0.04
			Correlation between IL-6 and: ESR, haptoglobin, haemoglobin CRP Disease complications	r= no correlation 0.296 No correlation		 ns 0.03 ns

Overall conclusions: in patients in stable clinical remission, IL6 and TNF were significantly higher than in controls. Patients with relapsing course had higher IL-6 and TNF levels than the ones without relapses and patients that still needed prednisone at evaluation time also had higher IL-6 levels, but not TNF. Circulating levels of both IL-6 and TNF remained significantly higher in patients who had been able to discontinue therapy than in healthy controls (mean ± SD 13 ±17 versus 5 ± 11 pg/ml; $P < 0.001$ for IL-6 and mean ±SD 32 ± 12 versus 16 ± 9 pg/ml; $P = 0.005$ for TNF). Il-6 levels correlated positively with time to maintenance dose and cumulative dose of prednisone. Neither Il-6 nor TNF correlated with disease complications. Longer duration of treatment observed in patients with elevated TNF or IL-6 levels did not result in more GC-related side effects.							
Van der Geest et al. 2015(30)	-	-	Serum markers in newly diagnosed	<u>HC</u>	<u>New GCA</u>	<u>New PMR</u>	
			BAFF	1013 (765-3794)	1321 (1019-1578)***	1204 (912-2064)**	
			CCL2	612 (445_924)	461 (295-960)*	634 (274-912)	
			CCL11	164 (88_414)	118 (49-463)*	132 (60-296)	
			CXCL9	35 (18_51)	88 (21-704)***	64 (39-333)***	
			CXCL10	65 (38_99)	68 (48-114)	95 (36-204)**	
			IL-6	2 (1_6)	15 (4-494)***	35 (11-175)***	
			IL-10	0.7 (0.4_1.7)	2.1 (0.7-29.0)*	0.7 (0.4-4.7)	
			sIL-2R	773 (638_980)	911 (722-1085)*	851 (756-1085)	
			Serum markers in GC induced remission GCA and PMR- data only on text, please see bellow				
			Correlations with ESR and CRP	-	r	r	
			BAFF		>0.75**	>0.75**	
			IL-6		>0.50**	>0.75**	
			CCL2		- 0.73**	No correlation	
			CCL11		-0.77**	No correlation	
			CXCL9		No correlation	>0.5*	
All Biomarkers evaluated: BAFF, CCL2, CCL3, CCL4, CCL5, CCL11, CXCL9, CXCL10, GM-CSF, IFN-a, IFN-g, IL-1b, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, TNF-a, sIL-1Ra, sIL-2R. Given the extensive panel, only significant values will be displayed. *P<0.05, **P<0.01, ***P<0.001 Patients vs controls. **Overall results:** compared with controls, GCA patients presented higher levels of BAFF, CXCL9, IL-6, IL-10, sIL-2R and lower levels of CCL2, CCL11. Compared with controls, PMR patients presented higher levels of BAFF, CXCL9, CXCL10 and IL-6. Serum CXCL9 and IL-6 provided excellent discrimination of newly diagnosed GCA and PMR patients from healthy controls, as indicated by AUCs>0.90. Serum BAFF also accurately distinguished newly diagnosed GCA and PMR patients from healthy controls, with AUCs>0.80.							

Serum levels of BAFF and IL-6 were significantly decreased in GCA and PMR patients in remission, whereas CCL11 was increased in both patient groups. Serum CCL2 was increased in GCA patients in remission, but not in PMR patients. BAFF and IL-6 showed stronger correlations with ESR and CRP in GCA and PMR patients than any other serum marker studied.							
Kyle et al. 1989(31)	Not stated	Not stated		PMR	GCA	PMR/GCA	
			ESR at pretreatment	70.21±4.22	76.28±4.96	70.59±5.95	ns
			CRP at pretreatment	43.5±6.3	79.4±20.3	54.9±9.1	No mention
			ESR levels at long term follow-up (during relapses, grade1)	26.3±2.3	42.1±6.91	28.2±2.9	<0.02*
			Correlation between abnormal ESR and abnormal CRP in patients with assessments at 0,1 and 4 weeks	r=0.575**	r=0.627**	-	p<0.01
*statistical difference due to differences between GCA and the other subgroups. **p<0.01 **Comment:** Five of 22 patients with PMR presented positive TAB. Eight patients who presented with PMR developed GCA, six within five weeks of starting treatment and two after six months or more. Four patients who presented with GCA developed PMR, all after more than four months' treatment. Patients were still classed under the subgroup of presentation for biomarkers assessment within the 1st 4 weeks. There might be some risk of subgroup misplacement. CRP evaluation method did not measure values below 6.0 mg/l (Beckman rate nephelometer). **Overall results:** ESR results during relapses were higher in GCA patients. During the initial follow up period CRP fell to normal more rapidly than the ESR at one week in patients who were judged completely well, but both tests were equally accurate thereafter. Neither test was helpful in consistently predicting relapse.							
Hernandez-Rodriguez et al. 2003(32)	Overall 76.4 (57-91)	69.8	Cytokine expression transcripts in TAB mRNA quantity (relative units)	With IE	Without IE		
			IL-1 beta	~5	~27		ns
			TNF-alpha	~5	~6		ns
			IL-6	~6	~28		0.013
			Circulating cytokine levels pg/ml				
			IL-1 beta	0.59	2.16		ns
			TNF-alpha	~median21	~median25		ns
			IL-6	~median 15	~median 20		0.002
Results are in partially on figure so the values are approximate, only to give a notion of proportion. IE> ischaemic events **Overall results:** Patients with ischaemic events (IE) had significantly lower IL-6 mRNA concentrations in their lesions, they also tended to have lower TNF-alpha and IL-1beta mRNA levels, but differences were not statistically significant. Serum IL-6 concentration was also significantly lower in patients with ischaemic complications and TNF-alpha tended to be lower, but the difference was not significant. The same for IL-1beta. Sub analysis: Because IL-6 was significantly reduced in patients with ischaemic events, both in serum and in tissue, the authors hypothesized that IL-6 might have direct effects on vascular components and conducted an experiment that proved that IL-6 activates a functional program related to angiogenesis that may compensate for ischaemia in patients with GCA.							

Weyand et al. 2000(33)	72.9 (59-88)	80	Results presented as % of patients with elevated marker	ESR	IL-6	
			Pretreatment			
			Treatment day 28	76.0	92.0	ns
			Follow-up visits with disease relapse	4.5	54.5	<0.001
			Follow-up visits with no disease relapse	58.3	88.9	0.03
			Post-treatment, in clinical remission	16.2	66.5	<0.001
				12.5	68.8	0.004
Overall conclusions: ESR tends no normalize quicker than IL-6. In patients with relapse, IL-6 was elevated in significantly more patients than ESR. Only 8% of untreated patients did not have elevated IL-6 levels, and only 11% of disease recurrences were not associated with increased plasma IL-6 concentrations. IL-6 appears to be more sensitive than ESR for disease activity and monitoring the efficacy of GC treatment.						
Gudmundsson et al. 1993(34)	67 (58-81) for men and 72 (51-87) for women	77.4	Results in Mean (SD)	With flare ups	No flare ups	
			Plasma viscosity (mPa s)	1.96(0.068)	1.75 (0.027)	<0.01
			ESR (mm/hr)	35(8)	12 (1.7)	<0.05
			CRP (ug/L)	7.2 (2.2)	6.0 (1)	ns
			Prednisolone (mg/day)	12 (2.8)	6 (0.9)	<0.05
Overall results: Plasma viscosity and ESR were elevated in all patients before treatment. There were no significant differences in plasma viscosity nor ESR, CRP and fibrinogen between patients with symptoms of temporal arteritis vs PMR. After 4 days of treatment, values of Plasma viscosity, fibrinogen, CRP significantly decreased, but not ESR. Plasma viscosity and ESR levels were significantly higher in patients with flare ups and these required higher prednisolone doses. The logistic regression analysis showed no overall preference between plasma viscosity, ESR, or both in predicting flare ups.						
Fukui et al. 2016(35)	Isolated PMR	Isolated PMR		Isolated PMR	GCA	
	76.2 ±7.8	51	Relapse (0/1/≥2)	-	-	ns
	GCA	GCA	CRP (mg/dL)	9.1 ± 5.7	11.2 ± 8.4	ns
	75.9 ± 6.7	41	ESR (mm/h)	87.7 ± 30.7	111.0 ± 29.4	<0.01
			Hb (g/dL)	11.0 ± 1.6	10.4 ± 1.5	ns
			MMP-3 (ng/mL)	230.5 ± 201.5	80.5 ± 47.5	<0.01
			Initial prednisolone doses mg/day	14.3 ± 7.1	39.2 ± 16.5	<0.01
			Correlations	r=	r=	p not shown
			Correlation CRP>ESR	0.62	0.41	+ correlation
			Correlation CRP> MMP-3	0.14	0.27	

