Prognosis and Disease Activity

6

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Abstract

Current evidence suggests that overall mortality is not increased in giant cell arteritis (GCA) although cardiovascular complications and comorbidities are more frequent than in the general population. This chapter gives an overview on current evidence of prognostic risks and biomarkers in GCA, including clinical, laboratory, and imaging markers, together with some future perspectives.

Keywords

Biomarker · Comorbidities · Mortality · Prognosis · Vasculitis

Current evidence suggests that overall mortality is not increased in giant cell arteritis (GCA) [1] although cardiovascular (CV) complications and comorbidities are more frequent than in the general population (Tables 6.1 and 6.2).

This chapter gives an overview on current evidence of prognostic risks and biomarkers in GCA, including clinical, laboratory, and imaging markers, together with some future perspectives.

6.1 Risk for Complications and Comorbidities During Disease Course

Overviews on the risk of CV complications and other comorbidities are given in Tables 6.1 and 6.2. In summary, GCA implies an about twofold increased risk for CV disease [2–4], especially for aortic aneurysm, stroke, myocardial infarction, and

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Table 6.1 Risks of increased cardiovascular complications in GCA patients compared to general population (Ranges given in brackets indicate 95% confidence intervals). Studies were excluded if not significant or already included in meta-analyses (marked as MA). *CerV* cerebrovascular, *CI* 95% confidence interval, *CIC* cranial ischemic complication, *HR* hazard ratio, *RaR* rate ratio, *MA* meta-analysis, *RiR* risk ratio, *RR* relative risk, *SHR* subhazard ratio

CV complications and comorbidities	Risk vs. general population	Ref.
CV disease	HR 1.49 (1.37–1.62) HR 2.01 (1.62–2.48)[a] HR 3.00 (1.78–5.13)	[2] [3] [4]
Arterial hypertension	RaR 1.31 (1.17–1.46) OR 1.12 (1.03–1.21) HR 1.24 (1.17–1.32)	[7] [8] [9]
Atherosclerosis	RR 1.44 (1.00–2.07) HR 3.70 (1.49–9.44)	[9] [4]
• Aortic aneurysm	HR 1.98 (1.50–2.62) SHR 1.92 (1.52–2.41)	[9] [10]
• CerV accident: Stroke, CIC	HR 1.40 (1.27–1.56) RaR 1.40 (1.12–1.74) HR stroke + TIA 1.41 (1.29–1.55)	MA [11] [7] [9]
• Coronary artery disease	RiR 1.51 (0.88–2.61) HR 4.9 (1.52–15.77)	MA [12] [4]
	OR 1.25 (1.15–1.36) HR 1.37 (1.18–1.59)	[8] [9]
• Pericarditis	OR 1.69 (1.16–2.14)	[13]
• Myocardial infarction • Angina pectoris • Heart failure • Atrial fibrillation	HR 1.57 (1.36–1.82) HR 1.77 (1.29–2.43) HR 1.94 (1.39–2.70)[a] HR 1.36 (1.17–1.58) RR 2.40 (1.74–3.32) HR 1.46 (1.29–1.65) HR 1.29 (1.19–1.39)	[9] [14] [3] [9] [15] [9] [9]
• Peripheral vascular disease	HR 1.88 (1.04–3.41) HR 1.75 (1.49–2.06)	MA [16] [9]
Venous thromboembolic events		
• Venous thromboembolism	HR 2.26 (1.38–3.71) HR 2.49 (1.45–4.30) HR 2.03 (1.77–2.33) RR 2.06 (1.75–2.44)	MA [17] [18] [9] [19]
• Deep venous thrombosis	HR 2.70 (1.39–5.54) HR 1.96 (1.57–2.46) HR 2.50 (1.62–3.85)	[18] [19] [15]
• Pulmonary embolism	HR 2.71 (1.32–5.56) RR 2.25 (1.78–2.85)	[18] [19]

[a]Adjusted for age and sex

peripheral vascular disease (Table 6.1). Similarly, the prevalence of venous thromboembolic events is increased in GCA patients by about twofold (Table 6.1) although antiphospholipid syndrome and GCA appear to be different and independent diseases [5]. The use of an immunosuppressant can be considered as a protective factor

