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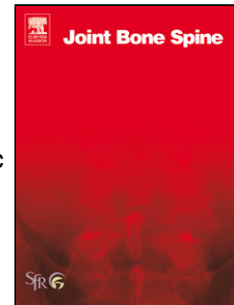
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Epidemiology and predictors of relapse in giant cell arteritis: a systematic review and meta-analysis

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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.

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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

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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

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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

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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.

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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, R² 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, R² 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

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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

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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 x 10^9/L versus 9.1 x 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

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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.

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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.

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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 …

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

Abbreviations: GC, glucocorticoids; GCA, giant cell arteritis; PMR, polymyalgia rheumatica; TAK, Takayasu arteritis
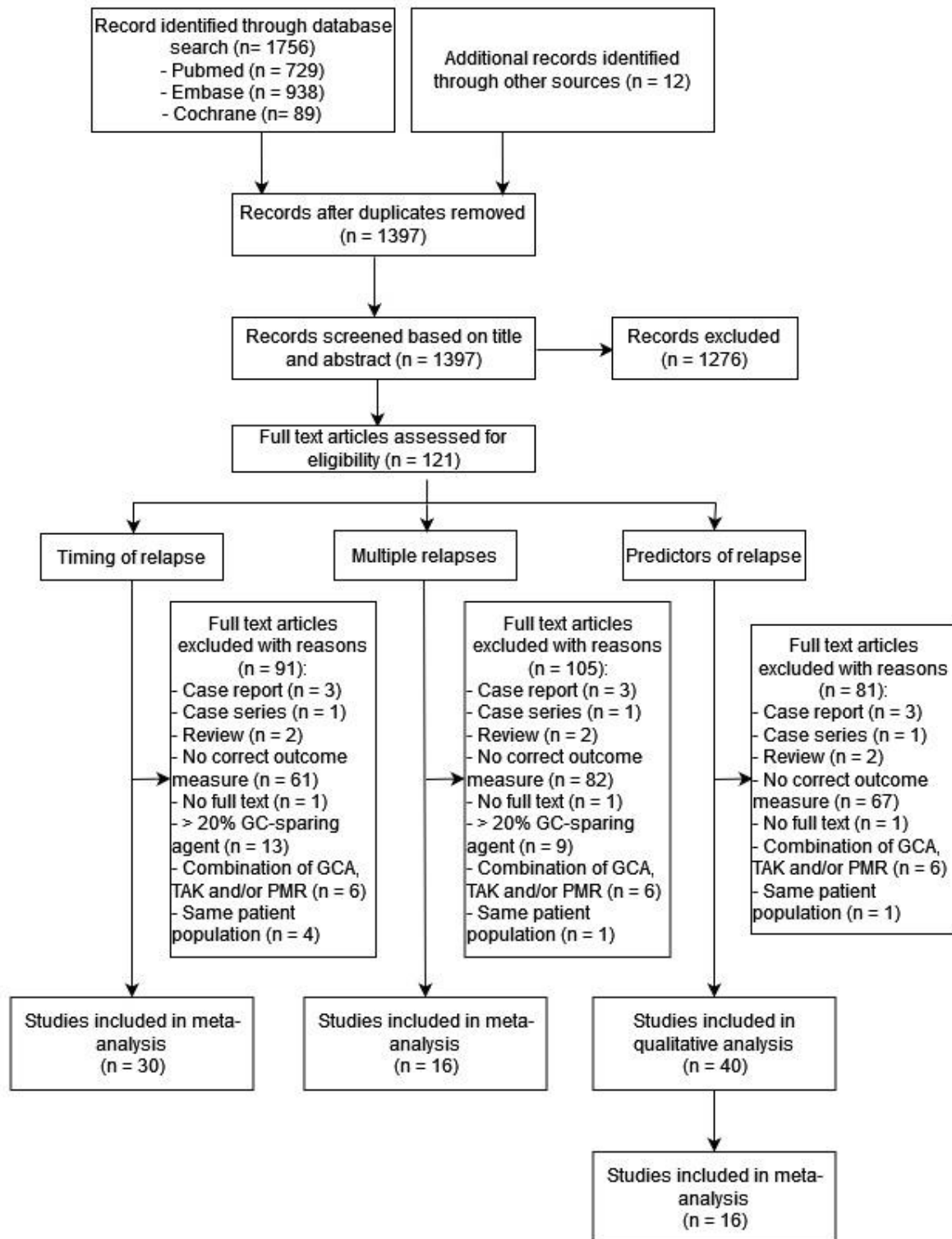
Figure 2: Risk of bias summary for the included studies. A. Randomized controlled trials
B. Observational studies. ■ Low risk of bias ■ Some concern of bias ■ High risk of bias