			Correlation ESR >MMP-3	0.17	- 0.03	No correlation No correlation
Overall conclusions: There was no difference regarding number of relapses in between groups. Initial GC requirements were higher in GCA. ESR was higher in GCA and MMP-3 was lower than in isolated PMR. No other differences were found regarding biomarkers. MMP-3 was also higher in GCA+PMR vs Isolated PMR. MMP-3 did not correlated with ESR nor CRP. The cutoff value of MMP-3 was 118.2 ng/mL, yielding sensitivity and specificity values of 91% and 73%, respectively. Accounting for gender difference: cutoff values for MMP-3 were 140.0 ng/mL in males and 118.2 ng/ mL in females with AUC, sensitivity and specificity of 0.93, 100%, and 78% in the males ($p < 0.01$), and 0.78, 89%, and 65% in the females ($p < 0.01$), respectively. With this results authors defend that if the MMP-3 level in a patient with PMR is lower than 118.2, the patient may have GCA in addition to PMR						
Gonzalez-Gay et al. 2005(36)			Values as (mean±SD)	With	Without	
			High ESR (>100 mm/h)			
			Constitutional syndrome	76 (76.0)	70 (50.0)	<0.001
			Visual manifestations	16 (16.0)	40 (28.6)	0.023
			Permanent visual loss	7 (7.0)	24 (17.1)	0.021
			Haemoglobulin	11.0 ± 1.3	12.3 ± 1.6	<0.001
			Platelet count	447,000 ± 127,000	376,000 ± 129,000	<0.001
			CRP	131 ± 69	74 ± 49	<0.001
			Albumin	3.1 ± 0.5	3.5 ± 0.5	<0.001
			Raised ALP	37 (37.0)	23 (16.4)	<0.001
			Alpha 2 globulin	1.1 ± 0.2	1.0 ± 0.2	0.009
			Leukocytosis (> 11,000/ mm3.)			
			Delay to diagnosis	7.5 ± 6.9	11.5 ± 12.3	0.002
			Platelet count	435,000 ± 140,000	394,000 ± 128,000	0.037
			Albumin	3.2 ± 0.5	3.4 ± 0.6	0.020

4.1.5 Supplementary Table 23. Biomarkers: risk of bias assessment (Newcastle-Ottawa scale for cohort studies)

			Thrombocytosis (>400,000/mm3)			
			Scalp tenderness	25 (21.4)	56 (45.5)	<0.001
			Constitutional syndrome	89 (76.1)	57 (46.3)	<0.001
			Dysphagia	2 (1.7)	10 (8.1)	0.035
			White blood cell count	10,066 ± 2,930	9226 ± 2843	0.035
			ESR	101 ± 21	86 ± 22	<0.001
			Haemoglobin	11.2 ± 1.5	12.3 ± 1.6	<0.001
			CRP	120 ± 70	75 ± 49	<0.001
			Albumin	3.2 ± 0.6	3.4 ± 0.5	<0.001
			Raised ALP	42 (35.9)	18 (14.6)	<0.001
			Anaemia (haemoglobin < 12 g/dL)			
			Women	84 (64.1%)	46 (42.2%)	0.001
			Constitutional syndrome	97 (74.1)	49 (45.0)	<0.001
			Abnormal temporal arteries	88 (67.2)	87 (79.8)	0.028
			Fever (temperature ≥38 ºC)	22 (16.8)	1 (0.9)	<0.001
			Severe ischaemic manifestations	64 (48.9)	67 (61.5)	0.05
			ESR	103 ± 19	81 ± 21	<0.001
			Platelet count	430,000 ± 133,000	376,000 ± 127,000	0.002
			CRP	114 ± 72	74 ± 43	0.001
			Albumin	3.2 ± 0.5	3.5 ± 0.5	<0.001
			Raised ALP	44 (33.6)	16 (14.7)	0.001
			Predictors of ischaemic complications			
			Haemoglobin <12 at diagnosis	OR, 0.53 95% CI (0.30–0.94)		0.03

Due to the extensive amount of results presented for each biomarker, only the more significant and available results are shown in the table, some are stated only below.

Overall conclusions: patients with leukocytosis had shorter delay to diagnosis, higher platelet counts and lower albumin levels. No other significant results, namely regarding ischaemic complications and other biomarkers like ESR and CRP. Patients with thrombocytosis presented more frequently with constitutional syndrome but reduced frequency of scalp tenderness and dysphagia. Thrombocytosis was associated with leukocytosis, higher values of ESR, CRP, and ALP and lower values of haemoglobin and serum albumin.

Anaemia was more commonly observed in women and patients with less frequency of severe ischaemic manifestations. Anaemia was more commonly observed in patients with constitutional syndrome or fever. Patients with anaemia had higher values of ESR, CRP, and platelet counts and lower values of albumin and raised ALP.

Patients with ESR greater than 100 mm/h presented more frequently with constitutional syndrome and less visual ischaemic complications, especially permanent visual loss. However, no differences were observed when severe ischaemic manifestations were considered as a whole. These patients also had higher platelet counts, CRP levels, raised ALP and alpha-2 globulin and decreased values of serum albumin. CRP levels greater than 100 mg/L were more commonly observed in women and in patients with fever (p =0.04), but had no relation to ischaemic complications. Patients with CRP values less than 50 mg/L more commonly had visual ischaemic manifestations. **Presence of anaemia at the time of diagnosis had a protective role for ischaemic complications.**						
Cid et al. 1998(37)	With ICIE 76 (64-86) Without ICIE 73 (57-92)	With ICIE 68.75 Without ICIE 68.85		With ICIE	Without ICIE	
			Duration of cranial symptoms before diagnosis, weeks	5.3	11	0.0214
			Amaurosis fugax %	32.3	6	0.0001
			Transient diplopia %	15.6	3.6	0.0179
			Other cranial symptoms %	-	-	ns
			Lower limb gangrene, claudication, angina, myocardial infarct	-	-	ns
			Fever %	18.8	56.9	0.0001
			Weight loss %	21.9	62	< 0.0001
			PMR %	-	-	ns
			ESR; mm/hour	82.7 (24-130)	104.4 (22-148)	0.0001
			Albumin, gm/liter	37.4 (20-63)	32.7 (16-55)	0.0024
			Haemoglobin, gm/dl	12.2 (10-16)	10.9 (7-15)	0.0001
			Haptoglobin, mg/dl	297 (213-370)	499 (187-936)	0.026
			Alkaline phosphatase, Alpha 2 globulin, platelets, von Willebrand factor, CRP	-	-	ns
			Predictors of ICIE			
			Absence of strong clinical inflammatory response (defined as having both fever and weight loss) and no biochemical inflammatory reaction (defined as having both an ESR of ≥ 85 mm/hour and a haemoglobin level of <11.0 gm/dl).	OR 5,95% CI 2.05-12.2		Increased risk for ICIE
			With clinical inflammatory response as defined above	OR 0.177, 95% CI 0.052-0.605		Decreased risk
			With biochemical inflammatory reaction as defined above	OR 0.226, 95% CI 0.076-0.675		Decreased risk

Fourteen of the 32 patients who had a cranial ischaemic event (43.8%) developed an additional ischaemic complication either simultaneously or consecutively within a 2-week period **Overall results:** There are no significant changes regarding clinical symptoms between the two groups, with exception to transient ocular events like amaurosis fugax and diplopia that were more frequent in patients with ICIE. These patients more frequently presented with less fever and weight loss and had lower ESR and haptoglobin levels. On the contrary, albumin and haemoglobin levels were higher. Absence of strong clinical and biochemical inflammatory reaction increased the risk for ICIE.							
Lopez-Diaz et al. 2008(38)	-	ESR <50 40 ESR ≥50 54	Visual ischaemic manifestations	ESR <50 4 (40)	ESR ≥50 57 (22)		ns
				ESR <50	ESR 50-69	ESR 70-100	ESR >100	
			Delay to diagnosis (mean± SD), wk	6.2 ± 3.8	7.9 ± 7.8	10.0 ± 9.9	11.0 ± 12.4	0.03
			Constitutional syndrome	5 (50)	10 (36)	63 (53)	85 (74)	<0.001
			Fever (temperature ≥38°C)	0 (0)	0 (0)	12 (10)	20 (17)	<0.001
			Jaw claudication	5 (50)	6 (21)	43 (36)	52 (45)	0.05
			Visual ischaemic manifestations	4 (40)	6 (21)	34 (28)	17 (15)	0.01
			Transient visual loss	2 (20)	4 (14)	15 (13)	11 (10)	ns
			Irreversible visual loss	1 (10)	1 (4)	25 (21)	8 (7)	0.07 ns
			Predictors for Ocular Ischaemic Manifestations					
			ESR 70 to 100 mm/h	2.29 (1.16 to 4.55)				0.02
			Polymyalgia rheumatica	0.47 (0.25 to 0.91)				0.03
			Predictors for permanent visual loss					
			ESR 70 to 100 mm/h	3.58 (1.51 to 8.49)				0.004
Overall results: patients with ESR below 50 presented higher haemoglobin levels and more visual ischaemic manifestations. This trend continued when the group with ESR>50 was subdivided in 3 (see above), with patients with lower ESR having higher haemoglobin levels. These patients also presented with less hypoalbuminemia, less thrombocytosis, leukocytosis and lower CRP levels. Overall visual ischaemic complications where more frequent in the group with ESR < 50 and 70-100. The group 70-100 was the one with higher frequency of irreversible visual loss, with a trend towards significance. ESR between 70-100 was the best predictor for ocular ischaemic manifestations and for permanent visual loss. Other predictors investigated were ESR<50, 50-69, constitutional syndrome and jaw claudication but these were not significant. PMR was a negative predictor for ocular ischaemic manifestations.							
Duhaut et al. 1998(39)	Case group 74.8±8.5 for females	Case group 70.8 Controls 66.7	aCL isotype, n(%)	Case group	Controls		
			IgG	36 (13.5)	3 (1.4)		3.4×10^{-7}
			IgM	20 (7.5)	3 (1.4)		0.002
			IgG+IgM	55 (20.7)	6 (2.9)		1.45×10^{-9}