Table 6.2 Summary on risks for non-cardiovascular comorbidities in GCA (ordered according to amount of risk compared to general population, with highest risk rated on top). The risk of diabetes was excluded, as recent data are contradictive [9, 15, 20]. Ranges in brackets indicate 95% confidence interval; *HR* hazard ratio, *MA* meta-analysis, *OR* odds ratio, *RaR* rate ratio, *RiR* risk ratio, *RR* relative risk, *SHR* subhazard ratio

Complication and comorbidity	Risk vs. general population	Ref.
Osteoporosis • Fractures	RR 2.90 (2.35–3.66) RaR 2.81 (2.33–3.37) RaR 1.56 (1.31–1.85)	[15] [7] [7]
Gastritis and duodenitis	RR 2.40 (1.39–4.29)	[15]
Thyroid disease • Hypothyroidism	RaR 1.55 (1.25–1.91) OR 1.30 (1.19–1.42)	[7] [21]
Renal disease, moderate to severe	HR 1.32 (1.25–1.39)	[9]
Psychiatric disease • Depression	RaR 1.28 (1.12–1.46) HR 1.37 (1.26–1.49)	[7] [9]
Dyslipidemia	HR 1.26 (1.15–1.37)	[9]
Obesity	HR 1.23 (1.14–1.32)	[9]
Malignancy	RiR overall 1.14 (1.05–1.22)	MA [22]

against new cardiovascular events, suggesting an effect against vascular inflammation that may favor the new vascular events in GCA [6].

Out of the other non-CV comorbidities, osteoporosis and gastritis are the most important risks of GCA patients (Table 6.2). Both these diseases depend on the use of glucocorticoids (GCs), which is still the first-line treatment for GCA. As a consequence, these diseases have to be routinely considered for monitoring and possible adjunctive treatment during follow-up.

In conclusion, GCA is not only affecting the risk for arterial but also for venous events, and both of them have to be monitored during disease course. Also, non-CV comorbidities should be monitored, especially for osteoporosis and gastritis. As all of the risks for CV and other morbidities mentioned above maybe clinically relevant, they should be included into the information for GCA patients and their carers, both at diagnosis and regularly during follow-up.

6.2 Risk Factors and Biomarkers for Disease Activity in Giant Cell Arteritis

Until today, a single sensitive prognostic clinical parameter or (composite) score to assess disease activity during the course of both cranial GCA and the extracranial large vessel type of GCA is not available. Prognostic risk factors, both the risk factors with increased and those with reduced risk for disease activity and CV complications are separately listed in Tables 6.3 and 6.4. The aim of these tables is to increase the awareness for improved patients' information especially for the factors with increased prognostic risk.

Table 6.3 Summary of prognostic factors for increased disease activity and cardiovascular complications in GCA (with 95% confidence intervals given in brackets). *Aaneurysm* aortic aneurysm, *Adilatation* aortic dilatation, *CHADS2* score of congestive heart failure, age > 75 years, diabetes, stroke, *CIC* cranial ischemic complication, *CRP* C-reactive protein, *CV* cardiovascular, *CEV* cerebrovascular, *DAA* dissection of AA, *ESR* erythrocyte sedimentation rate, *Hb* hemoglobin, *IHD* ischemic heart disease, *Ievent* ischemic event, *RF* risk factor, *LVI* large vessel involvement, *OR* Odds ratio, *pts.* patients, *vs.* versus, *SHR* subhazard ratio

