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Peer-reviewed author version

Moreel, Lien; Betrains, Albrecht; MOLENBERGHS, Geert; Vanderschueren, Steven & Blockmans, Daniel (2023) Epidemiology and predictors of relapse in giant cell arteritis: A systematic review and meta-analysis. In: JOINT BONE SPINE, 90 (1) (Art N° 105494).

DOI: 10.1016/j.jbspin.2022.105494
Handle: http://hdl.handle.net/1942/39282

Journal Pre-proof

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PII: S1297-319X(22)00154-3

DOI: https://doi.org/doi:10.1016/j.jbspin.2022.105494

Reference: BONSOI 105494

To appear in: *Joint Bone Spine*

Received Date: 29 August 2022

Revised Date: 27 September 2022

Accepted Date: 10 November 2022

Please cite this article as: Moreel L, Betrains A, Molenberghs G, Vanderschueren S, Blockmans D, Epidemiology and predictors of relapse in giant cell arteritis: a systematic review and meta-analysis, *Joint Bone Spine* (2022), doi: https://doi.org/10.1016/j.jbspin.2022.105494

Epidemiology and predictors of relapse in giant cell arteritis: a systematic review and meta-analysis

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Highlights

- Half of patients with giant cell arteritis experience relapse mainly during the first two years.
- 30% of patients had at least 2 relapses and 17% at least 3 relapses.
- Female sex and large vessel involvement are predictors of relapse.

Abstract

Objectives: The aim of this study was to estimate the timing of relapse, the prevalence of multiple relapses and the predictors of relapse in patients with giant cell arteritis (GCA).

Methods: PubMed, Embase and Cochrane databases were searched from inception till November, 30 2021. Outcome measures include cumulative relapse rate (CRR) of first relapse at year 1, 2, and 5 after treatment initiation, CRR of second and third relapse and predictors of relapse.

Results: Thirty studies (2595 patients) were included for *timing* of relapse, 16 studies (1947 patients) for prevalence of *multiple* relapses and 40 studies (4213 patients) for *predictors* of relapse. One-year, 2-year and 5-year CRRs were 32% [95% confidence interval (CI) 22 – 43%], 44% [95% CI 31 – 59%], and 47% [95% CI 27 – 67%], respectively. The duration of scheduled glucocorticoid therapy was negatively associated with the 1-year CRR (p = 0.03). CRR of second and third relapse were 30% [95% CI 21 – 40] and 17% [95% CI 8 – 33%], respectively. Female sex (OR 1.43) and large vessel involvement (OR 2.04) were predictors of relapse.

Conclusion: Relapse occurred in almost half of GCA patients mainly during the first two years after diagnosis. One in three patients had multiple relapses. The optimal glucocorticoid tapering schedule, which seeks a balance between the lowest relapse risk and the shortest glucocorticoid duration, needs to be determined in future studies. Longer scheduled glucocorticoid therapy or early introduction of glucocorticoid-sparing agents may be warranted in female patients and patients with large vessel involvement.

Keywords: Giant cell arteritis – GCA – relapse

1. Introduction

Giant cell arteritis (GCA) is a large vessel vasculitis that typically affects the cranial arteries, aorta, and its proximal branches [1,2]. GCA represents a heterogeneous group of patients with distinct presentations according to the pattern of vessel involvement (cranial versus large vessel vasculitis or combined).

Glucocorticoids (GC) are the cornerstone of GCA treatment. After GC initiation, clinical manifestations and systemic inflammation typically resolve quickly and ischemic complications become rare [2]. However, in a meta-analysis, Mainbourg et al. showed that relapse occurred in approximately half of patients during the disease course [3]. Frequent relapses require prolonged administration of GC, which implies a significant risk of GC-related toxicity [4,5]. In addition, relapses increase the risk of microvascular and macrovascular complications. The meta-analysis by Aussedat et al. showed that major relapses occurred in 8% of all relapsing patients, defined as an ophthalmological, neurological or other ischemic event or an aortic complication related to GCA [6]. Finding prognostic variables that may help in the early identification of patients at risk of relapse, may significantly reduce GC exposure. Patients with good prognostic factors could be treated with shorter courses of GC. On the other hand, bad prognostic variables could prompt longer scheduled GC therapy or early initiation of GC-sparing agents to minimize the risk of relapse and complications. However, data on the timing of relapse, the prevalence of multiple relapses and predisposing factors were not assessed in previous meta-analyses.

The aim of this systematic review and meta-analysis was to estimate the prevalence of relapse at specific time points, the prevalence of multiple relapses and predictors of relapse in patients with GCA.

2. Methods

This systematic review was informed by the Cochrane Collaboration Handbook and was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements [7,8]. This study was registered in advance in PROSPERO database (CRD42022302803).

2.1. Search strategy

We performed a systematic literature search in PubMed, Embase, and Cochrane database from inception till November 30, 2021. We used keywords for GCA and relapse, using both free text and MeSH and Emtree terms. Full search terms are described in Table S1 [See the supplementary material associated with this article online]. The search was limited to articles

published in English, French or Dutch. The references of relevant articles were screened to identify additional studies.

2.2. Study selection

We included studies fulfilling the following criteria: (1) randomized controlled trials (RCT) or observational studies, (2) only involving patients with GCA (3) treated with GC alone (entire study or control arm of trials testing GC-sparing agents) (4) reporting on the prevalence or predictors of relapse. For the estimation of the timing of relapses and the prevalence of multiple relapses, studies with several treatment options were only included if results of the different treatment groups were presented separately or if at least 80% of patients were treated with GC in monotherapy. For the determination of predictors of relapse, patients could be treated with GC in monotherapy or in combination with any GC-sparing agent. When several publications were based on a single cohort, the most extensive and recent study was selected.

Title and abstract screening were performed by a single investigator (LM). Afterwards, full text screening was performed by two investigators (LM and AB). Disagreements were resolved through discussion until consensus was reached.

2.3. Data extraction

Relevant data were extracted by two independent investigators (LM and AB) into a standardized electronic form, including first author's name, publication year, country, study design (RCT or observational study, retrospective or prospective, single or multicentre), criteria for diagnosis of GCA, relapse definition, number of included patients, number of patients who received only GC therapy, overall duration of follow-up (in months), mean age, proportion of women, initial GC dose (in prednisone equivalents), duration of GC tapering schedule (in months), cumulative relapse rate (CRR) of first relapse 1, 2 and 5 years after treatment initiation, CRR of second and third relapse and investigated predictors of relapse. Missing summary statistics for means were calculated based on the methods proposed by Wan et al. [9].

Risk of bias was assessed by two independent investigators (LM and AB). The 'Cochrane Collaboration risk of bias tool version 2' and an adapted version of the 'Newcastle-Ottawa scale' (Table S2) were used for RCTs and observational studies, respectively [10,11].

2.4. Statistical analysis

A meta-analysis was performed to estimate the 1-year, 2-year and 5-year CRR of first relapse and the CRR of second and third relapse. For the predictors of relapse pooled odds ratios (OR) and mean differences (MD) were calculated for binary and continuous outcomes, respectively. Meta-analysis was only performed when at least 3 studies were available. A narrative synthesis and construction of descriptive summary tables were made for studies not quantitatively pooled.