	72.2±8.1 for males Controls 74.8±8.5 for females 72.3±7.7 for males		OR for positivity of IgG+ IgM isotypes between cases and controls	8.86 [95% CI] 3.73-21.03		-
			Association of aCL positivity to disease complications	aCL positivity n(%)		
			visual disturbances patients with /without	15 (30.0)/ 39 (1 8.2)		ns
			blindness with /without	4 (44.4)/ 50 (19.6)		ns
			jaw claudication with /without	20 (31.7)/ 34 (16.8)		0.01
			biopsy positive/negative	39 (39)/ 10 (9.7)		0.00016
Note: in this study, multiple comparisons were made, between cases and controls, within anatomoclinical groups (GCA TAB +, GCA TAB -, PMR TAB +, PMR TAB -, GCA/PMR without TAB), within clinical groups (GCA without PMR symptoms, PMR symptoms alone, mixed symptoms),) biopsy positive vs negative. Only significant results related to the main outcome are shown. **Overall results:** Positivity for aCL varied significantly among anatomic clinical subgroups *(P* = 0.00009), as well as among clinical subgroups *(P* = 0.0003). Biopsy-positive temporal arteritis group had the highest aCL rate (31.2%). A positive biopsy finding alone, regardless of clinical features, seemed to be an important predictor of aCL positivity. In fact, 30% of cases with a positive biopsy finding (n = 130) were aCL positive versus 9.7% of cases with a negative biopsy finding (n = 103) aCL positivity was more frequent with patients with visual disturbances (blurred vision, diplopia or blindness) or blindness alone, but this was non-significant. aCL positivity was more frequent in patients with jaw claudication than without, and this was significant. On multivariate analysis including the biopsy result and aCL positivity as independent variables, visual disturbances and jaw claudication were only explained by a positive biopsy, presence of aCL was non-significant. Blindness tended to be explained by biopsy positivity (P = 0.075), no relation to aCL positivity.						
Liozon et al. 1995(40)	GCA 75 (56-94) Control group 74±6 (60.5-85)	GCA 72.3 Control group 60	Before treatment (59 GCA and 50 controls) n (%)	GCA	Control group	
			aCL negative	43(50)	46(92)	-
			aCL positive	43(50)	4(8)	0,0000007
			IgG negative	38(64.4)	48(96)	-
			IgG positive	21(35.6)	2(4)	0.00015
			IgM negative	49(83)	49(98)	-
			IgM positive	10(17)	1(2)	0.024
			After treatment (see below)	fig	-	-
				With IE	Without IE	
			aCL total, IgG and IgM comparison between GCA patients with ischaemic events vs without	-	-	All ns
Overall conclusions: Before treatment aCL (aCL total, IgG and IgM) positivity was significantly more frequent in GCA patients than controls. There were no differences concerning the frequency and mean values of antibodies between patients with and without ischaemic events, except for 3 patients that had upper limb events (all aCL positive) in these, the mean values						

of aCL total were significantly higher (p=0.04). aCL decreased rapidly during treatment, IgG isotype decreased initially and then increased after the 3rd month and IgM isotype decreased initially and then increased after the 2nd month.						
Chakravarty et al. 1995(41)	GCA/PMR 73.2 Controls 75	GCA/PMR 65.3 Controls 62	Conversion of pure PMR to GCA (%) during follow up Major vascular complications during follow up	High aCL n=20 5 (25) In fig (3 patients)	Normal aCL n=78 5 (6.4) In fig (0 patients)	 ns <0.004
			Relative risk of developing GCA in the presence of PMR and high aCL compared to normal aCL	4.82		
Overall conclusions: signs of GCA were significantly more frequent in the high aCL group. The relative risk of developing GCA in the presence of PMR and high aCL was significantly greater (4.82) than patients with pure PMR and normal aCL. Normal aCL PMR patients appeared to convert later, more than 12 months after diagnosis. During follow up, 3 out of 5 patients with pure GCA in the high aCL group had major complications (1 fatal stroke, 1 blindness, 1 minor stroke), none in the normal aCL group. **Note:** data regarding controls is only shown in one figure, there were no controls with high aCL.						
Liozon et al. 2000(42)	aCL+ 74.5 aCL- 73.8	aCL+ 51.9 aCL- 64.5	n (%) Ophthalmic ischaemic complications Relapses/Flares	aCL+ 9(33.3) 13(48.1)	aCL- 5(16.1) 9(29)	 ns ns
Overall results: there were no differences regarding the frequency of ophthalmic ischaemic complications nor relapses and flares. Once GC were introduced the level of aCL decreased, most cases became aCL- within 3 months. There were no secondary increases in aCL levels in patients whose disease was controlled permanently, either during and off therapy. Of note, the authors observed a significant rise in aCL levels in 14 aCL+ and 7 aCL- patients with analyzable inflammatory episodes related to GCA (Flares/relapses) vs patients with inflammatory episodes unrelated to GCA p<0.0000001. In this study, aCL helped detect GCA relapses/flares with a fairly good sensitivity (74%) and specificity (100%).						
Coll-Vinent et al. 1999(43)	GCA 74 (57-88) Controls 73 (60-88)	GCA 71.9 Controls 71.4	Adhesion molecule, mean (SD) sICAM-1 sICAM-3 sVCAM-1 sE-selectin sL-selectin	GCA active 360.55 (129.78) 38.4 (20.6) 705.21 (278.84) 44.46 (28.6) 540.13 (321.07)	GCA remission (recent + long term) 263.18 (92.71) 44.14 (21.46) 713.07 (435.32) 43 (27.82) 641.25 (397.04)	Controls 243.25 (47.43) 35.26 (24.674) 661.19 (254.64) 38.33 (31.12) 467.34 (233.95)	Only sICAM-1 was significant, <0.001 compared to controls and <0.01 compared with GCA remission
Overall results: sICAM-1 levels were significantly higher in GCA active than controls and were also higher than in patients in remission group (p<0.01 when compared to remission global and also <0.01 when compared to patients in long term remission). There were no other differences in between groups, namely remission vs controls and recent vs long term						

remission. A significant correlation was found between the number of inflammatory parameters (fever, weight loss, ESR > 85 mm 1st h, haemoglobin < 110 g/l), and sICAM-1 concentrations ($p < 0.05$). Data from the prospective observation of 13 patients is shown in figure, results as follows. **Subgroup analysis:** Agreeing with data from the cross-sectional study, sICAM-1 values decreased when clinical remission was achieved (from 369.63 (139.17) to 225.87 (64.25 ng/ml), $p < 0.01$), and remained at low concentrations when treatment was stopped (256.29 (75.15) ng/ml). A correlation was found between sICAM-1 concentrations and ESR values (Pearson's correlation coefficient, $p = 0.034$).						
Gil et al. 2008(44)	ANCA + 72,4±7.3 ANCA – 75,9±6.2	ANCA + 67 ANCA – 71		ANCA – 9(42.8) 28.5/31.5	ANCA+ 5(55.6) 15.8/6	 >0.05 ns 0.013
			Relapses n (%) Time to relapse, mean/median in months			
Overall results: There were no differences between groups regarding clinical features (systemic, visual disturbances, jaw claudication…), laboratory (leucogram, haemoglobin, hepatic screening, ESR, CRP). No Differences in frequency of relapses but ANCA + group relapsed sooner. Sub analysis of patients with relapse vs no relapse: patients that relapsed had significantly higher leucocyte and neuthrophil counts, and CRP levels (p= 0.014, p=0.009, p=0.009 respectively). Comparison of group with ANCA measurements vs no measurements, the later were younger, but no other differences were found.						
Martinez-Lado et al. 2011(45)	With flare 74.2 ± 6.2 Without flare 75.5 ± 7.0	With flare 53.5 Without flare 54.4	At diagnosis n=174 Clinical features at diagnosis ESR at diagnosis, Haemoglobin, at diagnosis Anaemia (haemoglobin <12 g/dL) at diagnosis Platelet count, Thrombocytosis, Albumin, alkaline phosphatase	With flare - - 21 (29.6) -	Without flare - - 18 (17.5) -	 ns ns 0.07 Nsp ns
			After 3 years of follow up n=165 Total duration of GC treatment, months Cumulative prednisone dose at end of follow-up, mg	With flare n=67 44.1 ± 30.5 12,482 ± 4805	Without flare n=98 28.1 ± 20.6 9194 ± 5088	 <0.001 <0.001
			Predictors of Flares (Relapses or Recurrences) at diagnosis: Leukocytosis (WBC >11,000/mm^3) Anaemia (haemoglobin <12 g/dL) Scalp tenderness	OR (95% CI) 1.86 (0.92-3.76) 2.17 (1.02-4.62) 1.73 (0.88-3.39)		 0.08 ns 0.04 0.11 ns
Overall results: There were no differences between groups regarding demographics nor presence of comorbidities (hypertension, diabetes, hypercholesterolemia) and clinical features. No difference in laboratorial results at diagnosis but there was a trend towards significance for anaemia that was integrated in a logistic regression analysis and presented as the only predictor of flare. Probability of flare (shown on fig) was higher in the first 5 years after disease diagnose. Total a cumulative dose of prednisolone was significantly higher in the flare group.						