A

B

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

Study	Events	Total	Proportion	Proportion	95%-CI
Cumulative relapse rate = year 1					
Alba 2014	34	106		0.32	[0.23; 0.42]
Beevers 1973	10	27		0.37	[0.19; 0.58]
Blockmans 2006	15	31		0.48	[0.30; 0.67]
Breuer 2013	19	79		0.24	[0.15; 0.35]
Chmelewski 1992	6	41		0.15	[0.06; 0.29]
Dumont 2020	83	326		0.25	[0.21; 0.31]
Espitia 2012	2	22		0.09	[0.01; 0.29]
Garcia-Martinez 2004	24	54		0.44	[0.31; 0.59]
Graham 1981	6	90		0.07	[0.02; 0.14]
Hoffman 2002	46	47		0.98	[0.89; 1.00]
Karabayas 2020	10	73		0.14	[0.07; 0.24]
Kyle 1993	24	35		0.69	[0.51; 0.83]
Labarca 2016	143	286		0.50	[0.44; 0.56]
Leon 2018	41	168		0.24	[0.18; 0.32]
Martinez-Lado 2011	19	174		0.11	[0.07; 0.17]
Nesher 2008	55	118		0.47	[0.37; 0.56]
Nesher 1997	16	77		0.21	[0.12; 0.32]
Pariente 2019	6	129		0.05	[0.02; 0.10]
Piette 1982	5	25		0.20	[0.07; 0.41]
Restuccia 2016	23	157		0.15	[0.10; 0.21]
Sailler 2001	1	15		0.07	[0.00; 0.32]
Schmidt 2020 6m	10	25		0.40	[0.21; 0.61]
Schmidt 2020 12m	10	27		0.37	[0.19; 0.58]
Seror 2014	26	35		0.74	[0.57; 0.88]
Stone 2017 6m	34	50		0.68	[0.53; 0.80]
Stone 2017 12m	25	51		0.49	[0.35; 0.63]
Vautier 2020	32	118		0.27	[0.19; 0.36]
Villiger 2016	8	10		0.80	[0.44; 0.97]
Vinckier 1984	4	12		0.33	[0.10; 0.65]
Random effects model		2408		0.32	[0.22; 0.44]
Heterogeneity: $I^2 = 91\%$, $\tau^2 = 1.29$, $p < 0.01$					
Cumulative relapse rate = year 2					
Alba 2014	50	106		0.47	[0.37; 0.57]
Beevers 1973	14	27		0.52	[0.32; 0.71]
Blockmans 2006	17	31		0.55	[0.36; 0.73]
Dumont 2020	136	326		0.42	[0.36; 0.47]
Espitia 2012	5	22		0.23	[0.08; 0.45]
Graham 1981	10	79		0.13	[0.06; 0.22]
Jover 2001	16	19		0.84	[0.60; 0.97]
Kyle 1993	32	35		0.91	[0.77; 0.98]
Labarca 2016	194	286		0.68	[0.62; 0.73]
Leon 2018	72	168		0.43	[0.35; 0.51]
Martinez-Lado 2011	43	174		0.25	[0.18; 0.32]
Nesher 1997	25	77		0.32	[0.22; 0.44]
Pariente 2019	9	129		0.07	[0.03; 0.13]
Piette 1982	8	23		0.35	[0.16; 0.57]
Restuccia 2016	37	157		0.24	[0.17; 0.31]
Stone 2021	81	101		0.80	[0.71; 0.87]
Van Sleen 2019	19	24		0.79	[0.58; 0.93]
Vautier 2020	34	118		0.29	[0.21; 0.38]
Vinckier 1984	5	12		0.42	[0.15; 0.72]
Random effects model		1914		0.44	[0.31; 0.59]
Heterogeneity: $I^2 = 94\%$, $\tau^2 = 1.33$, $p < 0.01$					
Cumulative relapse rate = year 5					
Alba 2014	69	106		0.65	[0.55; 0.74]
Beevers 1973	18	18		1.00	[0.81; 1.00]
Espitia 2012	10	22		0.45	[0.24; 0.68]
Graham 1981	16	79		0.20	[0.12; 0.31]
Labarca 2016	226	286		0.79	[0.74; 0.84]
Leon 2018	85	168		0.51	[0.43; 0.58]
Martinez-Lado 2011	50	165		0.30	[0.23; 0.38]
Pariente 2019	13	129		0.10	[0.05; 0.17]
Piette 1982	10	17		0.59	[0.33; 0.82]
Restuccia 2016	52	157		0.33	[0.26; 0.41]
Vautier 2020	62	118		0.53	[0.43; 0.62]
Random effects model		1265		0.47	[0.27; 0.67]
Heterogeneity: $I^2 = 95\%$, $\tau^2 = 1.18$, $p < 0.01$					