We used logit transformed proportions to stabilize the variance. As we expected high between-study heterogeneity, a random-effects model was implemented with an inverse variance method to weigh each study. The 95% confidence intervals (95% CIs) were adjusted with the Hartung-Knapp method. Tau was calculated using the restricted maximum likelihood method. Heterogeneity was measured by I^2 and the Cochrane's Q statistic. If at least 10 studies were available, subgroup analyses and univariable meta-regression were performed to explore heterogeneity. Sensitivity analyses were performed excluding (1) studies with a high risk of bias and (2) studies which did not specify the relapse criteria or used only clinical criteria for relapse. To assess small-study effects (which could indicate publication bias), funnel plots in combination with the Egger's regression test were used, although these results should be interpreted with caution as we aimed to estimate a pooled proportion of one group of patients rather than a comparison of interventions [12]. Small-study effects were only assessed for outcomes reported in at least 10 studies. A P value less than 0.05 was considered statistically significant. All analyses were performed using R Statistical Software (v2021.11.1) with the *meta* package. Risk of bias figures were constructed using RevMan 5.4 Software.

3. Results

3.1. Study characteristics and quality assessment

Our PubMed, Embase and Cochrane database searches identified 1756 articles and we identified 12 articles through other sources, resulting in 1397 articles after removal of duplicates (Fig. 1). Title and abstract screening yielded 121 articles eligible for full text analysis. In the final analysis, 30 studies were included for the 1-year, 2-year and 5-year CRR of first relapse (2595 patients) [13–40], 16 studies (1947 patients) [13–15,17,18,22,23,36,37,41–47] for the CRR of second and third relapse, 40 studies (4213 patients) [13,18–20,22,23,25,34,36–38,42,43,45,48–73] for the qualitative synthesis of predictors of relapse, and 16 studies (1961 patients) [13,18,23,36,37,42,45,52,55,56,58,64,66,68,69,71] for the meta-analysis of predictors of relapse. The characteristics of the included studies are presented in Table S3.

The quality assessment for specific bias domains of the included studies is summarized in Fig. 2. Overall, 9% of RCTs had a low risk of bias, 46% some concern of bias and 46% were at high risk of bias; 71% of observational studies were at low risk of bias and 29% at high risk of bias. Fig. S1 shows the risk of bias analysis for the individual studies.

3.2. Epidemiology of relapse

The 1-year, 2-year and 5-year CRR were reported in 27 (n = 2408) [13,14,16–28,31–40,42,74], 19 (n = 1914) [13–15,17,18,20,22,23,25,30,31,33,36,37,39,42,74] and 11 (n = 1265) [13,14,18,21–23,31,39,42,74] studies, respectively. The CRR was 32% [95% CI 22 – 44%] at year 1, 44% [95% CI 31 – 59%] at year 2 and 47% [95% CI 27 – 67%] at year 5 (Fig. 3). The heterogeneity between studies was high. Subgroup analysis and meta-regression were performed to explore between-study heterogeneity (Tables S4 – 9). The CRR was significantly higher in prospective studies compared to retrospective studies at year 1 (57% versus 21%, $p < 0.01$) and at year 2 (71% versus 31%, $p < 0.01$). RCTs had a significantly higher relapse rate than observational studies at year 1 (65% versus 23%, $p < 0.01$) and at year 2 (84% versus 36%, $p < 0.01$). The duration of follow-up was negatively associated with the 1-year CRR ($p < 0.05$, R^2 34%), but not with the 2-year CRR. There was a negative association between the duration of scheduled GC therapy and the 1-year CRR ($p < 0.05$, R^2 32%). In the subgroup of patients with a GC tapering schedule, the relapse rate was higher if the predefined GC tapering schedule had a duration of less than 12 months (77% versus 34%, $p < 0.05$). There was no significant difference in the 1-year, 2-year and 5-year CRR according to publication year, initial GC dose, age and sex. A sensitivity analysis excluding studies with a high risk of bias showed similar results for the 1-year and 5-year CRR (33% [95% CI 20 – 50%] and 48% [95% CI 30 – 66%], respectively). The 2-year CRR was substantially lower in studies with a low risk of bias compared to studies with a high risk of bias (36% [95% CI 26 – 48%] versus 58% [95% CI 26 – 85%]). A sensitivity analysis excluding studies without relapse criteria or with only clinical criteria for relapse did not change the 1-year, 2-year and 5-year CRR substantially (36% [95% CI 24% - 49%], 45% [95% CI 30 – 61%] and 48% [95% CI 33 – 64%], respectively)

The CRR of second and third relapse were reported in 16 (n = 1947) [13–15,17,18,22,23,36,37,41–47] and 7 (n = 762) [14,15,17,22,36,41,42,44] studies, respectively. The CRR of second and third relapse was 30% [95% CI 21 – 40] and 17% [95% CI 8 – 33%], respectively (Fig. 4). The CRR of second relapse was significantly higher in prospective studies and in RCTs (49% versus 23%, $p < 0.01$ and 55% versus 24%, $p < 0.01$, respectively) (Table S10). There was no significant difference in the CRR of second relapse according to publication year, duration of follow-up, initial GC dose, age and sex (Table S11). Exclusion of studies with a high risk of bias did not significantly impact the CRR of third

relapse (20% [95% CI 5 – 51%]). The CRR of second relapse was substantially lower in studies with a low risk of bias compared to studies with a high risk of bias (26% [95% CI 16 – 39%] versus 40% [95% CI 29 – 52%]). A sensitivity analysis excluding studies without relapse criteria or only clinical criteria for relapse showed similar CRR of second and third relapse (30% [95% CI 20 – 42%] and 18% [95% CI 7 – 37%]).
Visual inspection of the funnel plot and the Egger's test did not indicate publication bias for the 1-year, 2-year and 5-year CRR of first relapse and the CRR of second relapse (Fig. S2).

3.3. Predictors of relapse

The predictors of relapse reported in each included study are described in Table S3.

3.3.1. Meta-analysis of predictors of relapse

The results of the meta-analysis are shown in Fig. 5 for the binary predictors and Fig. 6 for the continuous predictors. Forest plots of the individual predictors are presented in Fig. S3 and S4. Female patients had a 1.43 times higher risk of relapse (OR = 1.43, [95% CI 1.04 – 1.98], $p < 0.05$, 13 studies, n = 1725). Large vessel involvement was associated with a twofold increased risk of relapse (OR 2.04, [95% CI 1.28 – 3.24], $p < 0.01$, 10 studies, n = 940). Patients with relapse were slightly younger than those without relapse (MD -1.00 years, [95% CI -1.75 – -0.24], $p < 0.05$, 12 studies, n = 1471). There were no significant differences in the other examined predictors of relapse.

3.3.2. Qualitative review of predictors of relapse

3.3.2.1. Demographics

Area of living (rural/urban) [18] and ethnicity [56] did not show a significant difference between patients with and without relapse. Martinez-Lado et al. reported no seasonal differences for GCA diagnosis between both groups [18].

3.3.2.2. Clinical symptoms

There were no differences between relapsing and non-relapsing patients for dysphagia [18], carotidynia [23], diplopia [13,68], dry cough [64], fatigue [42], anorexia [13], peripheral arthritis [23], transient ischemic attack [13], pulse loss [68], and vascular bruits [68].

3.3.2.3. Cardiovascular risk factors

Labarca et al. reported a higher frequency of prior venous thrombosis in patients with relapse (4% versus 1%, $p < 0.05$) [42]. A history of stroke was negatively associated with relapse in one study (4% versus 12%, $p < 0.05$, HR 0.43, $p < 0.05$) [36], but was not significant in

another study [71]. The relapse rate was not different in patients with and without chronic kidney disease [66] and history of coronary artery disease [36].