Cid et al. 2006(46)	1 year? Not clear	-		Sustained remission	Relapsing course	
			ESR (mm/h)	62±9	117±6	0.0022
			Hb (gm/l)	121±3	92±4	0.0022
			Time to prednisolone < 10 mg (weeks)	23±3	77±32	0.0087
			Cumulated prednisolone (mg)	4881±174	7796±663	0.0159
			Genes differentially expressed in temporal artery samples from relapsing patients compared with remitting patients. CCL2 was further analyzed, please see below.	Up regulated: PRL-1, TREB 36,RAD 52, Neuronatin, PCAF 65beta, MRP8, CCL2, RhoA, RhoB, HSP 27 Down regulated: PTP-2C, NK-3R, OSF,PNAT/MNAT		
Overall results: Relapsing group needed significantly more time to achieve prednisolone levels <10 mg. CCL2 was overexpressed in patients with relapsing course. In the extended series, CCL2 transcripts were much more abundant in GCA samples (31.4±15.6 relative units) than in normal GCA specimens (0.44±0.10 relative units) (P=0.0001). No significant differences were observed in CCL2 values between GC untreated and treated patients, indicating that GC treatment for <1 week is not sufficient to significantly down-regulate CCL2 expression. A significant correlation was found between CCL2 and IL-1 (R=0.45, P=0.02), TNF-alpha (R=0.47, P=0.013) and IL-6 (R=0.52, P=0.0053) transcripts, supporting an interrelated regulation of these cytokines in GCA. CCL2 transcripts were significantly less abundant in samples from patients with disease related ischaemic events (3.1±1.5 vs 39.7±20, P=0.0243) CCL2 mRNA levels were significantly higher in patients who suffered ≥2 relapses. Time required to achieve a stable maintenance dose of prednisolone <10 mg/day, was significantly longer in patients with CCL2 mRNA levels higher than three relative units > **overall data suggests that CCL2 expression may be involved in persistence of inflammatory activity in GCA. Needs to be replicated**						
Salvarani et al. 2007(47)	GCA 74±7 Controls matched	GCA 78.6 Controls matched		GCA	Controls	OR (95% CI)
			Allele A2, A1	-	-	1.3 (0.9–2.0)
			Genotype A2/A2, A1/A2, A1/A1	-	-	1.3 (0.8–2.1)
			Carriage rate A2/A2 + A1/A2, A1/A1, A1/A1 + A1/A2, A2/A2	-	-	1.5 (0.5–4.3)
				With CIC	Without CIC	
			Allele A2, A1	-	-	

						2.1 (1.1–4.1) *
			Genotype A2/A2, A1/A2, A1/A1	-	-	1.9 (0.8–4.4) *
			Carriage rate A2/A2 + A1/A2, A1/A1, A1/A1 + A1/A2, A2/A2	-	-	5.2(1.1–24.8)*
			ESR	85±28	95±30	0.05
			CRP	6.6±4.4	10.5±6.6	0.02
			With AION n=25 without AION n=125	With AION	Without AION	OR/corrected p
			Allele			
			A2	15 (30.0)	35 (15.2)	2.4 (1.2–4.8)/0.046
			A1	35 (70.0)	195 (84.8)	
			Genotype			
			A2/A2	4 (16.0)	3 (2.6)	
			A1/A2	7 (28.0)	29 (25.2)	-/0.048
			A1/A1	14 (56.0)	83 (72.2)	
			Carriage rate			
			A2/A2 + A1/A2	11 (44.0)	32 (27.8)	2.0 (0.8–5.0)
			A1/A1	14 (56.0)	83 (72.2)	
			A1/A1 + A1/A2	21 (84.0)	112 (97.4)	7.1 (1.6–30.6)/0.038
			A2/A2	4 (16.0)	3 (2.6)	

CIC: cranial ischaemic complications * corrected p values were all non-significant

Overall conclusions: There were no differences in genotype and allele frequencies between GCA patients and controls. The distribution of the P1A1/A2 genotype differed significantly between GCA patients with and without AION, with higher frequencies in the AION group. This related to higher frequencies of P1A2/A2 homozygosity in the GCA patients with AION.

Of note: Cranial ischaemic complications were present in 30 patients at diagnosis. 8 out of 19 patients (42.1%) receiving antiplatelet therapy presented with CIC, compared with 22 of 118 patients (18.6%) who were not receiving antiplatelet therapy (*P*= 0.03, OR 3.2 [95% CI 1.1–8.8]).

Prieto-Gonzalez et al. 2017(48)	Pooled cohort 80 (57–92) Controls matched	Pooled cohort 76.3 Controls matched	Serum OPN levels (ng/mL; mean±SD)	Pooled GCA cohort 116.75±69.61	Controls 41.10±22.65	<0.001
				Active disease at diagnosis 102.45±57.72	Remission 46.47±23.49	<0.001
				Remission 48.78±23.97	Controls 41.10±22.65	ns
				Relapsers 129.08±74.24	Non relapsers 90.63±41.02	0.03
			Serum OPN levels (ng/mL; mean ± SD)	Remission with Prednisone 43.55±21.36 high dose 55.62±24.87 low dose	Remission with TCZ* 51.91±36.25 “	ns ns
			CRP	0.25±0.24 high dose 0.28±0.19 low dose	0.06±0.16 “	0.017 <0.001
			sOPN concentrations on pooled GCA cohort according to presence or absence of the following	Presence	Absence	
			Cranial symptoms	104.78±59.60	118.56±75.16	ns
			Systemic symptoms	118.45±61.70	82.70±57.50	0.028
			Ischaemic symptoms	79.91±57.90	117.29±61.32	0.028
			Strong SIR	132.56±77.56	97.46±53.40	0.039
			PMR / LVV / aortic dilation	-	-	ns

*TCZ : tocilizumab alone or in combination with low dose prednisone

Overall results: sOPN levels were higher in the pooled cohort of patients with active disease vs controls and in active disease vs remission. Patients with active disease with systemic symptoms and patients with strong SIR had significantly higher sOPN levels, while patients with ischaemic symptoms had lower levels.

sOPN levels were higher in relapsers vs non-relapsers and within the group of relapsers, patients ≥ 1 relapse demonstrated significantly higher sOPN levels (194.00±77.02) than those with only 1 relapse (98.52±50.72; p=0.007).

When analyzing the subset of patients in remission on glucocorticoids alone vs TCZ, sOPN remain detectable with no differences between groups, while CRP was significantly lower in the TCZ group, as expected. These results suggest that, unlike CRP, sOPN might be an interesting disease activity biomarker to be explored in TCZ-treated patients

Note: Using ROC analysis, an sOPN cut-off of 59.79 ng/dL resulted in a sensitivity and specificity of 80% and 84%, respectively, for patients with active GCA compared with healthy controls (area under the curve (AUC) 0.862, 95% CI 0.788 to 0.937; p<0.001). Moreover, a sOPN cut-off of 67.28 ng/ dL resulted in a sensitivity and specificity of 77% and 78%, respectively, to detect disease activity when analysing active patients and those in remission (AUC 0.836, 95% CI 0.764 to 0.907; p<0.001).						
Lozano et al. 2010(49)	78 (58–91)	72.13		GCA patients	Healthy controls	
			overexpression of ET-1	0.979	0.280	0.028
			overexpression of ECE-1 and ETAR and ETBR	Fig. higher	Lower	Significant
			mRNA expression ET-1, ECE-1, ETAR and ETBR	Fig. lower	Higher	<0.001
			circulating ET-1	1.112	1.119	ns
				With IC	Without IC	
			overexpression of ET-1, ECE-1 and ETAR and ETBR	-	-	ns
			circulating ET-1	1.205	1.048	0.032
				With weak inflammatory response	With strong inflammatory response	
			circulating ET-1	1.120	0.990	0.002
ET-1 endothelin 1, ECE-1 endothelin-converting enzyme, ETAR and ETBR endothelin receptors A and B. IC Ischaemic complication						
Overall conclusions: there is a significant overexpression of ET-1, ECE-1, ETAR and ETBR in the lesions of patients with GCA vs controls, even though there were no differences in the circulating levels of ET-1. There were no differences between patients with IC vs patients without IC but circulating ET-1 levels were significantly higher is patients with IC and patients with weak inflammatory response. Evaluating the effects of GC, there were no differences in the ET-1 concentration between temporal arteries from active patients' vs patients treated for a median of 8 days but, in both groups, ET-1 remained elevated when compared with control arteries. ECE-1 and ETAR levels were significantly lower in treated patients (p= 0.021 and 0.005 respectively). There were no differences regarding ETBR. Given the overall results, the authors argue that Incomplete regulation of the endothelin system with glucocorticoid treatment may at least partly explain why some patients continue to lose sight during the first days after GC therapy.						

Study ID	**Selection** 1)Representativeness of exposed cohort	**Selection** 2)Selection of the non-exposed cohort	**Selection** 3)Ascertainment of exposure	**Selection** 4)Demonstration that outcome of interest was not present at start of study	**Comparability** 1)Comparability of cohorts on the basis of the design or analysis	**Outcome** 1)assessment of outcome	**Outcome** 2)Was follow-up long enough for outcomes to occur	**Outcome** 3)Adequacy of follow up of cohorts	**Total n of stars** (only comparability can have two ∗
Kyle et al. 1989(31)	No description	Nsp	No description	Nsp	Nsp	Self-report	*	No statement	1

Hernandez-Rodriguez et al. 2003(32)	No description	Nsp	Medical and laboratorial records	No	Nsp	*blinded to clinical data	*	No statement	2
Weyand et al. 2000(33)	No description	Na	Medical and laboratorial records	*	Na	Self-report	*	*	3
Gudmundsson et al. 1993(34)	No description	No description	Medical and laboratorial records	*	Nsp	Self-report	*	No statement	2
Fukui et al. 2016(35)	No description	No description	Medical and laboratorial records	No	Unclear	Through medical record	*	No statement	1
Gonzalez-Gay et al. 2005(36)	*somewhat representative	*	Medical and laboratorial records	No	*adjusts for CV factors	Through medical record	Not clear	No statement	3
Cid et al. 1998(37)	*somewhat representative	*	Medical and laboratorial records	No	Nsp	other	Not clear	No statement	2
Lopez-Diaz et al. 2008(38)	*somewhat representative	*	Medical and laboratorial records	No	Unclear	Through medical record	Not clear	No statement	2
Liozon et al. 2000(42)	no description	Nsp	Medical records	No	Nsp	other	*	* only 3 pts lost to follow up	2
Gil et al. 2008(44)	no description	Nsp	Medical and laboratorial records	*	Nsp	no description	*	* inferred from the results	3
Martinez-Lado et al. 2011(45)	*somewhat representative	*	Medical and laboratorial records	*	*	Through records	*	* inferred from the results	6
Cid et al. 2006(46)	No description	Nsp	Medical and laboratorial records	*	Nsp	Through records	Not clear	Not clear	1