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

Abbreviations: 95%-CI, 95% Confidence Interval

Study	Events	Total	Proportion	Proportion	95%-CI
Cumulative relapse rate = second relapse					
Alba 2014	38	106		0.36	[0.27; 0.46]
Beevers 1973	13	36		0.36	[0.21; 0.54]
Dumont 2020	47	326		0.14	[0.11; 0.19]
Espitia 2012	5	22		0.23	[0.08; 0.45]
Hernandez-Rodriguez 2002	27	75		0.36	[0.25; 0.48]
Hoffman 2007	7	16		0.44	[0.20; 0.70]
Jover 2001	9	19		0.47	[0.24; 0.71]
Kyle 1993	10	19		0.53	[0.29; 0.76]
Labarca 2016	153	286		0.53	[0.48; 0.59]
Liozon 2020	133	455		0.29	[0.25; 0.34]
Martinez-Lado 2011	14	174		0.08	[0.04; 0.13]
Mazlumzadeh 2006	19	27		0.70	[0.50; 0.86]
Piette 1982	4	33		0.12	[0.03; 0.28]
Prieto-Gonzalez 2017	16	76		0.21	[0.13; 0.32]
Proven 2003	19	120		0.16	[0.10; 0.24]
Restuccia 2016	29	157		0.18	[0.13; 0.25]
Random effects model		1947		0.29	[0.21; 0.40]
Heterogeneity: $I^2 = 92\%$, $\tau^2 = 0.67$, $p < 0.01$					
Cumulative relapse rate = third relapse					
Beevers 1973	4	36		0.11	[0.03; 0.26]
Dumont 2020	20	326		0.06	[0.04; 0.09]
Hoffman 2007	6	16		0.38	[0.15; 0.65]
Jover 2001	1	19		0.05	[0.00; 0.26]
Kyle 1993	4	19		0.21	[0.06; 0.46]
Labarca 2016	82	286		0.29	[0.24; 0.34]
Mazlumzadeh 2006	11	27		0.41	[0.22; 0.61]
Piette 1982	2	33		0.06	[0.01; 0.20]
Random effects model		762		0.17	[0.08; 0.32]
Heterogeneity: $I^2 = 89\%$, $\tau^2 = 0.82$, $p < 0.01$					