3.3.2.4. Laboratory data

Patients with microcytosis were more likely to have a relapse in one study (HR 2.8, $p = 0.03$) [67]. In the study of Hocevar et al., a higher white blood cell count (WBC) count was associated with relapse (10.3×10^9/L versus 9.1×10^9/L, $p < 0.05$) [64], but Martinez-Lado et al. failed to confirm a predictive value of WBC count [18]. Serum amyloid A (286 mg/L versus 101 mg/L, $p < 0.01$) [64], fibrinogen (8.3 g/L versus 7.0 g/L, $p < 0.05$) [64], haptoglobin (3.8 g/L versus 3.0 g/L, and 5.6 g/L versus 3.9 g/L, $p < 0.05$) [13,64] and osteopontin (129.1 ng/mL versus 90.6 ng/mL, $p < 0.05$) [45] were positively associated with relapse. Patients with a strong systemic inflammatory response, defined as composite measure comprising fever, weight loss, anaemia, thrombocytosis, leucocytosis and raised ESR, had a higher risk of relapse in 2 studies [13,19]. Tumour necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) levels were higher at diagnosis in patients with relapse in one study [61], however other studies failed to confirm these findings [45,64,73]. There were no significant differences in alkaline phosphatase [18], ferritin [64], anticardiolipin antibodies [64], IL-12p40 [73], transforming growth factor (TGF)-β [73], matrix metalloproteinase (MMP)-9 [73], intercellular adhesion molecule (ICAM)-1 [73] and platelet-derived growth factor (PDGF) [73].

3.3.2.5. Imaging and temporal artery biopsy (TAB)

De Mornac et al. reported on the association between CT imaging features and relapse and found more frequent involvement of the carotids and the brachiocephalic trunk in patients with relapse (32% versus 10%, $p < 0.05$ and 27% versus 14%, $p = 0.05$, respectively) and a lower risk of multiple relapses with involvement of the ascending thoracic aorta (HR 0.48) [55]. Aortic arch involvement was associated with a reduced relapse risk (HR 0.48) in one study [68], while aortic vasculitis increased the risk of relapse in another study (HR = 2.07, $p < 0.05$) [71]. Garcia-Martinez et al. reported a lower risk of developing an aortic dilatation or aneurysm in patients with relapse. There were no significant differences in relapse rate according to the total vascular score [25], SUVmax and ratio SUVmax aorta/liver [52], results of angioMRI [55] and fast-track approach with ultrasound [67].

Giant cells on TAB specimens were more frequently observed in patients with relapse (89% versus 75%, $p < 0.05$) [23], however this could not be confirmed by another study [49]. Patients with relapse more frequently had intraluminal acute thrombosis (19% versus 4%, $p < 0.01$) [23] and had a higher degree of inflammation ($p < 0.05$) [23], higher CD68+ cell count (2.4 cells/slice versus 1.1 cells/slice, $p < 0.05$, OR 1.30) [72] and higher CCL2 mRNA (127 versus 11 relative units, $p < 0.05$) [53] on TAB specimens. There were no differences in

laminar necrosis [23], calcification [23], intimal hyperplasia [23], IL-12 [54], IL-23 [54], IL-17A [57] and TNF-α expression [63] on TAB.

3.3.2.6. Treatment

There were no significant differences between relapsing and non-relapsing patients according to the use of angiotensin-converting enzyme (ACE)-inhibitors [55,65] and angiotensin II receptor blockers [48].

4. Discussion

In our meta-analysis assessing relapse in 2595 GCA patients in 30 studies, there were three key findings on the relapse rate. First, the relapse risk of GCA patients was low if relapse did not occur during the first two years after diagnosis, with at least one relapse occurring in 32% at year 1, 44% at year 2 and 47% at year 5 after diagnosis. Second, 30% of GCA patients had two or more relapses and 17% had at least three relapses, indicating that GCA is a relapsing-remitting disease in a considerable proportion of patients. Third, subgroup analysis showed that the relapse risk was much higher in RCTs and prospective studies (also including RCTs). This is best explained by the negative association between the duration of scheduled GC treatment and relapse risk. RCTs analysing the efficacy of GC-sparing agents often use shorter GC tapering schedules compared with routine clinical practice to increase the differential treatment effect. As such, observational studies may provide the best available evidence for the relapse rate in a real-life setting. These findings emphasize the need to define an optimal GC tapering schedule, which seeks a balance between a low risk of relapse and a short GC duration with a low cumulative GC dose. The relapse rate was higher in studies with a predefined GC tapering schedule of less than 12 months, but not enough studies were available to more specifically determine the optimal duration of a GC schedule with regard to relapse.

Our meta-analysis did not show a beneficial effect of high initial GC doses (≥ 60 mg/d) on the relapse rate. This is consistent with the meta-analysis of Mainbourg et al. [3] and with 2 retrospective studies [20,75]. This finding is also in line with the European recommendations, which recommend an initial dose of 40-60 mg prednisolone/day in the absence of visual symptoms [76–78]. The American College of Rheumatology (ACR)/Vasculitis Foundation guidelines however recommend an initial dose of 1 mg/kg/day with a maximum of 80 mg [79]. In conclusion, these findings suggest that the duration of GC treatment rather than the initial GC dose is essential for sustained remission.

The identification of prognostic variables which allow treating physicians to predict relapse and the resulting required duration of GC therapy and need of associated GC-sparing agents, may reduce cumulative GC exposure and the related toxicity. Our meta-analysis showed a higher risk of relapse in female patients (OR 1.43) and in patients with large vessel involvement (OR 2.04). We believe it is important to stratify and to perform subgroup analyses on both characteristics in RCTs examining GC-sparing and disease modifying agents. Patients with relapse were slightly younger compared to those without relapse, but this difference appears to be clinically irrelevant, which is supported by the fact that age was not associated with the CRR in meta-regression analysis. Several studies examined laboratory markers and molecular markers on TAB specimens as predictive factors of relapse, but these findings need to be confirmed in larger trials. Further research should focus on the identification of potential predictive factors to allow introduction of personalized medicine in the treatment of GCA based on early assessment of the relapse and complication risk. The presence of good prognostic factors could allow shorter courses of GC to minimize GC-related toxicity. On the other hand, the presence of predictive factors associated with relapse could prompt early introduction of GC-sparing and disease modifying treatment.

Our meta-analysis has several limitations. First, all outcome measures had high between-study heterogeneity, which was only partially explained by our prespecified subgroup analyses. The included studies used different diagnostic criteria for GCA and different relapse criteria. Excluding studies which did not specify the relapse criteria or used only clinical criteria for relapse, did not substantially change the results. Due to the low number of studies examining the 1-year, 2-year and 5-year CRR and the CRR for second and third relapse which also included patients with isolated large vessel vasculitis, subgroup analyses for different subtypes of GCA were not performed. Second, many studies had an observational design, which typically lowers the grade of evidence and confidence in the results. However, it is important to emphasize that GC treatment schedules in RCTs often do not reflect routine clinical practice. Third, many predictors of relapse were reported in less than 3 studies, which precludes analysis of pooled estimates. Fourth, we realize that a considerable number of hypothesis tests have been conducted. Therefore, interpretation should be done with caution, especially for p-values that approach the cut-off value of $p = 0.05$. Finally, a considerable number of studies included in our meta-analysis had a high risk of bias. After exclusion of studies with a high risk of bias, there was only a substantial difference in the 2-year CRR of first relapse and in the CRR of second relapse.

In conclusion, at least one relapse occurred in almost half of GCA mainly during the first two years after diagnosis. Approximately one in three patients had multiple relapses. Predefined GC tapering schedules with a short duration, which are typically observed in RCTs, were associated with an increased risk of relapse. With regard to specific risk factors, female sex and large vessel involvement were associated with a higher relapse risk. Our meta-analysis suggests that GCA is a relapsing-remitting disease in a considerable number of patients, who may potentially benefit from the early introduction of GC-sparing agents to avoid disease-related and treatment-related complications.

5. Note:

The study protocol and data extracted from the included studies are available upon reasonable request.