Prognostic factors	Effect on course of GCA	Ref.
Patients' characteristics		
Age • <85 years • >77 years	HR malignancy 2.68 (1.87–3.84) HR CV event (hospitalization) 5.0 (1.40–17.54)	[29] [30] [4]
Male gender	OR IHD 2.546 (2.316–2.799) SHR Aaneurysm 2.10 (1.38–3.19)	[8] [10]
Body mass index (1 kg/m^2 increment)	OR IHD 1.011 (1.003–1.018)	[8]
Disease characteristics		
Large vessel involvement		
• Symptomatic limb involvement	HR CV complication 5.73 (2.94–11.28)	[31]
• Jaw claudication	OR permanent vision loss 2.11 (1.09–4.10)	[30]
CHADS2-score [32] • =1 • ≥2	OR permanent vision loss 10.72 (1.23–93.8) OR permanent vision loss 24.78 (2.87–213.86)	[33] [33]
Laboratory parameters • Thrombocytosis • ESR >100 mm/h, Hb <11 g/dL or platelet count >450,000/mm^3	OR permanent vision loss 3.1 (1.02–10.14) HR Aaneurysm 3.71 (1.50–9.19)	[33] [34]
Imaging findings		
• Inflammation of aorta ± branches • Large-artery stenosis at diagnosis	HR CV event 3.42 (2.09–5.83) HR Adilatation 9.30 (3.74–31.05) HR new IE 1.86 (1.01–3.59) HR CV event 2.75 (1.80–4.15) HR new Ievent 6.08 (3.44–10.87)	[6] [6] [6] [6] [6]
Exposition and other risk factors		
Smoking status: • Ex-smoker • Current smoker	SHR Aaneurysm 2.20 (1.22–3.98) OR pericarditis: 1.55 (1.05–2.27) SHR Aaneurysm 3.79 (2.20–6.53) OR IHD 1.493 (1.363–1.635)	[10] [13] [10] [8]
Prior antihypertensive treatment Use of beta blockers	SHR Aaneurysm 1.62 (1.00–2.61) OR CEV Ievent 4.35 (CI, 1.33–14.2)	[10] [35]
Comorbidities • Diabetes mellitus • Arterial hypertension • Hyperlipidemia • CV comorbidities	OR IHD 1.665 (CI 1.530–1.812) HR CV event 2.03 (CI 1.14–3.41) HR new Ievent 3.61 (1.70–7.17) HR eye symptoms 1.29 (1.10–1.53) OR IHD 3.025 (2.700–3.394) HR eye symptoms 1.17 (1.03–1.32) HR Aaneurysm 4.73 (1.87–11.9) OR IHD 3.830 (3.291–4.478) HR CV event 6.20 (2.00–19.24)	[8] [6] [6] [36] [8] [34] [36] [8] [4]
• Previous coronary artery disease	HR new Ievent 5.10 (2.02–11.21)	[6]

Table 6.4 Summary of positive prognostic factors, indicative for a decreased disease activity and cardiovascular complications in GCA (with 95% confidence intervals given in brackets). *Aaneurysm* aortic aneurysm, *CI* 95% confidence interval, *CIC* cranial ischemic complication, *CV* cardiovascular, *CEV* cerebrovascular, *DAA* dissection of Aaneurysm, *HR* hazard ratio, *Ievent* ischemic event, *OR* Odds ratio, *SHR* subhazard ratio

Prognostic factors	Effect on course of GCA	Ref.
Patients' demographics		
Age	HR DAA 0.27 (0.09–0.86)	[29]
Female gender	HR eye symptoms 0.71 (0.64–0.79)	[36]
Disease characteristics		
• Axillary artery vasculitis	OR permanent vision loss 0.08 (0.03–0.27)	[33]
• Cranial signs	HR CV event 0.64 (0.42–0.98)	[6]
• Fever ≥38 °C	OR permanent vision loss 0.30 (0.14–0.64)	[30]
• Constitutional symptoms	OR permanent vision loss 0.28 (0.09–0.81)	[33]
Low ESR	OR CEV Ievent (0.94–0.99)	[35]
Comorbidities and treatment		
Prior diabetes mellitus	SHR Aaneurysm 0.19 (0.05–0.77)	[10]
Low-dose aspirin at follow-up	OR CIC 0.2 (0.03–0.7)	[37]
Statin use	HR CV event 0.993 (0.986–0.999)	[4]

More biomarkers for assessing disease activity in GCA are under ongoing investigation. Only a few studies applied scores. The Birmingham Vasculitis Activity Score (BVAS), which had been developed for different types of vasculitis, has been prospectively evaluated in the follow-up of GCA patients, but showed only limited utility in GCA [23]: Patients with active GCA disease could have a BVAS of 0, and many important ischemic symptoms attributable to active vasculitis were not included in the composite score.

