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Large vessel vasculitis is only a risk factor for relapse in giant cell arteritis patients without polymyalgia rheumatica: a retrospective cohort study

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Objectives: To evaluate differences in presentation and outcome of giant cell arteritis (GCA) patients with and without large vessel vasculitis (LVV) and according to the extent and severity of LVV.

Methods: Consecutive patients diagnosed with GCA between 2003 and 2020 who have had FDG PET imaging at diagnosis ≤3 days after initiation of glucocorticoids and followed for ≥12 months at the University Hospitals Leuven (Belgium), were included retrospectively. PET scans were visually scored (0-3) in 7 vascular areas and a total vascular score (TVS) was calculated. LVV was defined as FDG uptake ≥2 in any large vessel.

Results: We included 238 GCA patients, of which 169 (71%) had LVV. LVV patients were younger (69 vs 74 years, p<0.001) and more frequently female (72% vs 49%, p=0.001). In patients without PMR symptoms, the presence of LVV was positively associated with relapse (aOR 3.05 [95%CI 1.32-7.43], p=0.011) with a lower probability of stopping glucocorticoids (aHR 0.63 [95%CI 0.39-0.99], p=0.047). However, in those with PMR symptoms, there was no difference in relapse risk (aOR 1.20 [95%CI 0.53-2.66], p=0.657) and in the probability of stopping glucocorticoids (aHR 1.25 [95%CI 0.75-2.09], p=0.397) between patients with and without LVV. In addition, higher TVS was associated with a higher risk of relapse (aOR 1.06 [95%CI 1.02-1.10], p=0.001] in patients without PMR symptoms, but not in those with PMR symptoms (aOR 1.00 [95%CI 0.97-1.04], p=0.869).

Conclusion: LVV was only a risk factor for relapse in GCA patients without PMR symptoms with a higher relapse risk with higher TVS.

Introduction

Giant cell arteritis (GCA) is a large vessel vasculitis that preferentially affects the cranial arteries and the aorta and its proximal branches.[1] GCA represents a heterogeneous group of patients with distinct presentations according to the pattern of vessel involvement (cranial vs large vessel vasculitis or both). Presenting features of GCA may include symptoms related to vasculitis (such as temporal headache, jaw claudication, visual loss, or limb claudication), constitutional symptoms (such as fever, fatigue, weight loss, anorexia, or night sweats), and/or polymyalgia rheumatica (PMR).

For decades, glucocorticoids (GC), mostly in monotherapy, have been the cornerstone of GCA treatment. After GC initiation, clinical manifestations and systemic inflammation typically disappear quickly and ischemic complications become rare.[2] However, about half of GCA patients experience disease relapse.[3] These frequent relapses necessitate prolonged GC treatment, which implies a significant risk of GC-related toxicity.[4,5] Finding prognostic variables that may forecast the required duration of GC therapy and the need for early introduction of GC-sparing agents, is therefore crucial. In a previous meta-analysis by our group, we identified large vessel vasculitis (LVV), female sex and PMR as predictors of relapse in GCA patients.[3,6] However, it remains unclear if the presence of multiple predicting factors for relapse further increases the risk of relapse and if the extent and severity of LVV is associated with a higher risk of relapse.

The aim of this study was to evaluate differences in presentation and outcome of GCA patients with and without LVV and according to the extent and severity of LVV.

Methods

Patient population

We retrospectively included all patients with a final diagnosis of GCA, who were evaluated by the Department of General Internal Medicine or Rheumatology of the University Hospitals Leuven (Belgium) between July 2003 and December 2020, who underwent 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging ≤3 days after initiation of GC and who were followed for ≥12 months. Patients who were treated with GC for another disease, were excluded. The final diagnosis of GCA was based on the judgment of the treating physician, considering all available information (clinical data, biochemical, radiological, and temporal artery biopsy results, PET images and evolution during follow-up). The treatment was at the discretion of the treating physician.

The study was conducted in accordance with the Declaration of Helsinki and approved by the ethical committee of UZ Leuven. Informed consent was waived because of the retrospective nature of the study and the analysis used pseudonymized clinical data.

Data collection

We collected the following patient data from the electronic health record from GCA diagnosis through the last visit, death or end of the study follow-up period (December 31, 2022): age, sex, date of diagnosis, symptom duration until diagnosis, symptoms, biochemical results, temporal artery biopsy and PET result at diagnosis, duration of follow-up, dose (in equivalents of methylprednisolone) and duration of GC treatment and relapses during follow-up. Relapse was defined as recurrence of clinical symptoms compatible with PMR or GCA and/or increase of inflammatory markers requiring escalation of treatment.