6. Funding :

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

7. Conflicts of interest:

The authors declare no conflicts of interest

8. CRediT authorship contribution statement

Lien Moreel: Conceptualization, Methodology, Investigation, Formal analysis, Writing – Original Draft, Writing – Review & Editing, Visualization, **Albrecht Betrains:** Conceptualization, Methodology, Investigation, Writing – Review & Editing, **Geert Molenberghs**: Formal analysis, Writing – Review & Editing, **Daniel Blockmans:** Conceptualization, Writing – Review & Editing, Supervision, **Steven Vanderschueren:** Conceptualization, Writing – Review & Editing, Supervision

Online material. Supplementary data

Supplementary data (Fig. S1-S3, Tables S1-S11) associated with this article can be found in the online version at …

References

[1] Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 Revised International Chapel Hill consensus conference nomenclature of vasculitides. Arthritis Rheum 2013;65:1–11. https://doi.org/10.1002/art.37715.

[2] Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. Lancet 2008;372:234–45.

[3] Mainbourg S, Addario A, Samson M, Puéchal X, François M, Durupt S, et al. Prevalence of Giant Cell Arteritis Relapse in Patients Treated With Glucocorticoids: A Meta-Analysis. Arthritis Care Res (Hoboken) 2020;72:838–49.

[4] McDonough AK, Curtis JR, Saag KG. The epidemiology of glucocorticoid-associated adverse events. Curr Opin Rheumatol 2008;20:131–7.

[5] Castan P, Dumont A, Deshayes S, Boutemy J, Martin Silva N, Maigné G, et al. Impact of Glucocorticoid Cumulative Doses in a Real-Life Cohort of Patients Affected by Giant Cell Arteritis. J Clin Med 2022;11. https://doi.org/10.3390/jcm11041034.

[6] Aussedat M, Lobbes H, Samson M, Euvrard R, Lega JC, Mainbourg S. Epidemiology of major relapse in giant cell arteritis: A study-level meta-analysis. Autoimmun Rev 2022;21. https://doi.org/10.1016/j.autrev.2021.102930.

[7] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane Handbook for Systematic Reviews of Interventions. 2nd ed. Chichester (UK): John Wiley & Sons, Ltd; 2019.

[8] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006–12.

[9] Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:1–13. https://doi.org/10.1186/1471-2288-14-135.

[10] Higgins JPT, Savović J, Page M, Elbers R, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al., editors. Cochrane Handb. Syst. Rev. Interv. Version 6, London: Cochrane; 2022.

[11] Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses n.d.

[12] Ioannidis JPA, Trikalinos TA. The appropiateness of asymmetry tests for publication bias in meta-analyses: a large survey. Can Med Assoc J 2007;176:1091–6.

[13] Alba MA, García-Martínez A, Prieto-González S, Tavera-Bahillo I, Corbera-Bellalta M, Planas-Rigol E, et al. Relapses in patients with giant cell arteritis: prevalence,

characteristics, and associated clinical findings in a longitudinally followed cohort of 106 patients. Medicine (Baltimore) 2014;93:194–201.

[14] Beevers DG, Harpur JE, Turk KA. Giant cell arteritis - the need for prolonged treatment. J Chronic Dis 1973;26:571–84.

[15] Jover JA, Hernandez-Garcia, C, Immaculada CM, Vargas, Emilio, Banares, A, Fernández-Gutiérrez B. Combined Treatment of Giant-Cell Arteritis with Methotrexate and Prednisone: A Randomized, Double-Blind, Placebo-Controlled Trial. Ann Intern Med 2001;134:106–14.

[16] Karabayas M, Dospinescu P, Locherty M, Moulindu P, Sobti M, Hollick R, et al. Stratified glucocorticoid monotherapy is safe and effective for most cases of giant cell arteritis. Rheumatol Adv Pract 2020;4:1–5. https://doi.org/10.1093/rap/rkaa024.

[17] Kyle V, Hazleman BL. The clinical and laboratory course of polymyalgia rheumatica/giant cell arteritis after the first two months of treatment. Ann Rheum Dis 1993;52:847–50.

[18] Martinez-Lado L, Calviño-Díaz C, Piñeiro A, Dierssen T, Vazquez-Rodriguez TR, Miranda-Filloy JA, et al. Relapses and recurrences in giant cell arteritis: a population-based study of patients with biopsy-proven disease from northwestern Spain. Medicine (Baltimore) 2011;90:186–93.

[19] Nesher G, Nesher R, Mates M, Sonnenblick M, Breuer GS. Giant cell arteritis: Intensity of the initial systemic inflammatory response and the course of the disease. Clin Exp Rheumatol 2008;26:1–5.

[20] Nesher G, Rubinow A, Sonnenblick M. Efficacy and adverse effects of different corticosteroid dose regimens in temporal arteritis: a retrospective study. Clin Exp Rheumatol 1997;15:303–6.

[21] Pariente A, Guédon A, Alamowitch S, Thietart S, Carrat F, Delorme S, et al. Ischemic stroke in giant-cell arteritis: French retrospective study. J Autoimmun 2019;99:48–51.

[22] Piette AM, Dorra M, Betourne C, Levy R, Dechy H, Cassan P, et al. Maladie de horton: étude rétrospective de trente-trois cas et revue de la littérature. Sem Des Hop 1982;58:2819–24.

[23] Restuccia G, Boiardi L, Cavazza A, Catanoso M, Macchioni P, Muratore F, et al. Flares in Biopsy-Proven Giant Cell Arteritis in Northern Italy: Characteristics and Predictors in a Long-Term Follow-Up Study. Medicine (Baltimore) 2016;95:e3524.

[24] Sailler L, Carreiro M, Ollier S, Juchet H, Delobel P, Ferrand D, et al. Maladie de horton non compliquée: Traitement initial par trois bolus de 500 mg de méthylprednisolone suivis de 20 mg/j d'équivalent-prednisone. Évaluation chez 15 patients. Rev Med Interne 2001;22:1032–8.

[25] Blockmans D, Ceuninck L de, Vanderschueren S, Knockaert D, Mortelmans L,

Bobbaers H. Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. Arthritis Care Res (Hoboken) 2006;55:131–7.

[26] Schmidt WA, Dasgupta B, Luqmani R, Unizony SH, Blockmans D, Lai Z, et al. A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Sirukumab in the Treatment of Giant Cell Arteritis. Rheumatol Ther 2020;7:793–810.

[27] Seror R, Baron G, Hachulla E, Debandt M, Larroche C, Puéchal X, et al. Adalimumab for steroid sparing in patients with giant-cell arteritis: results of a multicentre randomised controlled trial. Ann Rheum Dis 2014;73:2074–81.

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

[29] Stone JH, Spotswood H, Unizony SH, Aringer M, Blockmans D, Brouwer E, et al. New-onset versus relapsing giant cell arteritis treated with tocilizumab: 3-year results from a randomized controlled trial and extension. Rheumatology (Oxford) 2021. https://doi.org/10.1093/rheumatology/keab780.

[30] van Sleen Y, Graver JC, Abdulahad WH, van der Geest KSM, Boots AMH, Sandovici M, et al. Leukocyte dynamics reveal a persistent myeloid dominance in giant cell arteritis and polymyalgia rheumatica. Front Immunol 2019;10:1–13.

[31] Vautier M, Dupont A, de Boysson H, Comarmond C, Mirault T, Mekinian A, et al. Prognosis of large vessel involvement in large vessel vasculitis. J Autoimmun 2020;108:102419.

[32] Villiger PM, Adler S, Kuchen S, Wermelinger F, Dan D, Fiege V, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet (London, England) 2016;387:1921–7.

[33] Vinckier L, Hatron PY, Coget J, Devulder B. Le doppler artériel dans la maladie de Horton Étude prospective de 24 observations. La Rev Med Interne 1984;5:291–7.