4.1.6 Supplementary Table 24. Biomarkers: risk of bias assessment (Newcastle-Ottawa scale for case-control studies)

Study ID	**Selection** 1) Is the case definition adequate?	**Selection** 2)Representativeness of the cases	**Selection of Controls** 3) Selection of Controls	**Selection** 4)Definition of Controls	**Comparability** 1)Comparability of cases and controls on the basis of the design or analysis	**Exposure** 1)Ascertainment of exposure	**Exposure** 2)Same method of ascertainment of cases and controls	**Exposure** 3)Non-response rate	**Total n of stars** (only comparability can have two ∗
Garcia-Martinez et al. 2010(29)	*	Nsp	No description	*	*	*	*	NA	5
Van der Geest et al. 2015(30)	*	Nsp	No description	*	*	*	*	NA	5
Duhaut et al. 1998(39)	Yes, medical filled questionnaire	*	*	*	*	*	*	NA	6
Liozon et al. 1995(40)	*	Nsp	No description	*	Nsp	*	*	NA	4
Chakravarty et al. 1995(41)	*	*	*	*	Nsp	*	*	NA	6
Coll-Vinent et al. 1999(43)	*	Nsp	No description	*	*	*	*	NA	5
Salvarani et al. 2007(47)	*	*	*	*	*	*	*	NA	7
Prieto-Gonzalez et al. 2017(48)	*	Nsp	No description	*	*	*	*	NA	5
Lozano et al. 2010(49)	*	Nsp	No description	*	Nsp	*	*	NA	4

5) PROGNOSTIC AND THERAPEUTIC IMPLICATIONS OF COMPLICATIONS/COMORBIDITIES

5.1 OBSERVATIONAL STUDIES (Prognostic and therapeutic implications of complications/comorbidities)

5.1.1 Supplementary Table 25. Evidence retrieved regarding prognostic and therapeutic implications of complications/comorbidities for giant cell arteritis: overview of included studies

Study ID	Study design	LoE	Overview	Inclusion criteria	Exclusion criteria	End of follow-up for analysis
GCA						
Prognostic implications						
Prospective						
Schmidt et al. 2016(50)	Prospective Case-control Multicenter	2b	Aims to verify the incidence of infection related hospitalizations and mortality in GCA patients	Newly diagnosed GCA fulfilling ACR criteria	malignancy, infectious disease, rheumatoid arthritis, systemic lupus erythematosus, periarteritis nodosa	1991-2009
Liozon et al. 2001(51)	Prospective cohort Single center	3b	Evaluates predictors of visual complications with emphasis on platelet count	Biopsy proven GCA fulfilling ACR criteria	No platelet count at diagnosis	Jan 1978 to Nov 1992
Garcia-Martinez et al. 2014(52)	Prospective Cohort	3b	Evaluates development of aortic structural damage and other disease outcomes like relapses	Biopsy proven GCA	-	Nsp
Retrospective						
Gonzalez-Gay et al.	Retrospective cohort Single center	3b	Focus on predictors of ischaemic visual complications	Biopsy proven GCA	-	January 1981 to December 1998

2000(53)						
Saleh et al. 2016(54)	Retrospective Cohort Multicentric	2b	Studies factors associated with visual complications and compares clinical and laboratorial patterns between patients with and without visual complications	Biopsy proven GCA	Absence of confirmation of visual complications by an ophthalmologist or visual complication preceding the onset/ unrelated to GCA or incomplete data > exclusion	1991 to 2010
Pego-Reigosa et al. 2004(55)	Retrospective cohort Single center	2b	Evaluates incidence and predictors of cerebrovascular accidents	Biopsy proven GCA	-	January 1981 to December 2001
Gonzalez-Gay et al. 2009(56)	Retrospective Cohort Single center	2b	Evaluates incidence and predictors of strokes	Biopsy proven GCA fulfilling ACR criteria	patients who had brief episodes of isolated vertigo or dysarthria, transient neurologic disturbances, transient ischaemic attacks, including those involving the carotid or the vertebrobasilar territories, were excluded	January 1st, 1981 to April 30th, 2008
Nesher et al. 2004(57)	Retrospective cohort Multicentric	2b	Evaluates risk factors of cranial ischaemic complications (CICs)	Biopsy proven GCA (152) + GCA fulfilling ACR criteria (239)	Less than 3 months of follow up	1980-2000
Grossman et al. 2017(58)	Retrospective Single center	2b	Evaluates the relationship of cardiovascular risk factors, baseline clinical features and selected medications with the development of severe cranial ischaemic events	Biopsy proven GCA Biopsy negative GCA patients were diagnosed according to physicians' judgment and fulfilled ACR criteria	Patients with only temporal biopsy demonstrating only vasa vasorum vasculitis were excluded	2000-2016

Hachulla et al. 2001(59)	Retrospective Single center	2b	Evaluates relapses and survival rates of GCA patients according to clinical, biological and treatment data	GCA fulfilling ACR criteria (at least 3) or 2 criteria + positive biopsy	-	1977 to 1995
Graham et al. 1981(60)	Retrospective Cohort Single center	3b	Evaluated survival, relapses and causes of death of GCA patients	GCA diagnosis	-	1968 to 1978
Kermani et al. 2013(61)	Retrospective Cohort Single center	2b	Evaluates time trends, influence of large vessel involvement in survival and predictors of large vessel involvement	GCA fulfilling ACR criteria	-	Used a cohort diagnosed between 1950 and 2004 and followed up until death or 31st December 2009
Uddhammar et al. 2002(62)	Retrospective Cohort Single center	2b	Evaluates cause specific mortality and factor that may relate to cardiovascular events	Biopsy proven GCA fulfilling ACR criteria PMR according to existence of myalgia and concordance with criteria suggested by Bird et al.	-	Patients diagnosed from 1973 to 1979 and followed until December 1995 or death.

5.1.2 Supplementary Table 26. Complications/comorbidities: outcome definition and statistical analysis

Study ID	Outcome/endpoint	Definition of outcome and others	Validation of outcome	Notes on analysis	Censoring at event
Schmidt et al. 2016(50)	Infection related hospitalizations Infection related mortality and overall mortality	Infection related hospitalizations: severe infections that required hospitalization	Nsp	Descriptive statistics, Wilcoxon's rank sum test, student t test, chi-square test, Fisher's exact test. Kaplan-Meier	Nsp
Liozon et al. 2001(51)	Visual ischaemic events Predictors of visual complications	Visual ischaemic events included visual events that occurred before therapy or within 2 weeks after its initiation, observed clinically or recalled by the patient. Included transient symptoms like amaurosis fugax, intermittent blurred vision and transient diplopia, and	Nsp	Descriptive statistics, Student *t* test, chi-squared, Fisher exact tests, Logistic regression analysis	Nsp

		permanent visual loss validated by a staff ophthalmologist (amaurosis due to either anterior ischaemic optic neuropathy or central retinal artery occlusion)			
Garcia-Martinez et al. 2014(52)	Aortic structural damage Remission Relapses Mortality	Aortic structural damage (ASD): focal dilatation (saccular or fusiform aneurysm) or, in the case of diffuse dilatation, when the aortic diameter exceeded 4 cm at the ascending aorta or reached at least 4 cm in the aortic arch/descending aorta or 3 cm at the abdominal aorta Relapses: recurrence of cranial, polymyalgic or systemic symptoms, including anaemia not attributable to other causes, which completely resolved by increasing prednisone 10 mg above the previously effective dose.	Nsp	Descriptive statistics, Student *t* test, Fisher exact tests, Kaplan-Meier survival analysis and log-rank test	Nsp
Gonzalez-Gay et al. 2000(53)	Disease complications with focus on visual Predictors of visual complications	Permanent visual loss was considered if partial or complete permanent visual involvement related to GCA was observed, despite any possible partial improvement related to GC therapy Cerebrovascular accidents: stroke and/or transient ischaemic attacks (attributed to GCA if they occurred at the onset of GCA manifestations or in a period no longer than 3 months after the pathologic diagnosis of GCA)	Nsp	Descriptive statistics, student T test, chi square test, fisher exact test, Wilcoxon rank-sum test, logistic regression analysis, ROC curves	Nsp
Saleh et al. 2016(54)	Predictors of visual complications	Visual complications identified by record linkage using ICD-10 codes as follows: Central retinal artery disorders H 34.0–34.2; Optic nerve pathologies, including optic nerve atrophy and optic disc atrophy H 47.0–47.2; Blindness, diplopia, visual field defect, subjective visual symptoms H 53–H 54; Amaurosis fugax G 45.3.	Nsp	Descriptive statistics, Mann-Whitney U; Student t Test; chi-square test; logistic regression	Nsp
Pego-Reigosa et al. 2004(55)	Predictors of cerebrovascular accidents (CVA) Mortality	CVA: stroke and/or transient ischaemic attack (TIA) evaluated within 2 years prior to, at the diagnosis of GCA, or thereafter	Nsp	Descriptive statistics, Student T test, chi square test, fisher exact test, Cox proportional hazard regression model, Nelson Aalen method	Nsp
Gonzalez-Gay et al. 2009(56)	Incidence of stroke Predictors of stroke	Stroke diagnosis was ascertained by positive imaging (CT and/or MRI read by neuroradiologist) + corresponding clinical features ascertained by a neurologist.	Neurologist reviewed CT and MRIs	Descriptive statistics Mann-Whitney U test, Fisher exact test, logistic regression models	Nsp
Nesher et al. 2004(57)	Cranial ischaemic complications (CICs)	CICs: Included CICs as presenting features or developing within 2 weeks of diagnosis. CICs developing later, during tapering of GC dose or following discontinuation of GC, were considered GCA related only	Nsp	Descriptive statistics Fisher exact test, multiple logistic regression models	Nsp