PET imaging and analysis

Patients were required to fast for at least 6 hours before intravenous injection of 4-5 MBq/kg of ^{18}F-FDG, and glycemia levels were determined in all patients (as per procedure, should be < 140 mg/dl). A whole-body PET scan was performed 60 min after tracer administration. PET scans were consecutively acquired on four different PET cameras (ECAT HR+ PET, Hirez Biograph 16 PET/CT, Truepoint Biograph 40 PET/CT [Siemens, Knoxville, TN, USA] or Discovery MI-4 PET/CT [GE, Milwaukee, WI, USA]). Since gamma rays from the positron annihilation in PET are absorbed by the body, a correction for this attenuation allows quantitatively accurate judgement of internal regions in the body. On the PET/CT systems, either a low-dose CT scan or a diagnostic, high-dose CT scan was performed immediately before PET acquisition. The CT scan was used for attenuation correction and for anatomical localization. For the older HR+ acquisitions, no attenuation correction was performed, but this will only affect the most central body areas. Attenuation-corrected PET images were thus only available for the patients scanned on a PET/CT system (n=134, 56%). PET data were corrected for scatter and randoms. Data were reconstructed using iterative OSEM reconstruction, with image quality parameters improving over the years.

Reconstructed PET images were re-evaluated visually by a specialist in nuclear medicine (LB), who was blinded to all other patient information. FDG PET uptake was visually scored at 7 vascular regions (thoracic and abdominal aorta, subclavian, axillary, carotid, iliac, and femoral arteries) as 0 (no FDG uptake), 1 (minimal but not negligible FDG uptake), 2 (clearly increased FDG uptake), or 3 (very marked FDG uptake). FDG uptake ≥ grade 2 was considered indicative for vasculitis. A total vascular score (TVS) was calculated as a measure of the extent and severity of LVV and ranges from 0 (no vascular FDG uptake in

any of the 7 vascular regions) to 21 (vascular FDG uptake scored 3 in all 7 segments).[7] Subclavian, axillary, carotid, iliac, and femoral arteries were counted as 1 vascular region each: when the score differed from right to left artery, the highest score was taken for that vascular region. Furthermore, to assess cranial vasculitis, the vertebral, maxillary, occipital and temporal arteries were scored similarly.

In addition, FDG PET uptake was visually scored at 12 skeletal regions (cervical spinous processes, lumbar spinous processes, left and right sternoclavicular joint, left and right ischial tuberosity, left and right greater trochanter, left and right hip, and left and right shoulder) as 0 (no elevated FDG uptake), 1 (moderately elevated FDG uptake, but less than mean liver uptake) or 2 (intense FDG uptake, equal or more than average liver uptake). The Leuven score was calculated by summing the 12 skeletal regions and ranges from 0 to 24.[8]

Statistical analysis

Categorical and continuous variables were expressed as count (percentage) and as mean ± standard deviation (SD) or median ± interquartile range (IQR) as appropriate. Comparison of the characteristics in GCA patients with and without LVV was performed by chi square tests, Fisher's exact tests, Mann-Whitney U tests or unpaired T-tests as appropriate. Logistic regression analyses were used to estimate the association between the presence of LVV and the proportion of patients with relapse at last follow-up, with and without adjustment for differences in clinical presentation. The best model was selected by backward stepwise selection and by examining possible interactions. Differences in the number of relapses were analyzed by Poisson regression, with and without adjustment for the variables in the best model. Cox proportional hazard analysis was used to estimate the association between presence of LVV and the proportion of patients able to stop GC adjusted for the variables in the best model. The change in GC doses during follow-up was estimated by using a non-linear mixed effect model with random intercept and slope in time.

In addition, the importance of the extent and severity of LVV, expressed in the summary measure TVS, was examined in the whole cohort and in the subgroup of patients with LVV. Since the assumptions of linear regression were not met, Spearman correlations were measured between TVS on the one hand and age, symptom duration, biochemical results, the Leuven score, duration of GC treatment and cumulative GC dose in the first 2 years on the other hand. Logistic regression analyses were performed to determine the association between TVS and outcomes of interest, including sex, symptoms at diagnosis, temporal artery biopsy result and FDG uptake in the cranial vessels. The association between TVS and relapse was analyzed by logistic regression analyses, with and without adjustment for confounders. Cox proportional hazard analysis was used to estimate the association

between TVS and the proportion of patients able to stop GC adjusted for the variables in the best model. All statistical tests were performed using 2-tailed tests with significance set at the $p<0.05$ level. Statistical analysis was performed in R Studio (version 2022.06.23, The R Foundation for Statistical Computing) and SAS OnDemand for Academics.

Results

After exclusion of 3 patients who were treated with GC for another disease, 80 patients who were followed for less than 12 months, 65 patients who did not have had a PET scan, 14 patients in which the images of the PET scan were not available in the electronic health record and 45 patients who had a PET scan more than 3 days after GC initiation, a total of 238 patients were included in this study (**Figure 1**). 26 (11%) patients received GC for less than three days prior to PET imaging; 212 (89%) were steroid-naïve. The median duration of follow-up was 46 months (IQR 25-86).