[34] Breuer GS, Nesher R, Reinus K, Nesher G. Association between histological features in temporal artery biopsies and clinical features of patients with giant cell arteritis. Isr Med Assoc J 2013;15:271–4.

[35] Chmelewski WL, McKnight KM, Agudelo CA, Wise CM. Presenting features and outcomes in patients undergoing temporal artery biopsy. A review of 98 patients. Arch Intern Med 1992;152:1690–5.

[36] Dumont A, Parienti JJ, Delmas C, Boutemy J, Maigné G, Silva NM, et al. Factors associated with relapse and dependence on glucocorticoids in giant cell arteritis. J Rheumatol 2020;47:108–16.

[37] Espitia O, Néel A, Leux C, Connault J, Espitia-Thibault A, Ponge T, et al. Giant cell

arteritis with or without aortitis at diagnosis. A retrospective study of 22 patients with longterm followup. J Rheumatol 2012;39:2157–62.

[38] García-Martínez A, Hernández-Rodríguez J, Grau JM, Cid MC. Treatment with statins does not exhibit a clinically relevant corticosteroid-sparing effect in patients with giant cell arteritis. Arthritis Rheum 2004;51:674–8.

[39] Graham E, Holland A, Avery A, Russell RWR. Prognosis in giant-cell arteritis 1981;282:269–71.

[40] Hoffman GS, Cid MC, Hellmann DB, Guillevin L, Stone JH, Schousboe J, et al. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. Arthritis Rheum 2002;46:1309–18.

[41] Hoffman GS, Cid MC, Rendt-Zagar KE, Merkel PA, Weyand CM, Stone JH, et al. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis a randomized trial. Ann Intern Med 2007;146:621–30.

[42] Labarca C, Koster MJ, Crowson CS, Makol A, Ytterberg SR, Matteson EL, et al. Predictors of relapse and treatment outcomes in biopsy-proven giant cell arteritis: A retrospective cohort study. Rheumatology 2016;55:347–56.

[43] Liozon E, Dumonteil S, Parreau S, Gondran G, Bezanahary H, Palat S, et al. Risk profiling for a refractory course of giant cell arteritis: The importance of age and body weight: “Risk profiling for GC resistance in GCA.” Semin Arthritis Rheum 2020;50:1252–61.

[44] Mazlumzadeh M, Hunder GG, Easley KA, Calamia KT, Matteson EL, Griffing WL, et al. Treatment of giant cell arteritis using induction therapy with high-dose glucocorticoids: A double-blind, placebo-controlled, randomized prospective clinical trial. Arthritis Rheum 2006;54:3310–8.

[45] Prieto-González S, Terrades-García N, Corbera-Bellalta M, Planas-Rigol E, Miyabe C, Alba MA, et al. Serum osteopontin: a biomarker of disease activity and predictor of relapsing course in patients with giant cell arteritis. Potential clinical usefulness in tocilizumab-treated patients. RMD Open 2017;3:e000570.

[46] Proven A, Gabriel SE, Orces C, O’Fallon WM, Hunder GG. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. Arthritis Rheum 2003;49:703–8.

[47] Hernández-Rodríguez J, García-Martínez A, Casademont J, Filella X, Esteban M-J, López-Soto A, et al. A strong initial systemic inflammatory response is associated with higher corticosteroid requirements and longer duration of therapy in patients with giant-cell arteritis. Arthritis Rheum 2002;47:29–35.

[48] Alba MA, García-Martínez A, Prieto-González S, Espígol-Frigolé G, Butjosa M, Tavera-Bahillo I, et al. Treatment with angiotensin II receptor blockers is associated with prolonged relapse-free survival, lower relapse rate, and corticosteroid-sparing

effect in patients with giant cell arteritis. Semin Arthritis Rheum 2014;43:772–7.

[49] Armstrong AT, Tyler WB, Wood GC, Harrington TM. Clinical importance of the presence of giant cells in temporal arteritis. J Clin Pathol 2008;61:669–71.

[50] Barrier J, Tournemaine N, Maulaz D, Mainguy-Fonteneau B, Rojouan J, Potel G, et al. Évolution, traitement et pronostic de la maladie de Horton. Ann Med Interne (Paris) 1983;134:428–35.

[51] Behn AR, Perera T, Myles AB. Polymyalgia rheumatica and corticosteroids: how much for how long? Ann Rheum Dis 1983;42:374–8.

[52] Bellan M, Puta E, Croce A, Sacchetti GM, Orsini F, Zecca E, et al. Role of positron emission tomography in the assessment of disease burden and risk of relapse in patients affected by giant cell arteritis. Clin Rheumatol 2020;39:1277–81.

[53] Cid MC, Hoffman MP, Hernández-Rodríguez J, Segarra M, Elkin M, Sánchez M, et al. Association between increased CCL2 (MCP-1) expression in lesions and persistence of disease activity in giant-cell arteritis. Rheumatology (Oxford) 2006;45:1356–63.

[54] Conway R, O'Neill L, McCarthy GM, Murphy CC, Fabre A, Kennedy S, et al. Interleukin 12 and interleukin 23 play key pathogenic roles in inflammatory and proliferative pathways in giant cell arteritis. Ann Rheum Dis 2018;77:1815–24.

[55] de Mornac D, Espitia O, Néel A, Connault J, Masseau A, Espitia-Thibault A, et al. Large-vessel involvement is predictive of multiple relapses in giant cell arteritis. Ther Adv Musculoskelet Dis 2021;13:1–12.

[56] de Souza AWS, Kajiyama Okamoto KY, Abrantes F, Schau B, Santos Bacchiega AB, Shinjo SK. Giant cell arteritis: A multicenter observational study in Brazil. Clinics 2013;68:317–22.

[57] Espígol-Frigolé G, Corbera-Bellalta M, Planas-Rigol E, Lozano E, Segarra M, García-Martínez A, et al. Increased IL-17A expression in temporal artery lesions is a predictor of sustained response to glucocorticoid treatment in patients with giant-cell arteritis. Ann Rheum Dis 2013;72:1481–7.

[58] Felten L, Leuchten N, Aringer M. Glucocorticoid dosing and relapses in giant cell arteritis—a single centre cohort study. Rheumatology 2021:1–9. https://doi.org/10.1093/rheumatology/keab677.

[59] Friedman G, Friedman B. Prolonged Corticosteroid Treatment in the Management of Temporal Arteritis. Klin Wochenschr 1988;66:1167–70.

[60] García-Martínez A, Hernández-Rodríguez J, Arguis P, Paredes P, Segarra M, Lozano E, et al. Development of aortic aneurysm/dilatation during the followup of patients with giant cell arteritis: A cross-sectional screening of fifty-four prospectively followed patients. Arthritis Care Res 2008;59:422–30.

[61] García-Martínez A, Hernández-Rodríguez J, Espígol-Frigolé G, Prieto-González S,

Butjosa M, Segarra M, et al. Clinical relevance of persistently elevated circulating cytokines (tumor necrosis factor alpha and interleukin-6) in the long-term followup of patients with giant cell arteritis. Arthritis Care Res (Hoboken) 2010;62:835–41.

[62] Hachulla E, Boivin V, Pasturel-Michon U, Fauchais AL, Bouroz-Joly J, Perez-Cousin M, et al. Prognostic factors and long-term evolution in a cohort of 133 patients with giant cell arteritis. Clin Exp Rheumatol 2001;19:171–6.

[63] Hernández-Rodríguez J, Segarra M, Vilardell C, Sánchez M, García-Martínez A, Esteban MJ, et al. Tissue production of pro-inflammatory cytokines (IL-1β, TNFα and IL-6) correlates with the intesity of the systemic inflammatory response and with corticosteroid requirements in giant-cell arteritis. Rheumatology 2004;43:294–301.