As an important consequence for the clinic, each single sign and symptom has to be separately considered as possible marker for disease deterioration or relapse. Laboratory and imaging biomarkers may then be helpful to provide additional information and support the clinical suspicion or exclusion of GCA disease activity.

From the laboratory perspective, GCA lacks disease-specific serum biomarkers for prognostic purposes. Although multiple parameters have been proposed, these are all unspecific for GCA and have not been validated for monitoring disease activity and estimating disease prognosis [24]. It appears that the most promising biomarkers are serum amyloid A (SAA, 83× > control median values), interleukin-23 (IL-23, 58×), and interleukin-6 (IL-6, 11×), with changed levels of SAA, C-reactive protein (CRP), haptoglobin, erythrocyte sedimentation rate (ESR), MMP-1, MMP-2, and TNF-alpha associated with relapse and visual disturbances [24]. In patients without cranial involvement, antibodies against ferritin maybe useful activity markers [25]. For patients treated with tocilizumab (TCZ), CRP is not valid. As an alternative, osteopontin was proposed for monitoring of these patients under current treatment with tocilizumab [26].

Concerning prognostic imaging biomarkers, the use of sonography, FDG-PET, MR, and CT-angiograms has not been studied sufficiently. Although not yet established, new imaging scores may become helpful for the future [27]. For assessing changes in arterial wall inflammation in response to GCs and methotrexate (MTX), the results are mixed and represent only small patient cohorts. In a prospective study by Blockmans et al., no difference in the predictive value of FDG uptake was found between relapsing and non-relapsing patients [28].

6.3 Additional Biomarkers for Assessment of Prognosis-Relevant Comorbidities

Prognosis-relevant comorbidities maybe age-, disease-, and treatment related. For clinical follow-up of prognosis-relevant comorbidities, selected parameters routinely available and usually applied are listed in Table 6.5.

For immune aging with increased risk of infection and malignancies, but also with increased risk for CV events, no specific laboratory test has been established so far. For experimental purposes, FACS analysis can be performed to evaluate the percentage of proinflammatory $CD4^+CD28^-$ T cells out of the $CD3^+CD4^+$ T cells [38, 39].

Table 6.5 Summary of prognosis-relevant comorbidities and possible clinical use of biomarkers before and during treatment of GCA (including data from [40], modified). *GC* glucocorticoid, *CT(A)* CT with angiogram, *CV* cardiovascular, *ECG* electrocardiogram, *GC* glucocorticoids, *IL6R* interleukin6-receptor (e.g., with tocilizumab), *MR(A)* MR with angiogram, *MTX* methotrexate

Prognosis-relevant comorbidities	Biomarkers used in clinical practice
Age-related	
• CV-diseases (e.g., atherosclerosis, myocardial infarction)	Sonography, echocardiography, ECG, Trop T/Trop I, Myoglobin
• Immune aging with increased risk of infection and malignancies	CRP, procalcitonin
• Renal dysfunction (e.g., with hyperuricemia)	Creatinine
GCA-related	
• Visual deterioration and visual loss	Ophthalmological exam
• GCA-specific CV-diseases (e.g., aortic dilatation/aneurysm, arterial stenosis/occlusion)	Chest radiograph, echocardiography, sonography, MR(A), CT(A), FDG-PET
Treatment-related	
• Under GCs (e.g., weight gain, arterial hypertension, diabetes mellitus, renal dysfunction, osteoporosis, peptic ulcer disease, glaucoma)	Body weight, blood pressure, HbA1c, creatinine, bone density, gastroscopy, gonioscopy/tonometry
• Under IL6R-blockade (e.g., hyperlipidemia, neutropenia, elevation of liver enzymes)	Lipids, neutrophils, liver enzymes
• Under MTX (e.g., leucopenia, elevation of liver enzymes)	Blood count, liver enzymes

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