Comparison of GCA patients with and without LVV

Baseline characteristics of this cohort are presented in **Table 1**. GCA patients with LVV were younger (69 vs 74 years, $p<0.001$) and more frequently female (72% vs 49%, $p=0.001$). They had a significantly longer symptom duration before diagnosis (10 vs 4 weeks, $p<0.001$), and this both for PMR (17 vs 5 weeks, $p=0.003$), cranial (8 vs 4 weeks, $p<0.001$), and constitutional symptoms (9 vs 4 weeks, $p<0.001$). GCA patients with LVV more frequently reported constitutional symptoms (84% vs 68%, $p=0.006$) and less frequently cranial symptoms (63% vs 81%, $p=0.006$), which also included less permanent visual loss (7% vs 17%, $p=0.017$). All 5 patients with limb claudication had LVV, however this difference did not reach significance due to the low numbers. There was no difference in the occurrence of PMR symptoms (49% vs 52%, $p=0.668$). Those with LVV had lower C-reactive protein (CRP) (77 vs 99 mg/L, $p=0.041$) and hemoglobin levels (11.4 vs 12.4 g/dL, $p<0.001$) and lower white blood cell (8.5 vs 9.9 $*10^9$/L, $p<0.001$) and neutrophil count (5.8 vs 7.3 $*10^9$/L, $p<0.001$). They more frequently had FDG uptake in the cranial vessels (51% vs 37%, $p=0.040$), while there was no difference in the Leuven score (7 vs 7, $p=0.866$) and in the proportion of patients with a positive temporal artery biopsy (61% vs 56%, $p=0.484$).

Without adjustments, logistic regression analysis showed a higher risk of relapse in patients with LVV at last follow-up (OR 1.82 [95%CI 1.04-3.22], $p=0.037$) with a higher number of relapses (1.50 vs 1.13 relapses, $p=0.026$). There was no difference in the median time to first relapse (14 vs 12 months, $p=0.709$) and the median daily dose of methylprednisolone at that time (1.0 vs 1.5 mg methylprednisolone, $p=0.802$). There were no differences in the symptoms at first relapse; 64% vs 73% of patients with relapse had PMR symptoms at time

of first relapse (p=0.361), 29% vs 40% had cranial symptoms (p=0.242), 43% vs 27% constitutional symptoms (p=0.117) and 91% vs 90% had raised inflammatory markers at time of first relapse (p=0.729).

After adjustment for age, sex, symptom duration, PMR, cranial symptoms, constitutional symptoms and limb claudication, presence of LVV was not significantly associated anymore with the risk of relapse (aOR 1.64 [95%CI 0.84-3.20], p=0.144). After backward stepwise selection and examining possible interactions, the model with the best fit was the model with only adjustment for PMR with an interaction between the presence of LVV and PMR (**Figure 2**). In patients without PMR symptoms, the presence of LVV was positively associated with relapse (aOR 3.05 [95%CI 1.32-7.43], p=0.011) with a higher number of relapses (1.58 vs 0.64 relapses, p<0.001). However, in patients with PMR symptoms, there was no significant difference in the relapse risk (aOR 1.20 [95%CI 0.53-2.66], p=0.657) and in the number of relapses (1.41 vs 1.58 relapses, p=0.472) between patients with and without LVV.

In the subgroup of patients without PMR symptoms, patients with LVV were treated with significantly higher GC doses from 5 months after diagnosis (**Figure 3A, Supplementary Table 1**). This resulted in a higher cumulative GC dose in the first 2 years after diagnosis (4.4 g vs 3.8 g, p=0.043). GC duration was significantly longer in patients with LVV without PMR symptoms (26 vs 17 months, p=0.006) with a lower probability of stopping GC (aHR 0.63 [95%CI 0.39-0.99], p=0.047) (**Figure 4**) compared to patients without LVV.
In contrast, in the subgroup of patients with PMR symptoms, there was no difference in GC doses during follow-up (**Figure 3B, Supplementary Table 2**), in the cumulative GC dose in the first 2 years after diagnosis (4.2 g vs 4.1 g, p=0.386), in GC duration (29 vs 30 months, p=0.952) and in the probability of stopping GC (aHR 1.25 [95%CI 0.75-2.09], p=0.397) (**Figure 4**).

Evaluation of the association between TVS and outcomes in the whole cohort

Without adjustments, logistic regression analysis showed a higher risk of relapse with higher TVS (OR 1.05 [95%CI 1.01-1.09], p=0.017). After adjustment for confounders, TVS was still significantly associated with relapse (aOR 1.06 [95%CI 1.01-1.11], p=0.010). Using the best model with only adjustment for the interaction between TVS and PMR symptoms, TVS was positively associated with relapse in patients without PMR symptoms (aOR 1.06 [95%CI 1.02-1.10], p=0.001), but not in those with PMR symptoms (aOR 1.00 [95%CI 0.97-1.04], p=0.869) **(Figure 5A)**.