[64] Hocevar A, Rotar Z, Jese R, Semrl SS, Pizem J, Hawlina M, et al. Do Early Diagnosis and Glucocorticoid Treatment Decrease the Risk of Permanent Visual Loss and Early Relapses in Giant Cell Arteritis. Med (United States) 2016;95:1–5.

[65] Ma J, Khalidi N, Wierzbicki O, Alqutami A, Ioannidis G, Pagnoux C. Impact of diabetes, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use, and statin use on presentation and outcomes in patients with giant cell arteritis. Int J Rheum Dis 2020;23:1233–9.

[66] Matsumoto K, Kaneko Y, Takeuchi T. Body mass index associates with disease relapse in patients with giant cell arteritis. Int J Rheum Dis 2019;22:1782–6.

[67] Monti S, Bartoletti A, Bellis E, Delvino P, Montecucco C. Fast-Track Ultrasound Clinic for the Diagnosis of Giant Cell Arteritis Changes the Prognosis of the Disease but Not the Risk of Future Relapse. Front Med 2020;7:589794.

[68] Muratore F, Boiardi L, Restuccia G, Cavazza A, Catanoso M, Macchioni P, et al. Relapses and long-term remission in large vessel giant cell arteritis in northern Italy: Characteristics and predictors in a long-term follow-up study. Semin Arthritis Rheum 2020;50:549–58.

[69] Narváez J, Bernad B, Nolla JM, Valverde J. Statin therapy does not seem to benefit giant cell arteritis. Semin Arthritis Rheum 2007;36:322–7.

[70] Schmidt J, Kermani TA, Muratore F, Crowson CS, Matteson EL, Warrington KJ. Statin Use in Giant Cell Arteritis: A Retrospective study. J Rheumatol 2013;40:910–5.

[71] Sugihara T, Hasegawa H, Uchida HA, Yoshifuji H, Watanabe Y, Amiya E, et al. Associated factors of poor treatment outcomes in patients with giant cell arteritis: clinical implication of large vessel lesions. Arthritis Res Ther 2020;22:72.

[72] Sultan H, Smith S V, Lee AG, Chévez-Barrios P. Pathologic Markers Determining Prognosis in Patients With Treated or Healing Giant Cell Arteritis. Am J Ophthalmol 2018;193:45–53.

[73] Visvanathan S, Rahman MU, Hoffman GS, Xu S, García-Martínez A, Segarra M, et al.

Tissue and serum markers of inflammation during the follow-up of patients with giant-cell arteritis--a prospective longitudinal study. Rheumatology (Oxford) 2011;50:2061–70.

[74] Leon L, Rodriguez-Rodriguez L, Morado I, Rosales Z, Vadillo C, Freites D, et al. Treatment with methotrexate and risk of relapses in patients with giant cell arteritis in clinical practice. Clin Exp Rheumatol 2018;36 Suppl 1:121–8.

[75] Delecoeuillerie G, Joly P, Cohen de Lara A, Paolaggi JB. Polymyalgia rheumatica and temporal arteritis: a retrospective analysis of prognostic features and different corticosteroid regimens (11 year survey of 210 patients). Ann Rheum Dis 1988;47:733–9.

[76] Hellmich B, Agueda A, Monti S, Buttgereit F, De Boysson H, Brouwer E, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2020;79:19–130.

[77] MacKie SL, Dejaco C, Appenzeller S, Camellino D, Duftner C, Gonzalez-Chiappe S, et al. British Society for Rheumatology guideline on diagnosis and treatment of giant cell arteritis. Rheumatol (United Kingdom) 2020;59:E1–23.

[78] Bienvenu B, Ly KH, Lambert M, Agard C, André M, Benhamou Y, et al. Management of giant cell arteritis: Recommendations of the French Study Group for Large Vessel Vasculitis (GEFA). La Rev Med Interne 2016;37:154–65.

[79] Maz M, Chung SA, Abril A, Langford CA, Gorelik M, Guyatt G, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis. Arthritis Care Res 2021;73:1071–87.

Figure 1: PRISMA flow chart of study selection from literature search

Abbreviations: GC, glucocorticoids; GCA, giant cell arteritis; PMR, polymyalgia rheumatica; TAK, Takayasu arteritis

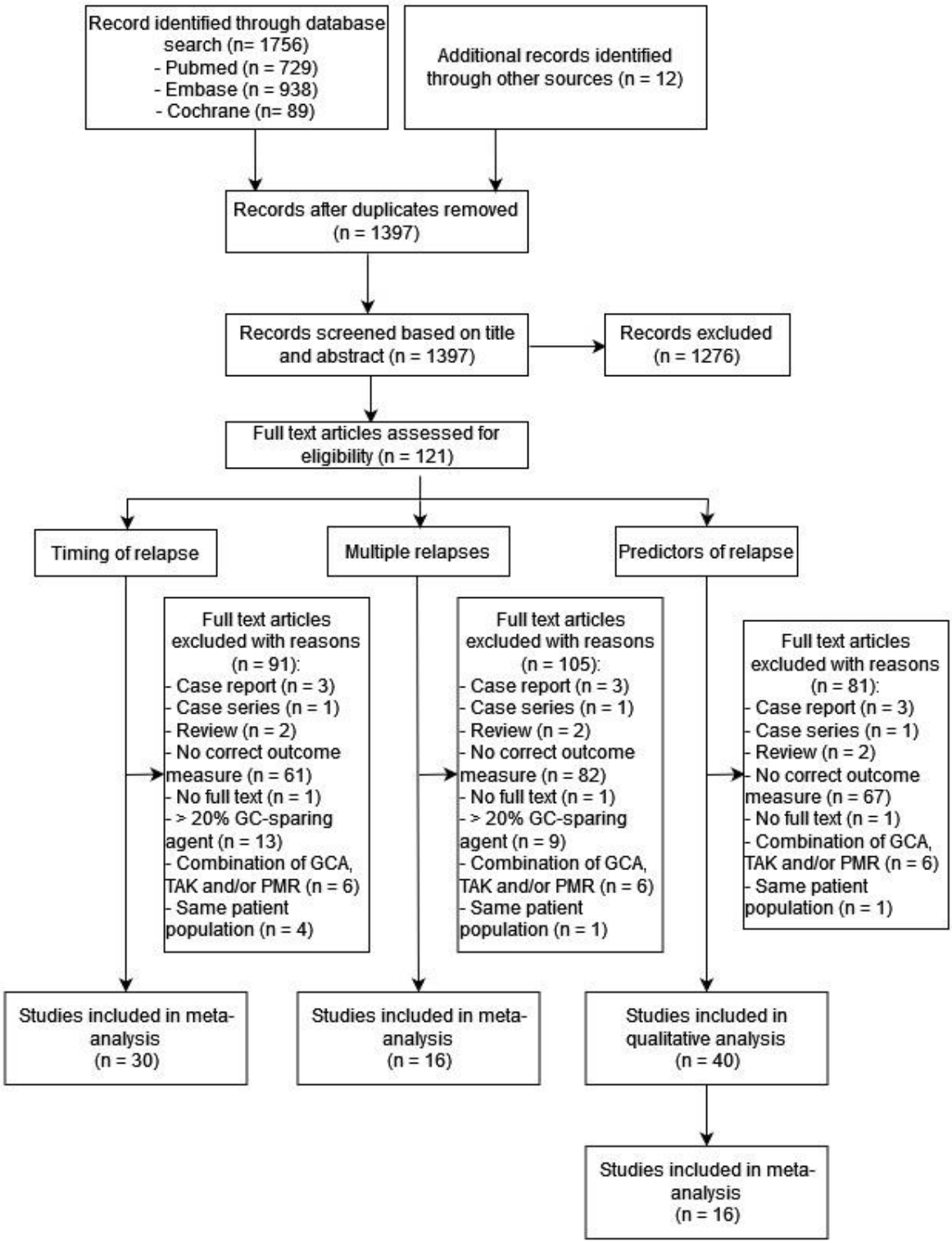
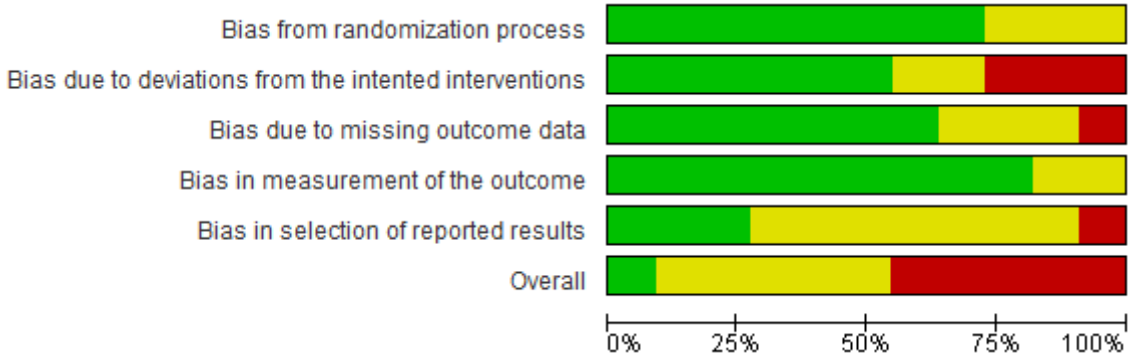