0   0.2   0.4   0.6   0.8   1

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

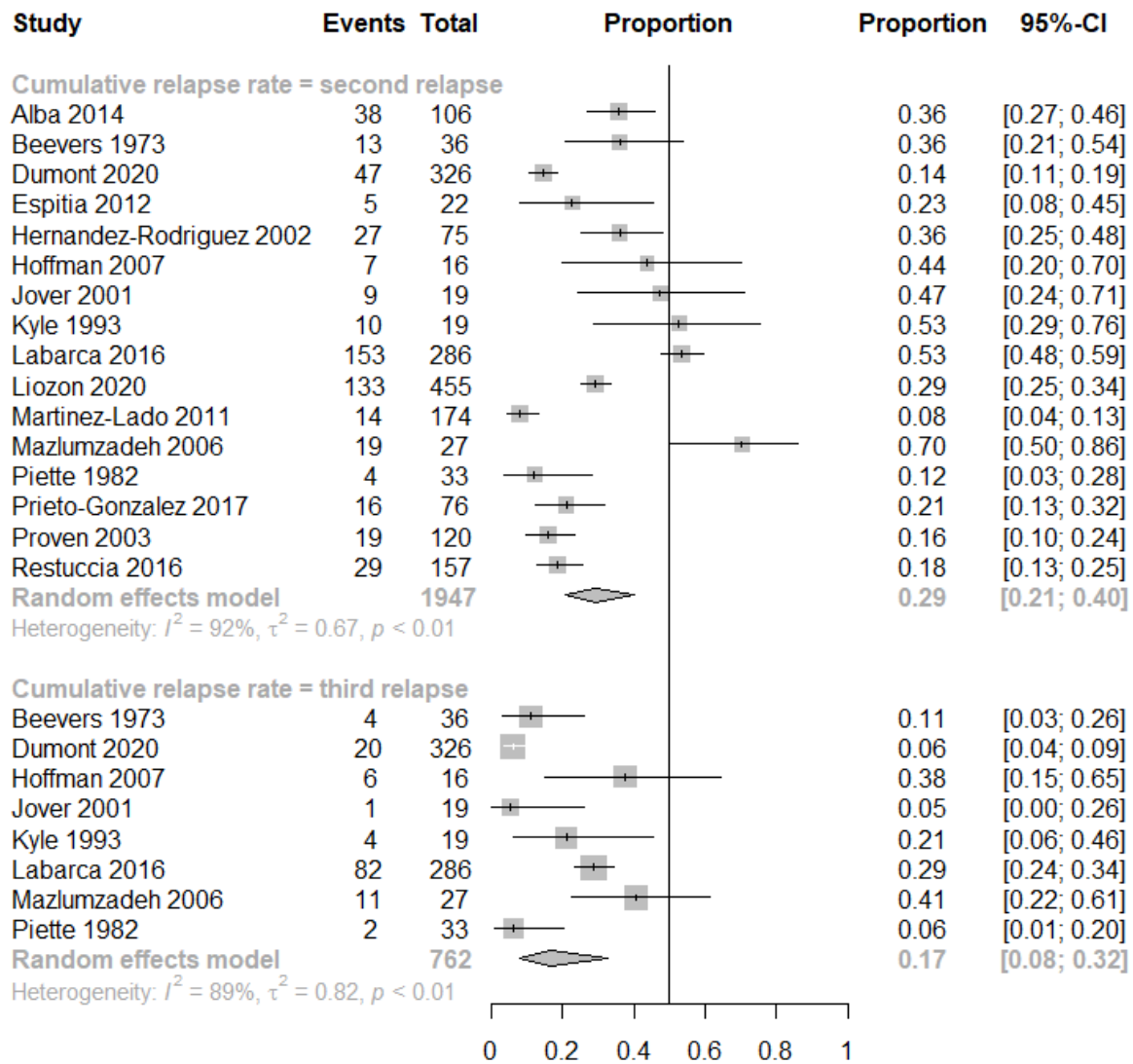| Predictor	Studies	Patients	OR (95% CI)	P value
Female sex	13	1725	1.43 (1.04 - 1.98)	0.03
LVV	10	940	2.04 (1.28 - 3.23)	0.01
Headache	9	1368	0.90 (0.65 - 1.25)	0.48
Scalp tenderness	5	837	1.40 (0.61 - 3.22)	0.32
Jaw claudication	9	1368	1.00 (0.69 - 1.45)	1.00
Abnormal temporal artery	6	917	0.81 (0.65 - 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