In the 119 GCA patients without PMR symptoms, higher TVS was significantly correlated with higher cumulative GC dose in the first 2 years after diagnosis (r_s=0.24, p=0.012), a longer duration of GC treatment (r_s = 0.25, p=0.006) and a lower probability of stopping GC (aHR 0.96 [95%CI 0.93-0.99], p=0.015) **(Supplementary Figure 1A)**. In contrast, in the subgroup of GCA patients with PMR symptoms, there was no correlation between TVS and the cumulative GC dose in the first 2 years (r_s=0.12, p=0.225), the GC duration (r_s = 0.01, p=0.876) and the probability of stopping GC (aHR 1.01 [95%CI 0.98-1.04], p=0.624).

Evaluation of the association between TVS and clinical presentation and outcomes in the subgroup of patients with LVV

In the subgroup of 169 patients with LVV **(Table 2)**, TVS was not correlated with age and symptom duration of PMR symptoms, but was positively correlated with symptom duration of cranial symptoms (r_s=0.36, p<0.001). There was also a trend towards a longer symptom duration in constitutional symptoms (r_s=0.17, p=0.057). Higher TVS was associated with female sex (OR 1.10 [95%CI 1.04-1.17], p<0.001), constitutional symptoms (OR 1.09 [95%CI 1.02-1.18], p=0.017) and limb claudication (OR 1.21 [95%CI 1.01-1.56], p=0.042). In addition, higher TVS was associated with a lower odds of having PMR symptoms (OR 0.93 [95%CI 0.88-0.98], p=0.007). There was no significant association with cranial symptoms (OR 0.98 [95%CI 0.92-1.03], p=0.344). In contrast, higher TVS was associated with a higher odds of having a positive temporal artery biopsy (OR 1.13 [95%CI 1.06-1.21], p<0.001) and FDG uptake in cranial vessels (OR 1.11 [95%CI 1.06-1.18], p<0.001). There was a negative correlation between TVS and the Leuven score (r_s=-0.16, p=0.044). In terms of laboratory results, TVS was positively correlated with ESR (r_s=0.21, p=0.013) and CRP (r_s=0.18, p=0.018) and negatively with hemoglobin (r_s=-0.30, p<0.001). There was a trend towards a positive correlation with platelets (r_s=0.14, p=0.076).

Without adjustment, there was no significant association between TVS and the relapse risk in the subgroup of patients with LVV (OR 1.04 [95%CI 0.98-1.09], p=0.177). With adjustment for the interaction between TVS and PMR symptoms, higher TVS was associated with a higher risk of relapse (aOR 1.09 [95%CI 1.01-1.18], p=0.037] in LVV patients without PMR symptoms, but not in LVV patients with PMR symptoms (aOR 1.00 [95%CI 0.93-1.08], p=0.915) (**Figure 5B**).

Cox regression analyses showed no association between TVS and the probability of stopping GC in LVV patients with (aHR 1.00 [95%CI 0.96-1.04], p=0.918) and without PMR symptoms (aHR 0.97 [95%CI 0.93-1.02), p=0.224) (**Supplementary Figure 1B**). There was no correlation between TVS and GC duration both in the subgroup with (r_s=0.02, p=0.842)

and without PMR symptoms (r_s=0.12, p=0.296). There was a trend towards a higher cumulative GC dose in the first 2 years in the subgroup of patients without PMR symptoms (r_s=0.19, p=0.091), while there was no correlation in the subgroup of patients with PMR symptoms (r_s=0.09, p=0.429).

Discussion

In this study, we found that GCA patients with LVV were younger and more frequently female compared to those without, which is consistent with the results of a recent meta-analysis.[9] They had a significantly longer symptom duration before diagnosis, and this was true both for PMR, cranial, and constitutional symptoms. GCA patients with LVV more frequently reported constitutional symptoms and less frequently cranial symptoms with no differences in the occurrence of PMR symptoms.

To the best of our knowledge, this is the first study looking at differences in presentation of LVV patients according to the severity and extent of LVV. In the subgroup of GCA patients with LVV, higher TVS was positively associated with female sex, but not with age. Patients with a higher TVS had a higher odds of having constitutional symptoms and a lower odds of having PMR symptoms with a lower Leuven score on PET imaging without difference in the occurrence of cranial symptoms. However, they more frequently had a positive temporal artery biopsy and FDG uptake in the cranial vessels. Higher TVS was associated with higher inflammatory markers.