Figure 2: Risk of bias summary for the included studies. A. Randomized controlled trials B. Observational studies. Low risk of bias Some concern of bias High risk of bias

A



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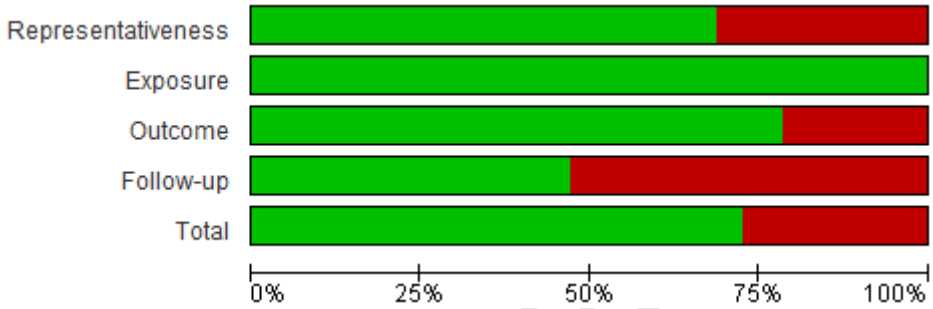

Figure 3: Forest plot of the cumulative relapse rate of first relapse at year 1, 2 and 5 after treatment initiation.