		when associated with at least 1 of the other GCA-related signs or symptoms, or laboratory evidence of acute-phase reaction (elevation of C-reactive protein or ESR).			
Grossman et al. 2017(58)	Severe cranial ischaemic events	Severe cranial ischaemic events: visual manifestations (transient or permanent visual loss) or CVA (stroke or transient ischaemic attack). Isolated diplopia was not considered a severe ischaemic event. Severe cranial ischaemic events were attributed to GCA if they occurred at diagnosis or up to 4 weeks after initiation of GC	Nsp	Descriptive statistics, Chi-Square test, independent t-test, multivariate analysis	Nsp
Hachulla et al. 2001(59)	Relapse Survival	Relapse: increase in ESR over 30 mm/h and/or CRP over 15 mg/L for more than 3 weeks, with or without symptoms, without intercurrent etiology (particularly without any kind of infection), that required increasing GC therapy with a favorable outcome	Nsp	Descriptive statistics, Chi-Square test, multivariate analysis, Kaplan-Meier and Mantel-Menszel methods	Nsp
Graham et al. 1981(60)	Survival Relapses Cause of death	Relapses: recurrence of symptoms and raised erythrocyte sedimentation rate	Nsp	Used a computer program (Surv-C) for survival analysis	Nsp
Kermani et al. 2013(61)	Time trends in large vessel involvement, mortality Survival Cause of death	Large vessel (LV) involvement was defined as LV complications including large artery stenosis, aortic aneurysm or aortic dissection/rupture detected within 1 year before diagnosis of GCA or at any time thereafter. Diagnosis of LV disease required confirmation by imaging, histopathology or autopsy.	Nsp	Descriptive statistics, Poisson regression models, Cox proportional hazards model, Gray's methods, Kaplan–Meier curves	Nsp
Uddhammar et al. 2002(62)	Survival Cause specific mortality Cardiovascular events	Transient ischaemic attack was defined as a focal neurological deficit of presumed ischaemic origin that persisted < 24 hours. Cardiovascular event also included dissecting aortic aneurysm, coronary angioplasty, amputation due to arterial insufficiency, pulmonary embolism diagnosed by pulmonary angiography or at autopsy, and deep vein thrombosis verified by phlebography.	Nsp	Descriptive statistics, Mann-Whitney U test, Kaplan-Meyer (survival), Cox regression analysis	-

5.1.3 Supplementary Table 27. Complications/comorbidities: intervention/treatment

5.1.4 Supplementary Table 28. Complications/comorbidities: population characteristics and control and comparison (results of outcome assessment and other results of interest)

Study ID	Follow-up duration	Age	Overall n. of patients	% females	Intervention	Outcomes/results of interest	Group 1	n	Group 2	n	Treatment Group 1	Treatment Group 2	p-value
Schmidt et al. 2016(50)	5 years	GCA 74.9±7.8 (women) 73.6±7.3 (men) Healthy controls matched	972	75	Symptom assessment Laboratorial workup	Incidence of infection during the first 12 months after diagnosis	GCA	486	Healthy controls	486	Nsp	Nsp	
											11.1/100 patient-years, [CI 8.3–14.6]	5.9/100 patient-years [CI 4–8.4]	Significant
Liozon et al. 2001(51)	Nsp		174	Healthy controls matched	Symptom assessment Laboratorial workup	Incidence of infection after the first year of diagnosis	With permanent visual loss	23	Without permanent visual loss	151	Standardized treatment protocol		
						Overall mortality				-		-	ns
						Deaths attributable to infection				fig		fig	<0.0003*
										23 (28%)		3 (6.5%)	< 0.0001
Garcia-Martinez et al. 2014(52)	Mean follow up of 10.3 (4-16.6) years		54		Symptom assessment Laboratorial workup Diagnostic imaging (x-ray, US, CT)	Infection-related hospitalization rates	1st screening (mean 5.4 y follow up) n=54 2nd screening (mean 8.7 y follow up) n= 36 3rd screening (mean 12.8 y follow up) n= 14				Nsp		
											36% in each 6-month period of evaluation		-
						Factors associated with overall mortality							
						GCA diagnosis					HR 2.22, 95% CI 1.54–3.21		< 0.0001
Gonzalez-Gay et al. 2000(53)	-		161		Symptom assessment Laboratorial workup Genetic analysis	Occurrence of a severe infection	With visual manifestations	42	Without visual manifestations	119	Standardized initial treatment		
											HR 2.08, 95% CI 1.30–3.33		0.0022
						Factors associated with overall mortality in GCA patients							
						occurrence of a severe infection	ns				HR 3.19, 95% CI 1.76–5.53		0.025
						GC ≥10 mg after 12 months of treatment					HR 1.93, 95% CI 1.08–3.47		0.0001
Saleh et al. 2016(54)	-		167		Symptom assessment Laboratorial workup	sex, a diagnosis of cancer during follow-up, diabetes, positive TAB, PMR symptoms, relapse of GCA, initial dose of GC, ESR	With visual complication	85	Without visual complications	82 -	Standardized initial treatment + immunosuppressive agents (MTX or azathioprine) when needed,		0.0001 ns
Pego-Reigosa et al. 2004(55)	62 ± 50 months Range: 3 days -240 months?		210		Symptom assessment Laboratorial workup	Factors associated with infection related mortality	With CVA	30	Without CVA	180	Standardized treatment protocol		
						GCA diagnosis					HR 9.3, 95% CI 2.7–31		0.0003
Gonzalez-Gay et al. 2009(56)	Minimum 4 weeks after diagnosis		287		Symptom assessment Laboratorial workup CT and/or MRI	diagnosis of diabetes (prior to inclusion or during the follow-up)	With stroke	8	Without stroke	279	Standardized treatment		
											HR 2.7, 95% CI 1.1–6.2		0.017
Nesher et al. 2004(57)	Minimum 3 months		175		Symptom assessment Laboratorial workup	GCA patients				175	Nsp		
Grossman et al. 2017(58)	Minimum 4 weeks after diagnosis		83		Symptom assessment Laboratorial workup		With severe cranial ischaemic	24	Without severe cranial	59	Nsp		

				Factors associated with infection related mortality in GCA patients			
				diagnosis of diabetes		HR 3.3, 95% CI 1.4–7.7	0.006
Hachulla et al. 2001(59)	Mean follow-up of 66.7 months [range 0.5 - 215]	133	Symptom assessment Laboratorial workup Diagnostic imaging	GC >10 mg after 12 months of treatment	133	Standardized treatment HR 4.61, 95% CI 1.58–15.56 -	0.0127 ns
Graham et al. 1981(60)	Mean 5 years (12 months to 12 years)	90	Symptom assessment Laboratorial workup	GCA patients	90	Standardized treatment	
Kermani et al. 2013(61)	8.8 years	204	Symptom assessment Laboratorial workup Diagnostic imaging	GCA	204	-	ns
Liozon et al. 2001(54)	75±7	63					
Udhaymar et al. 2002(62)	10 years (0-22)	171	Symptom assessment Laboratorial workup Diagnostic imaging	GCA PMR	136 35		

*testing according to inclusion period, overall mortality was significantly higher in the period of 1991 to 1997, but after 1997 the difference was non-significant.

Overall results: Severe infection was significantly more common in GCA patients than in general population during the first year after diagnosis. Subjects who developed a severe infection during the follow-up period were older than those who did not develop an infection (median age 77 years [range 51–95 years] versus 74 years [range 52–95 years]; P<0.0001). Infection related mortality was increased in GCA patients, especially if diagnosed with diabetes or requiring more than 10 mg/day of GC after the first year of treatment. Occurrence of infection was an important determinant of overall mortality.

Predictors of visual loss	OR, 95% CI	
Polymyalgia rheumatica	0.04 (0.01–0.5)	0.02
Constitutional symptoms	0.14 (0.02–0.77)	0.01
History of transient visual ischaemic symptoms	6.3 (1.4–29)	0.02
Jaw claudication, Abnormal temporal artery, positive TAB	-	All ns
CRP	0.35 (0.13–0.92)	0.03
Platelet count	3.7 (1.8–7.9)	0.001
Haptoglobin, Orosomucoid, Fibrinogen, Haemoglobin, Albumin, Hepatic abnormalities, ESR	-	All ns

Overall results: In this sample of patients 28% had visual ischaemic symptoms and 13% had permanent visual loss. Transient visual ischaemic symptoms and an increased platelet count were risk factors for permanent visual loss, whereas polymyalgia rheumatica, constitutional symptoms, and an elevated CRP level were associated with a reduced risk. Upper limb artery involvement was also associated with a favorable outcome: permanent visual loss developed in none of the 29 patients with this manifestation, compared with 23 (16%) of the remaining 145 patients (*P*=0.02). Risk of permanent visual loss was especially high in patients with platelet counts > 600 x 10^9/L.