In concordance with a previous meta-analysis of our group[3], we found that GCA patients with LVV had a higher risk of relapse compared to those without LVV with a higher number of relapses. After adjustment for confounding factors, examining possible interactions and selecting the best model, we observed that this was only true in the subgroup of patients without PMR symptoms. Patients with only PMR symptoms, those with only LVV and those with both LVV and PMR symptoms had a similarly high relapse risk. So, we can conclude that both PMR and LVV were risk factors for relapse, but having both risk factors did not further increase the risk of relapse compared to having only one of these risk factors. As a result, only in the subgroup of patients without PMR symptoms, the presence of LVV was associated with higher GC doses and longer GC treatment with a lower probability of stopping GC over time. In the subgroup of patients with PMR symptoms, there were no differences in doses and duration of GC treatment. Nevertheless, EULAR guideline does not recommend a different and more aggressive therapeutic approach for GCA patients with LVV and/or PMR symptoms.[10] We believe it is important to stratify and to perform subgroup analyses on both characteristics in randomized controlled trials examining GC sparing and

disease modifying agents to examine if there is a difference in effectiveness between these patients.

Several studies examined the association between the extent and severity of LVV and the future relapse risk. In 2 studies[11,12], a greater extent and severity of LVV on PET during remission was associated with a higher risk of relapse, while this was not significant in 3 other studies.[13–15] Three studies did not find an association between TVS at diagnosis and the future relapse risk, however the sample size of these studies was rather small.[7,14,15] Esperança Almeida et al. observed that the halo count at diagnosis was positively associated with relapse, but this was not significant anymore in the subgroup of patients with a halo in at least one vessel.[16] However, halo count also includes the cranial vessels. Similarly, without adjustment for confounders, we found a positive association between TVS at diagnosis and the future relapse risk in the whole cohort, but not in the subgroup of patients with LVV. However, with adjustment for the interaction between PMR and TVS, we observed that TVS at diagnosis was positively associated with relapse risk in LVV patients without PMR symptoms, but not in LVV patients with PMR symptoms. In contrast to our analysis in the whole cohort of GCA patients, we did not find an association between TVS and GC doses and duration in LVV patients.

Our study has several limitations. First, we only included patients with PET imaging at diagnosis within 3 days of GC initiation, which could have introduced selection bias. Second, due to the long inclusion period, PET scans were performed on different PET systems with increasing device quality over time. In particular, improved spatial resolution and contrast may enhance detection of vasculitis in smaller vessels and thus increase sensitivity over time. Third, this was a single-centre study in a tertiary care hospital, limiting the overall generalizability. Fourth, treatment was at the discretion of the physician, so we cannot rule out the possibility that treatment differences may have affected some of our findings. Finally, the retrospective design may be associated with information bias.

In conclusion, GCA patients with LVV were younger, more frequently female, had a longer symptom duration before diagnosis, more frequently reported constitutional symptoms and less frequently had cranial symptoms compared to those without. In the subgroup of GCA patients with LVV, higher TVS was positively associated with female sex, constitutional symptoms and inflammatory markers and negatively with PMR symptoms. LVV was only a risk factor for relapse in GCA patients without PMR symptoms. Higher extent and severity of LVV further increased the relapse risk in patients without PMR symptoms. This needs to be confirmed in a large, prospective study.

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Figure 1: Flow diagram of study patients