0.1   0.5   1   2   10

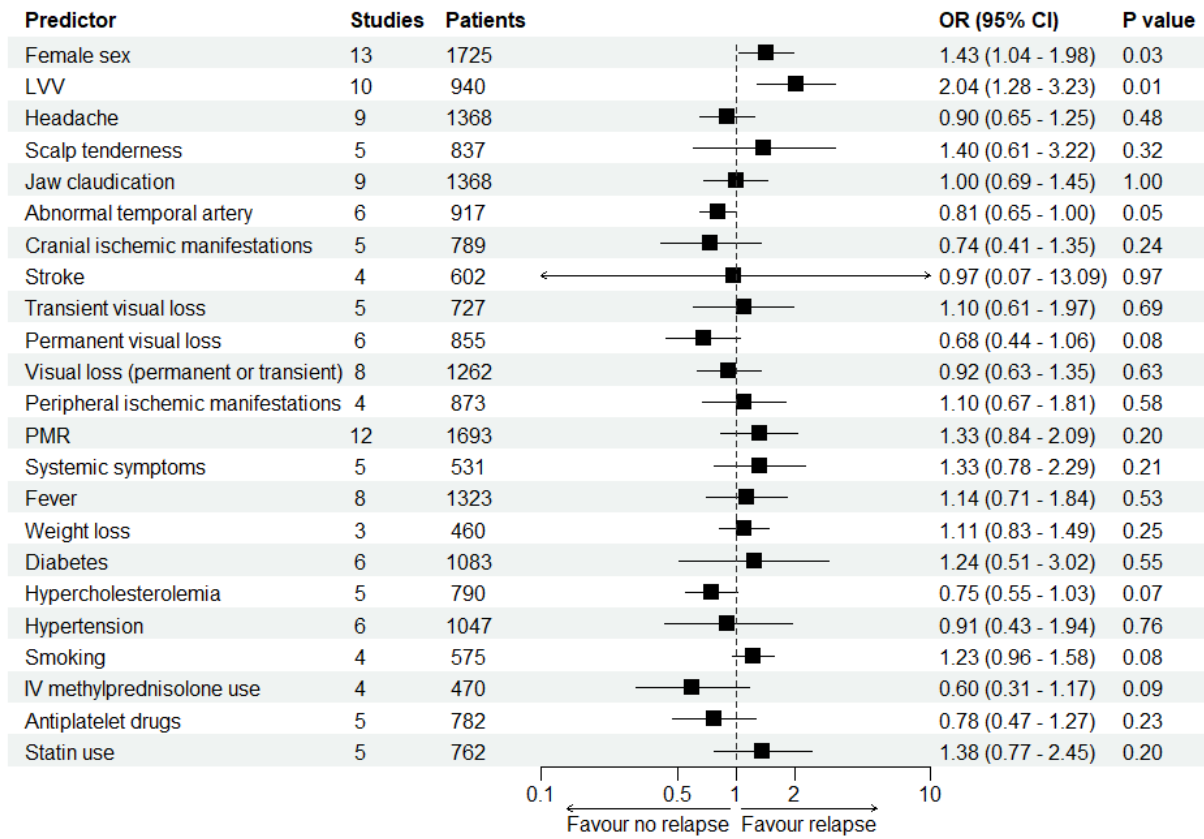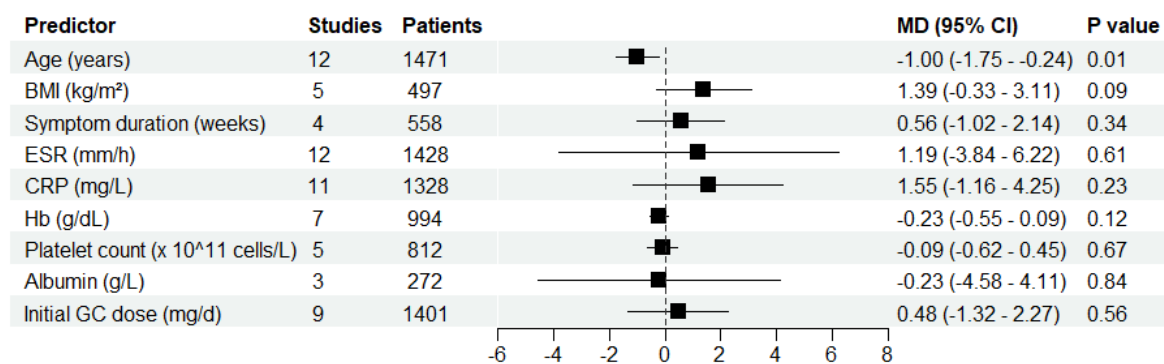Favour no relapse   Favour relapse

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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