Abbreviations: 95%-CI, 95% Confidence Interval

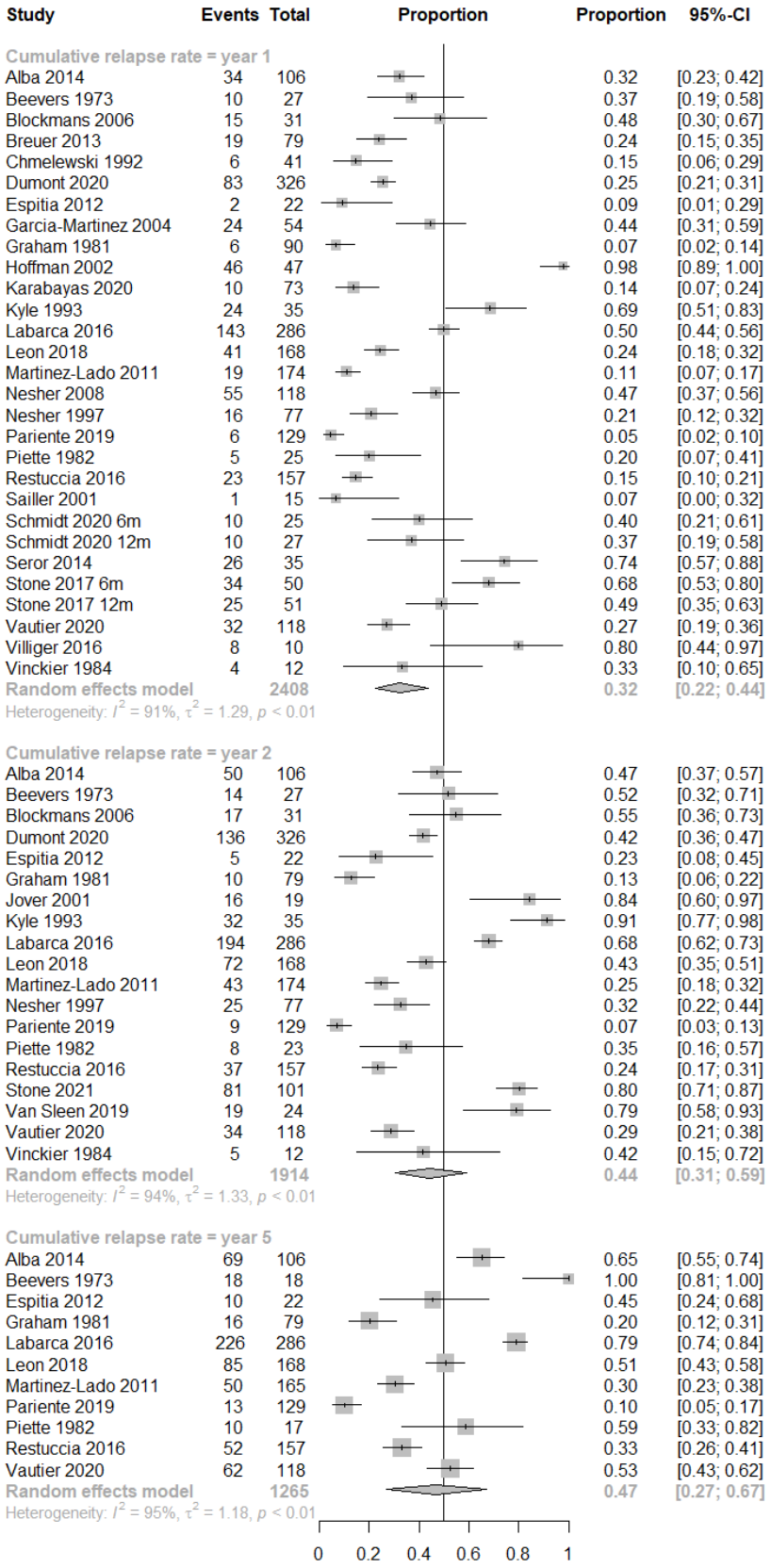

Figure 4: Forest plot of the cumulative relapse rate of second and third relapse

Abbreviations: 95%-CI, 95% Confidence Interval

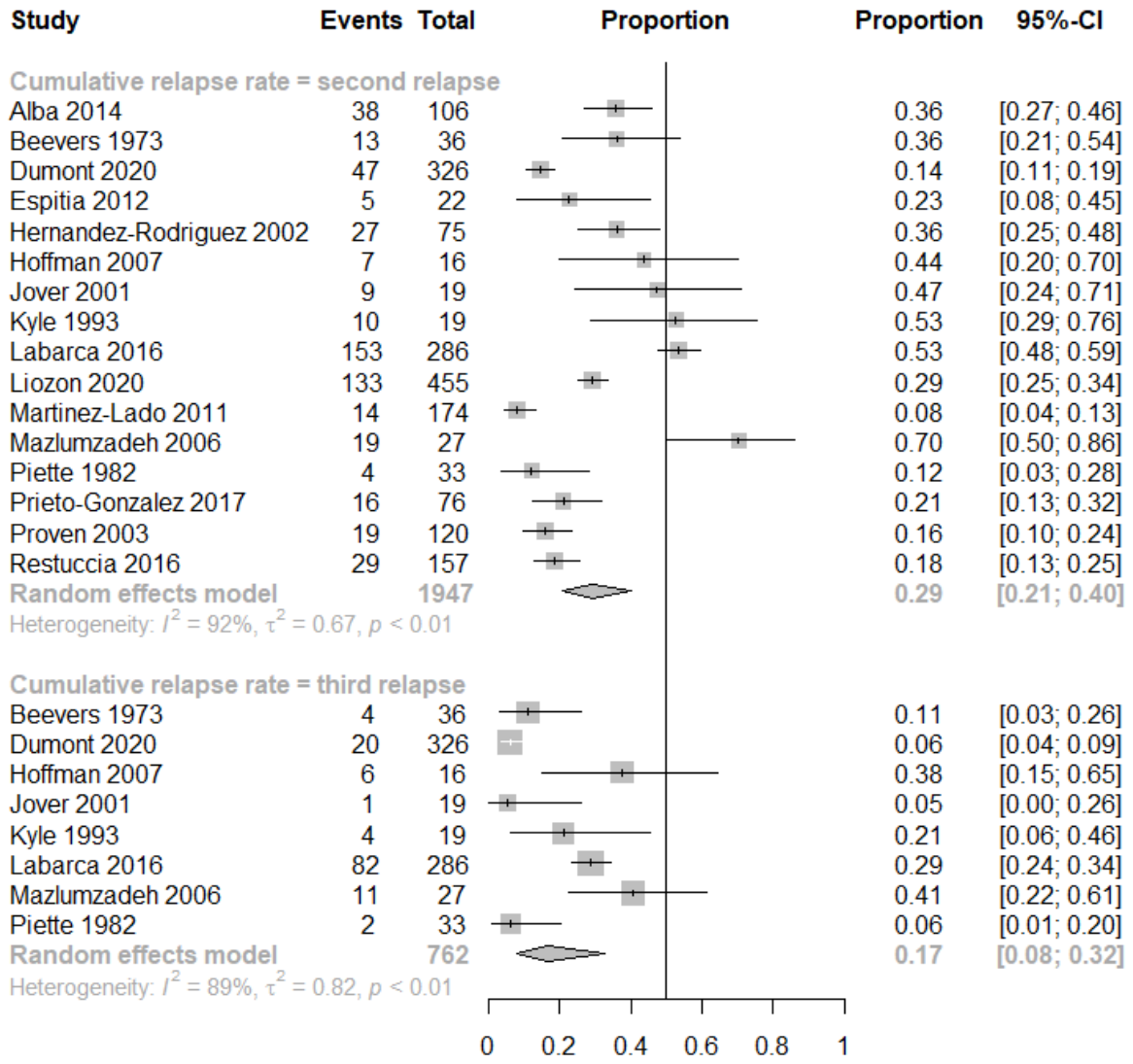

Figure 5: Forest plot of binary predictors of relapse

Abbreviations: 95%-CI, 95% Confidence Interval ; IV, intravenous; LVV, large vessel vasculitis ; OR, odds ratio ; PMR, polymyalgia rheumatica

Predictor	Studies	Patients	OR (95% CI)	P value
Female sex	13	1725	1.43 (1.04 - 1.98)	0.03
LVV	10	940	2.04 (1.28 - 3.23)	0.01
Headache	9	1368	0.90 (0.65 - 1.25)	0.48
Scalp tenderness	5	837	1.40 (0.61 - 3.22)	0.32
Jaw claudication	9	1368	1.00 (0.69 - 1.45)	1.00
Abnormal temporal artery	6	917	0.81 (0.65 - 1.00)	0.05
Cranial ischemic manifestations	5	789	0.74 (0.41 - 1.35)	0.24
Stroke	4	602	0.97 (0.07 - 13.09)	0.97
Transient visual loss	5	727	1.10 (0.61 - 1.97)	0.69
Permanent visual loss	6	855	0.68 (0.44 - 1.06)	0.08
Visual loss (permanent or transient)	8	1262	0.92 (0.63 - 1.35)	0.63
Peripheral ischemic manifestations	4	873	1.10 (0.67 - 1.81)	0.58
PMR	12	1693	1.33 (0.84 - 2.09)	0.20
Systemic symptoms	5	531	1.33 (0.78 - 2.29)	0.21
Fever	8	1323	1.14 (0.71 - 1.84)	0.53
Weight loss	3	460	1.11 (0.83 - 1.49)	0.25
Diabetes	6	1083	1.24 (0.51 - 3.02)	0.55
Hypercholesterolemia	5	790	0.75 (0.55 - 1.03)	0.07
Hypertension	6	1047	0.91 (0.43 - 1.94)	0.76
Smoking	4	575	1.23 (0.96 - 1.58)	0.08
IV methylprednisolone use	4	470	0.60 (0.31 - 1.17)	0.09
Antiplatelet drugs	5	782	0.78 (0.47 - 1.27)	0.23
Statin use	5	762	1.38 (0.77 - 2.45)	0.20

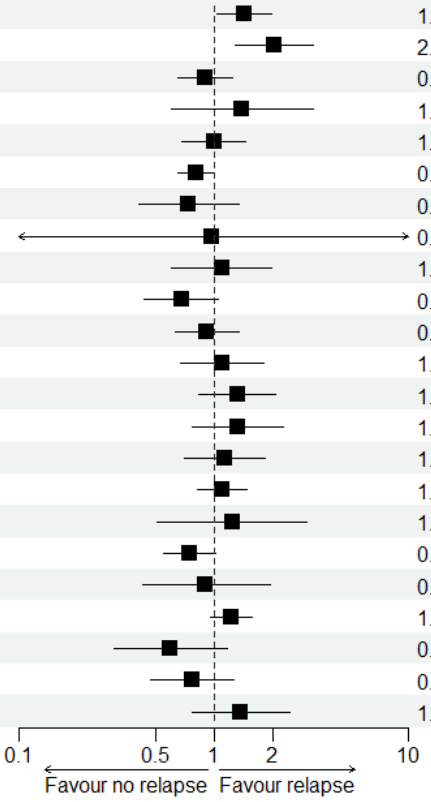

Figure 6: Forest plot of continuous predictors of relapse

Abbreviations: 95%-CI, 95% Confidence Interval; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GC, glucocorticoids; Hb, haemoglobin; MD, mean difference

Predictor	Studies	Patients	MD (95% CI)	P value
Age (years)	12	1471	-1.00 (-1.75 - -0.24)	0.01
BMI (kg/m²)	5	497	1.39 (-0.33 - 3.11)	0.09
Symptom duration (weeks)	4	558	0.56 (-1.02 - 2.14)	0.34
ESR (mm/h)	12	1428	1.19 (-3.84 - 6.22)	0.61
CRP (mg/L)	11	1328	1.55 (-1.16 - 4.25)	0.23
Hb (g/dL)	7	994	-0.23 (-0.55 - 0.09)	0.12
Platelet count (x 10^11 cells/L)	5	812	-0.09 (-0.62 - 0.45)	0.67
Albumin (g/L)	3	272	-0.23 (-4.58 - 4.11)	0.84
Initial GC dose (mg/d)	9	1401	0.48 (-1.32 - 2.27)	0.56