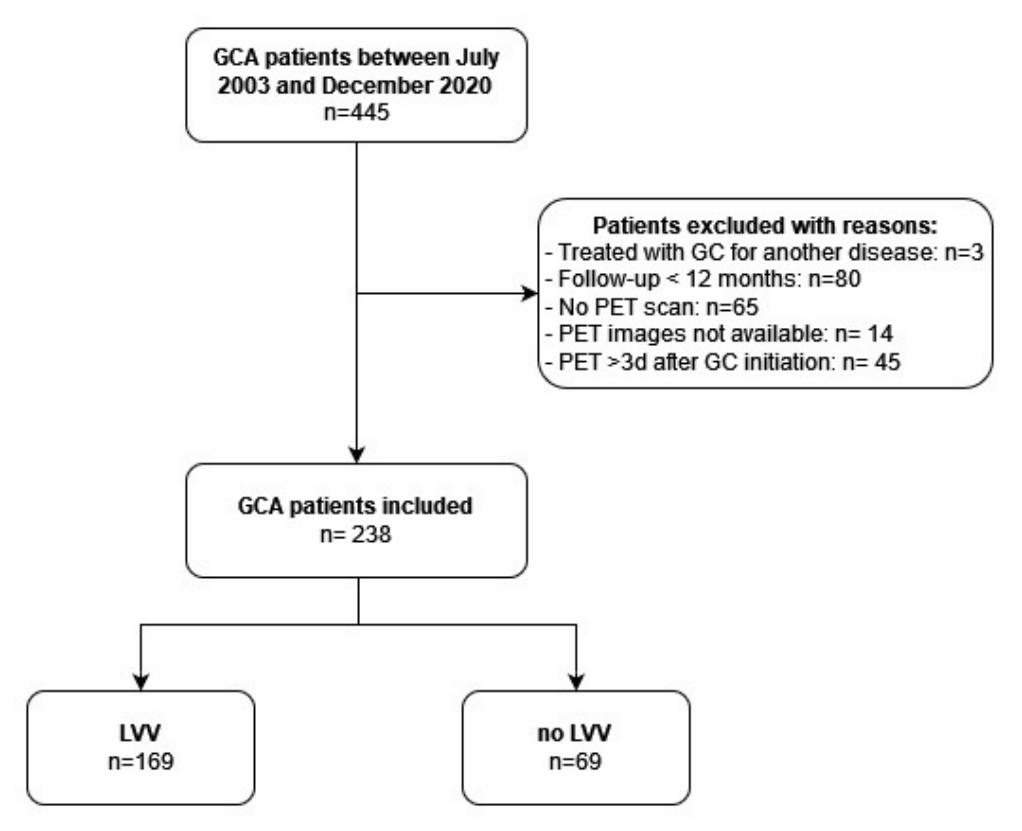


Figure 2: (A) Logistic regression analysis for the risk of relapse and **(B)** poisson regression analysis for the number of relapses in the model with the best fit with an interaction between LVV and PMR

Abbreviatons: LVV, large vessel vasculitis; PMR, polymyalgia rheumatica

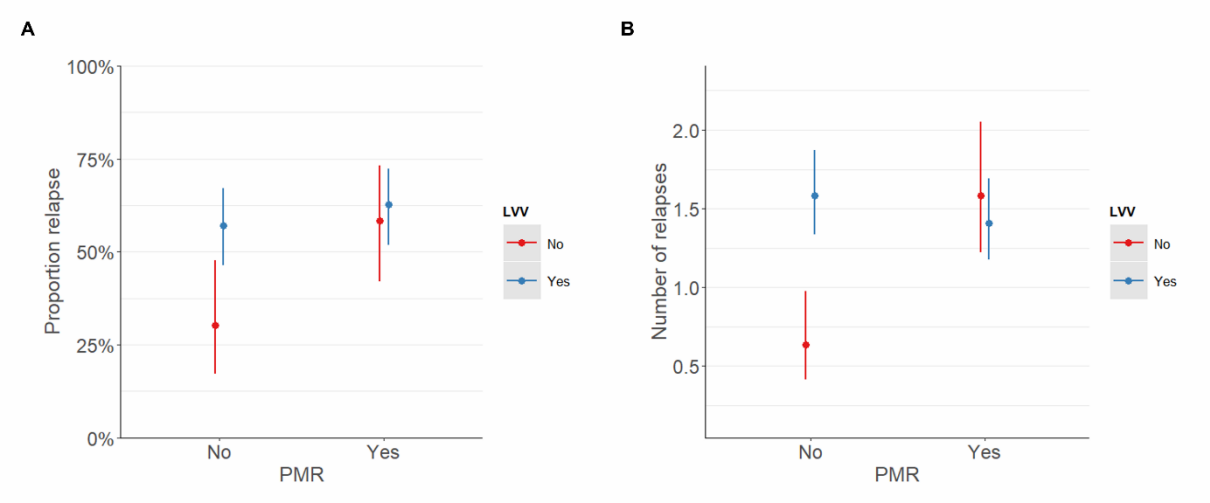


Figure 3: Non-linear mixed-effects model estimates for the change in GC dose (expressed in methylprednisolone equivalents) comparing GCA patients with and without LVV. Figure 3A shows GCA patients with PMR symptoms, figure 3B GCA patients without PMR symptoms