Garcia-Martinez et al. 2014(52)	At 1st screening 79 (63-96)	At 1st screening 74.1	Patients that developed ASD from the initial cohort n (%)	16 (29.6)	
			Mortality directly related to aortic complications*	At least 1,9%	-
			Increased remission rate in patients with ASD vs without	-	0.004
			Lower rate of relapses in patients with ASD vs without	0.9±1.2 vs 2±1.5	0.006

			Shorter time to achieve a maintenance prednisone dose lower than 10 mg/day in patients with ASD vs without	45±32 vs 79 ±65 weeks	0.015
			Shorter time to withdraw treatments in patients with ASD vs without	213±37 vs 423±41 weeks	0.0001
ASD: aortic structural damage *missing data. 1st screening n=54 >8 died, 10 dropped out > 2nd screening n=36 > 4 died, 3 dropped out > 3rd screening n=29. **Overall results**: Aortic diameters increased over time, significantly in the case of ascending and descending aorta. This was at the expenses of patients with ASD in the first CT scan. Due to ASD, 8 patients had indication for surgery, however only 3 had surgery. In the remaining 5, surgery was not advised because of advanced age and comorbidities or patients' denial. There was a trend towards an increased mortality (any cause) among patients with ASD although differences did not reach statistical significance p=0.082. At the end of the follow-up period, 36 patients had been able to withdraw therapy. Patients who developed ASD exhibited lower levels of the acute phase reactants erythrocyte sedimentation rate and haptoglobin at different time points compared with patients who did not develop aortic dilatation (fig.). Patients with ASD had increased remission rates, fewer relapses and shorter time to achieve low prednisone doses when compared with patients without ASD.					
Gonzalez-Gay et al. 2000(53)	With visual manifestations 75.1±6.7 Without visual manifestations 74.6±6.0	With visual manifestations 54.8 Without visual manifestations 47.1		With visual manifestations (n=42)	
			Permanent visual loss n (%)	24(14.9)	
			Unilateral/bilateral	16(9.9)/8 (5.0)	
			Without amaurosis fugax/ After amaurosis fugax	12(7.5%)/12(7.5%)	
			Predictors of visual ischaemic complications		
			HLA DRB1*04 +	7.47 (2.01- 44.5)	0.004
			Anaemia (haemoglobin <12 g/dL)	0.07 (0.01- 0.40)	0.003
			Predictors of Permanent visual loss		
			Amaurosis fugax	12.63 (4.42 – 36.12)	<0.001
			Cerebrovascular accidents	26.51 (2.31- 304.00)	0.008
Overall results: Constitutional syndrome was more frequent in patients without visual manifestations (78.2% vs 59.5% p=0.019) and haemoglobin levels were lower in patients without visual manifestations (11.55 vs 12.07 p=0.034). There were no differences when comparing clinical and laboratorial features between patients with or without permanent visual loss, except for cerebrovascular accidents and amaurosis fugax, both more frequent in patients with visual complications (p= 0.0006 and p=<0.0001 respectively) On multivariate analysis, HLA DRB1*04 positivity and absence of anaemia were predictors of visual ischaemic complications and amaurosis fugax and cerebrovascular accidents were predictors of permanent visual loss.					
Saleh et al. 2016(54)	With visual complications	With visual complications		With visual complications	Without visual complications

	78.0 ± 7.3 Without visual complications 77.9 ± 6.6	69.4 Without visual complications 69.5	Complete visual loss (unilateral or bilateral)	21%	-	-
			Headache n (%)	63 (74)	73 (89)	0.01
			Jaw claudication n (%)	36 (42)	27 (33)	ns
			Fever n (%)	13 (23)	24 (40)	0.04
			Temporal artery tenderness n (%)	28 (33)	42 (51)	0.01
			Albumin g/l, median (IQR)	33 (29–35)	29 (26–34)	0.03
			CRP mg/l mean (SD)	83 (±52)	116 (±74)	0.002
			β - adrenergic inhibitors use	31 (37)	15 (18)	0.009
			hospitalizations (for any reason)	63 (74)	32 (40)	< 0.001
			median initial oral glucocorticoid dose mg (IQR)	60 (50-60)	40 (40-50)	< 0.001
			Predictors of visual complications (multivariate analysis)	OR 95% CI		
			β-adrenergic inhibitors use	6.98, 1.29–37.8		0.02
Overall results: patients with visual complications were less likely to have headaches, fever, and a palpable tender temporal artery and presented higher frequency of Beta-adrenergic inhibitors usage. Patients with visual complications had significantly lower CRP levels and those with a CRP level within the highest tertile (≥ 108 mg/l) had a reduced risk of visual complications compared with those in the lowest tertile (≤ 60 mg/l, OR 0.31, 95% CI 0.13–0.76). Absence of headache or abnormal temporal artery at clinical examination and the use of β-adrenergic inhibitors were significantly associated with a higher risk of visual complications on univariate analysis but only β-adrenergic inhibitors remained significant in multivariate analysis. The incidence rate of visual complications among patients with biopsy-proven GCA was 20.9 per 1000 person-years (95% CI 17.0–25.4) compared with 6.9 per 1000 person-years (95% CI 5.8–8.2) among the reference background population.						
Pego-Reigosa et al. 2004(55)	With CVA 74.8 ± 6.9 Without CVA 73.3 ± 7.5	With CVA 52.8 Without CVA 60.0	clinical and laboratory features at the time of diagnosis*	With CVA -	Without CVA -	ns
			Predictors of CVA	HR, 95% CI		
			Hypertension at diagnosis	2.68; 1.29 – 5.59		0.009
			Hyperlipidemia at diagnosis	2.37; 1.04 – 5.38		0.039
			Anaemia at diagnosis	0.52; 0.22 – 1.23		ns
			Anaemia, from the time of diagnosis until 120 months	0.34; 0.12 – 1.00		0.050
			Mortality in GCA patients with CVA vs without CVA	HR=1.53		ns
			Standardized mortality ratio in GCA due to CVA using the Spanish population 50 years and older as a reference	1.17		
*included (Headache, Constitutional syndrome, Abnormal temporal arteries, Jaw claudication, PMR, fever, Visual manifestations, Permanent visual loss, ESR, haemoglobin)						

Overall results: The incidence rate of CVA in biopsy proven GCA was 2,781/100,000 person-years in people 50 years and older. There were no differences between groups regarding clinical and laboratorial features nor regarding mortality rates. Comorbidities like Hypertension and hyperlipidemia at diagnosis were positively associated with development of CVA. Anaemia at diagnosis, was negatively associated with CVA however, in a longer follow up this was not observed.						
Gonzalez-Gay et al. 2009(56)	With stroke 74.4±9.0 Without stroke 75.3±6.8	With stroke 12.5 Without stroke 55.2		With stroke	Without stroke	
			Hypertension, hypercholesterolemia, diabetes mellitus	-	-	All ns
			Current smoker	4 (50.0)	41 (14.9)	0.02
			Visual ischaemic manifestations*	4 (57.1)	62 (22.1)	0.05
			Irreversible visual loss*	3 (42.9)	33 (11.8)	0.05
			ESR mm/1st h	81.6±20.0	93.8±22.7	ns
			Haemoglobin g/dL	13.2±1.5	11.7±1.6	0.009
				OR (95% CI)		
			Predictors of stroke (Carotid + Vertebrobasilar Territory)	(ROC) curve: 0.87		
			Female sex	0.10 (0.04-0.26)		<0.001
			Arterial hypertension	5.06 (1.02-25.12)		0.05
			Permanent visual loss	5.42 (1.26-23.39)		0.02
			Anaemia (hg<12)	0.11 (0.04-0.32)		<0.001
			Predictors of stroke Involving the Vertebrobasilar Territory	(ROC) curve: 0.84		
			Headache	0.15 (0.02-0.99)		0.05
			Anaemia (hg<12)	0.13 (0.04-0.47)		0.002
			Permanent visual loss, Current smoker	-		Both ns
*comparison between patients with vertebrobasilar Stroke vs without vertebrobasilar stroke at time of disease diagnosis **Overall results.** Frequency of strokes was significantly reduced in women compared to men (risk difference [RD] 4.66%; 95% CI, 63%-8.68%; p = 0.03). This difference by sex was also statistically significant when comparing GCA patients with vertebrobasilar stroke with the rest of GCA patients (RD, 3.90%; 95% CI, 0.13%-7.67%; p = 0.05). Smoking was more common in patients with stroke. There were no significant differences regarding comorbidities/other CV risk factors. Arterial hypertension and permanent visual loss were positive predictors of stroke while anaemia and female sex were negative predictors. For vertebrobasilar stroke only headache and anaemia presented as significant negative predictors.						
Nesher et al. 2004(57)	With CIC 75.3 ± 9.5 Without CIC	All patients 62,9	At presentation	With CICs		
			acute loss of vision n (%)	32 (18.3)		
			cerebrovascular accidents (CVA) n (%)	13 (7.4)		

	73.6 ± 8.12		Variables Associated with CIC at Presentation	OR, 95% CI	
			Transient cerebro-ophthalmic ischaemic episodes	4.3 1.8–10.3	0.001
			Male sex	2.5 1.1–5.4	0.02
			Systemic symptoms (Fatigue, fever, or anorexia)	0.3 0.1–0.6	0.002
			Aspirin use	0.3 0.08–1.02	0.06
			Variables Associated with CIC during follow-up		
			CIC at presentation	8.3 2.5–27.8	0.001
			Low-dose aspirin during follow-up	0.2 0.03–0.7	0.02
Overall results: At presentation, transient ischaemic episodes and male sex were positively associated with CICs while systemic symptoms (emphasis on fever) presented as protective. Aspirin use presented borderline significance as a protective factor. In 5 patients (36%) the late CICs developed within the first 2 weeks of GC therapy; in 6 others developed in the first year and in 3 occurred up to 30 months following initiation of GC. Altogether, 9 of the 42 patients with CICs at presentation developed late CICs despite GC therapy. In comparison, only 5 of the 124 without CICs at presentation developed late CICs, during the follow-up. During follow up, CICs at presentation were positively associated with late CIC occurrence and low dose aspirin use presented as a protective factor. There was no association with cardiovascular risk factors at presentation or during follow up. Transient ischaemic episodes were not evaluated as predictors in multivariate analysis during follow up given the small n (n=8), but were significant in univariate analysis (OR 14.8, CI 3.2–68.1, p=0.002)					
Grossman et al. 2017(58)	With severe CIC 74 ± 8 Without severe CIC 72 ± 9	With severe CIC 62.5 Without severe CIC 67.8		With severe CIC	Without severe CIC
			Predictors for severe cranial ischaemic events	OR, 95% CI	
			ESR	0.967, 0.94-0.99	0.043
			Beta blocker use	4.35, 1.33-14.2	0.015
			Jaw claudication, haemoglobin	-	Both ns
*comorbidities: Hypertension, Diabetes mellitus, Hypercholesterolemia, Congestive heart failure, Ischaemic heart disease, Cerebrovascular accident, Heavy smoking **Overall results:** jaw claudication was more common in patients with ischaemic complications and these presented with lower ESR and haemoglobin levels. There were no differences regarding other clinical or laboratorial features, comorbidities or selected medications, with exception to beta blockers, more common among patients with ischaemic complications. Beta blocker usage presented as a positive predictor of severe cranial ischaemic events while ESR was a negative predictor or, in other words, lower ESR appear to be "protective".					
Hachulla et al. 2001(59)	72 [56 - 89]	71.43	Transient visual loss n (%)	2 (1.5)	-
			Permanent visual loss n (%)	11 (8.2)	-
			Relapse during GC treatment n (%)	83 (62.5)	-
			Relapse after end of GC (prednisolone vs prednisone)	27 out of 47 vs 0 out of 9	<0.001
			Deaths n (%)	41 (30.7)	-
			Deaths related to GCA n (%)	3 (9.75)	-

			Reduction of survival in men vs women	Fig	0.02
			Reduction of survival in presence of initial visual loss vs absence	Fig	0.04*
			Better survival in patients treated with prednisolone vs prednisone	Fig	0.006*
			Better survival odds in patients requiring less than 10 mg /day of GC after 6 months of treatment vs requiring more	Fig	<0.001*
*were not significant on multivariate analysis. **Overall results:** There was a slight correlation of relapse with initial ESR ($p < 0.001$, $r = 0.29$), but not with CRP. No correlation was found between relapse of the disease and age, number of ACR criteria, initial GC dose, duration of initial attack treatment, number of relapses during the treatment, duration of the treatment and initial ESR. Relapses after end of treatment were more frequent in patients treated with prednisolone vs prednisone. There were no differences in survival when compared initial daily GC dose, duration of attack dose, presence versus absence of headache, ESR more versus less than 50 mm/h, relapse vs recurrence of disease. Men and patients with initial visual loss presented worse survival rates compared to women and absence of visual loss respectively. Patients with prednisolone presented better survival than patients on prednisone as did patients requiring less than 10 mg /day of GC after 6 months of treatment. Patients with prednisone developed more diabetes mellitus (6/47 vs 7/86), fractures (7/47 vs 10/86) and cardiovascular deaths (6/12 vs 10/28) but the differences were non-significant.					
Graham et al. 1981(60)	Range 55 to 88	71.11	Number of deaths	32	
			Number of patients with relapses	18	
			Factors with prognostic relevance concerning survival		
			Visual loss		0.0024
			Dizziness with diplopia		0.0291
			Daily GC dose >10 mg		0.0003
			Sex, headache, PMR, tender scalp, angina, relapse, season of presentation, ESR, haemoglobin, White blood cell count		All ns
Overall results: There was a significantly increased mortality among women vs general female population (p=0 007) but no significant difference in men (p=0 67). Visual loss and daily GC dose above 10 mg related to increased mortality.					
Kermani et al. 2013(61)	76±8.2	80	(HR, 95% CI)	Large artery stenosis	Aortic aneurysm/ dissection
			Smoking, ever	2.4 (1.04 to 5.4)	1.8 (0.9 to 3.8)	Significant
			Bruit at diagnosis of GCA	11.7 (3.6 to 37.4)	0.8 (0.1 to 6.0)	Significant
			Coronary artery disease before incidence of GCA	1.4 (0.5 to 4.4)	5.3 (2.2 to 13.1)	Significant

			Transient ischaemic attack/stroke before incidence of GCA	3.5 (1.3 to 9.6) -	0.8 (0.2 to 3.2) -	Significant
			Age, sex, headache, jaw claudication, scalp tenderness at diagnosis, PMR, Haemoglobin, ESR, glucocorticoids dose, hypertension, hyperlipidemia, number of relapses			All ns
			Influence of LV manifestations on survival	HR, 95% CI		
			higher mortality in GCA with LV involvement vs without	HR=2.4; 95% CI 1.6 to 3.6		
			higher mortality in GCA with aortic dissection/aneurysm	HR=3.4; 95% CI 2.2 to 5.4		
			Similar mortality in patients with artery stenosis vs without	HR=1.5; 95% CI 0.9 to 2.5		
Time trends: Cumulative incidence of LV manifestations was significantly higher in patients diagnosed between 1980-2004 (24.9%) vs 1950-1979 (8.3%), p=0.004, aortic dissection did not follow this time-trend. Rate of occurrence of any LV disease was high within the first year of GCA (5 events per 100 person-years); the incidence of artery stenosis remained relatively constant beyond 5 years from diagnosis of GCA (p=0.77) but the incidence of aortic aneurysm/dissection increased after 5 years (p=0.009). There were no time trends on mortality analysis. **Survival**: overall survival of the cohort was similar to general population. Survival was reduced if any LV manifestations occurred (log-rank p<0.001). Survival was worse in patients with aortic dissection/ aneurysm but not according to stenosis. **Cause specific mortality:** standardized mortality ratios (SMR) of entire cohort vs general population were not significantly different except for digestive system and vascular diseases, more common in the case cohort. SMR of the subset with aortic manifestations vs general population had significant differences, with patients dying more due to circulatory system disease, respiratory system and all-cause mortality.					
Uddhammar et al. 2002(62)			Standard mortality ratio (SMR) in women with GCA and PMR	133 (95% CI 110–162)		
			Death due to cardiovascular disease (SMR)			
			Men	149 (95% CI 118–189)		
			Women	158 (95% CI 112–224)		
			SMR			
			Female patients with ESR ≥ 110 mm/h	178 (95% CI 124–256)		
			Female with initial prednisolone dose ≤ 40 mg/day	175 (95% CI 127–240)		
			Female with prednisolone dose of ≥10 mg/day at 12 months	157 (95% CI 104–238)		

			Factors associated with first cardiovascular event		
			Hypertension	1.78 (95% CI 1.11–2.83)	
			SMR in GCA women		
			Ischaemic heart disease	157 (95% CI 105–233)	
			Cerebrovascular disease	142 (95% CI 79–255)	
			Aneurysm	208 (95% CI 54–805)	
			SMR in GCA men		
			Ischaemic heart disease	180 (95% CI 115–279)	
			Cerebrovascular disease	58 (95% CI 15–228)	
			Aneurysm	120 (95% CI 17–849)	
Overall results: Death due to CVD was significantly increased in both women and men. Increase was mainly due to ischaemic heart disease (IHD), SMR GCA and PMR = 151 (95% CI 107–213) and SMR = 189 (95% CI 123–287), respectively for women and men. Similar results were obtained for GCA group only. Female patients with ESR ≥ 110 mm/h at diagnosis, initial prednisolone dose ≤ 40 mg/day, or prednisolone dose 10 mg/day at 12 months had a significantly increased mortality. Mortality due to cardiovascular disease was higher in patients with GCA compared with PMR (p = 0.05). Overall survival rate did not differ between male and female patients (p=0.26).					

5.1.5 Supplementary Table 29. Complications/comorbidities: risk of bias assessment (Newcastle-Ottawa scale for cohort studies)

Study ID	**Selection** 1)Representativeness of exposed cohort	**Selection** 2)Selection of the non-exposed cohort	**Selection** 3)Ascertainment of exposure	**Selection** 4)Demonstration that outcome of interest was not present at start of study	**Comparability** 1)Comparability of cohorts on the basis of the design or analysis	**Outcome** 1)assessment of outcome	**Outcome** 2)Was follow-up long enough for outcomes to occur	**Outcome** 3)Adequacy of follow up of cohorts	**Total n of stars** (only comparability can have two *)
Liozon et al. 2001(51)	*	*	* structured interview	No	*	Medical records and self-report	Not clear	No statement	3
Garcia-Martinez et al. 2014(52)	No description	Na	Medical evaluation	No	Na	*	*	High rate of drop outs	2
Gonzalez-Gay et al. 2000(53)	*	*	Case records	No	*	Medical records	Not clear	No statement	3

Saleh et al. 2016(54)	*	*	*	No	*	Medical records	Not clear	No statement	4
Pego-Reigosa et al. 2004(55)	*	*	Case records	No	*	Medical records	*	*	5
Gonzalez-Gay et al. 2009(56)	*	*	*	No	*	Medical records	*	*	6
Nesher et al. 2004(57)	*	*	Case records	No	*	Medical records	*	*	5
Grossman et al. 2017(58)	*	*	Medical records	No	*	Medical records	*	*	5
Hachulla et al. 2001(59)	*	*	Medical records	No	*	Medical records	*	*	6
Graham et al. 1981(60)	No description	Na	Case notes	No	*	Medical records	*	*	3
Kermani et al. 2013(61)	*	Na	*	No	Na	*	*	No statement	4
Uddhammar et al. 2002(62)	*	Na	Case records	*	Na	*	*	No statement	4

5.1.6 Supplementary Table 30. Complications/comorbidities: risk of bias assessment (Newcastle-Ottawa scale for case-control studies)

Study ID	**Selection** 1)Is the case definition adequate?	**Selection** 2)Representativeness of the cases	**Selection of Controls** 3) Selection of Controls	**Selection** 4)Definition of Controls	**Comparability** 1)Comparability of cases and controls on the basis of the design or analysis	**Exposure** 1)Ascertainment of exposure	**Exposure** 2)Same method of ascertainment of cases and controls	**Exposure** 3)Non-response rate	**Total n of stars** (only comparability can have two ∗)
Schmidt et al. 2016(50)	No description	unclear	*	*	**	*	*	Na	6

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