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

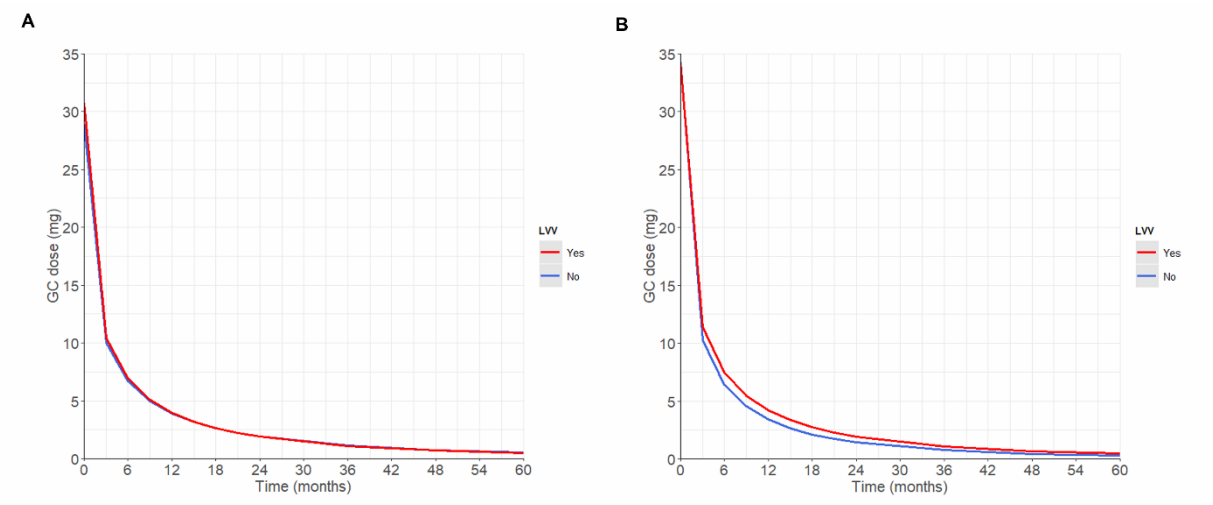
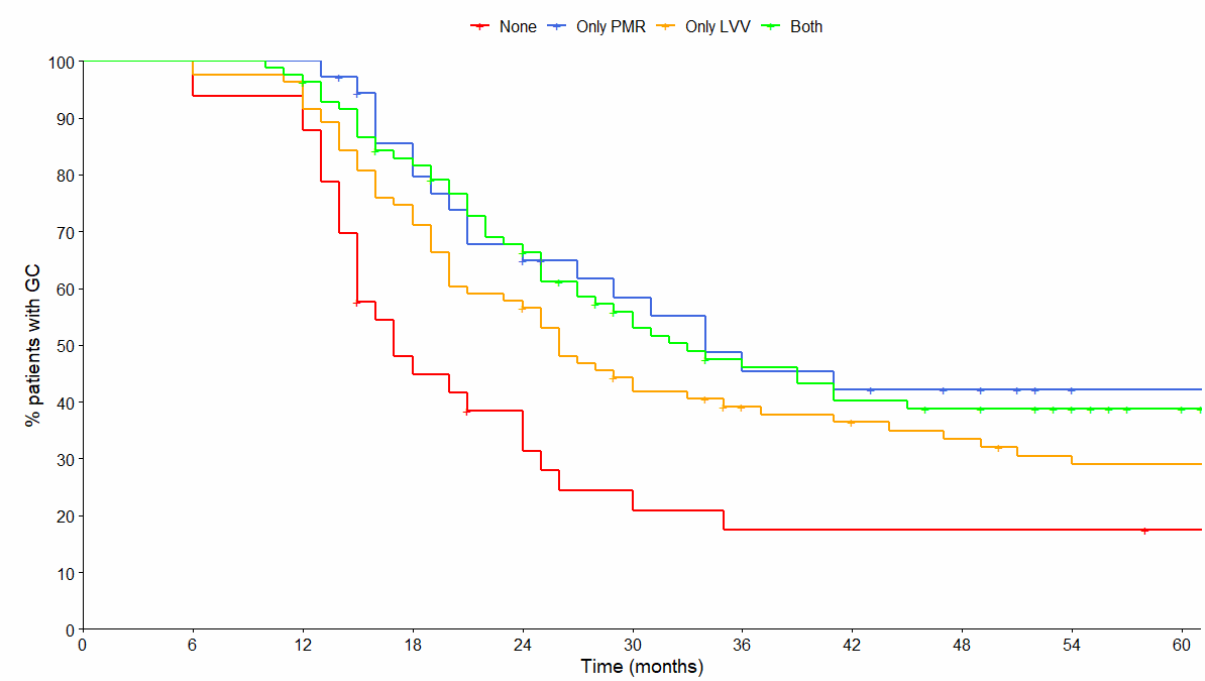


Figure 4: Kaplan-Meier estimates for the proportion of patients on GC treatment comparing GCA patients with and without LVV and PMR symptoms

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



Number at risk

None	33	33	31	15	11	7	5	5	5	5	4
Only PMR	36	36	36	29	23	18	15	13	11	8	7
Only LVV	83	83	80	62	48	35	29	26	23	20	19
Both	83	83	81	66	53	40	33	28	26	22	18

Figure 5: Logistic regression analysis for the risk of relapse with an interaction between TVS and PMR **(A)** in the whole cohort and **(B)** in the subgroup of patients with LVV, defined as FDG uptake ≥ grade 2 in at least one large vessel

Abbreviations: LVV, large vessel vasculitis; PMR, polymyalgia rheumatica; TVS, total vascular score

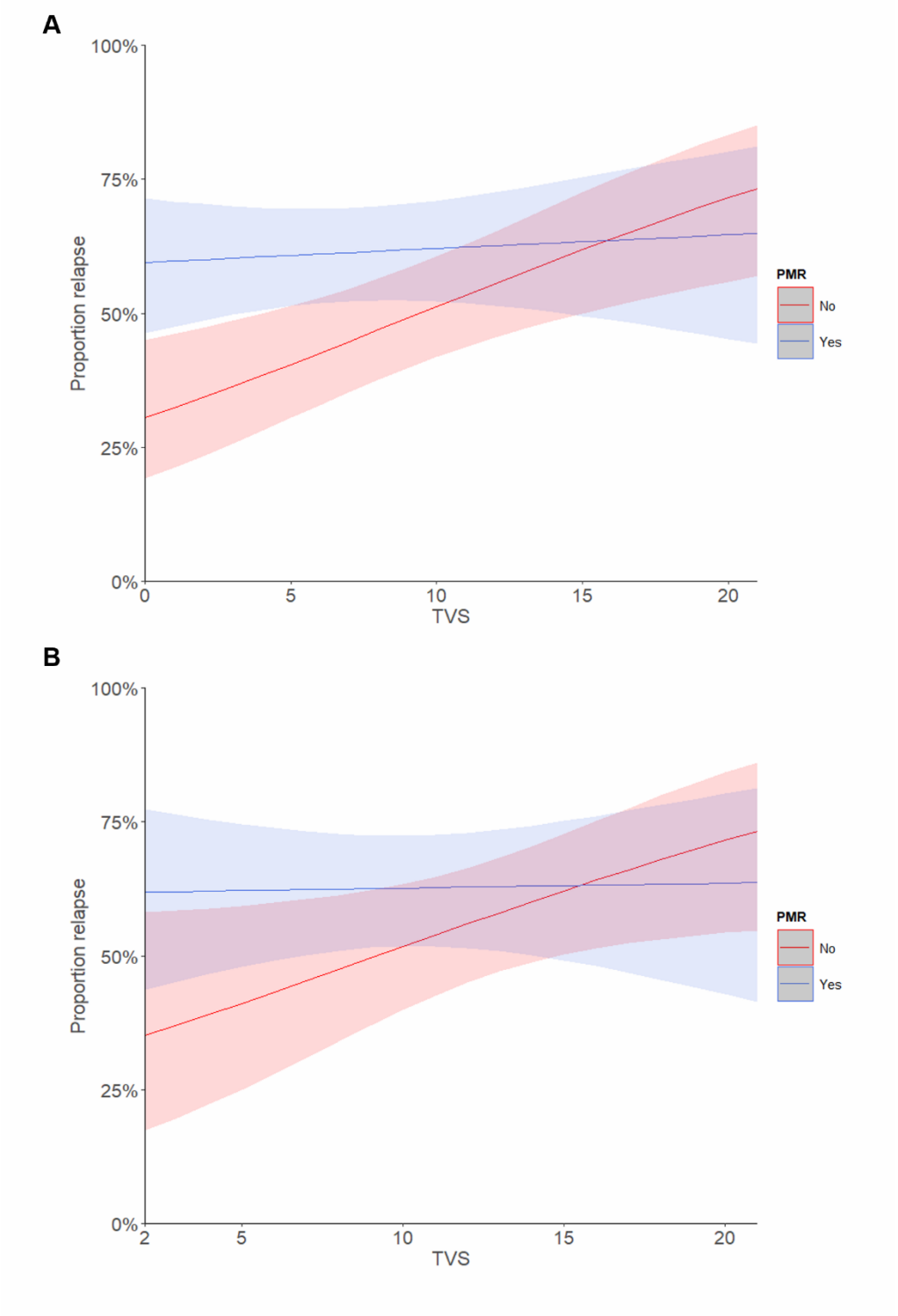


Table 1: Baseline characteristics of GCA patients with and without LVV, defined as FDG uptake ≥ grade 2 in any large vessel

Characteristics	Total (n = 238)	LVV (n = 169)	No LVV (n = 69)	P-value
Age at inclusion, years, mean (SD)	71 (8)	69 (8)	74 (8)	**<0.001**
Sex, no. of females, n (%)	155 (65%)	121 (72%)	34 (49%)	**0.001**
Symptom duration until diagnosis, weeks, median (IQR)				
○ **Any symptom**	8 (4-19)[21]	10 (5-23)[17]	4 (2-7)[4]	**<0.001**
○ **PMR symptoms**	14 (4-26)[136]	17 (8-26)[97]	5 (3-20)[39]	**0.003**
○ **Cranial symptoms**	6 (2-15)[91]	8 (4-17)[74]	4 (2-6)[17]	**<0.001**
○ **Constitutional symptoms**	7 (4-17)[71]	9 (4-22)[43]	4 (2-6)[28]	**<0.001**
Symptoms at diagnosis, n (%)				
○ **Constitutional symptoms**	189 (79%)	142 (84%)	47 (68%)	**0.006**
▪ **Fever**	67 (28%)	44 (26%)	23 (33%)	0.256
▪ **Fatigue**	146 (61%)	114 (67%)	32 (46%)	**0.002**
▪ **Anorexia**	111 (47%)	85 (50%)	26 (38%)	0.077
▪ **Weight loss**	109 (46%)	83 (49%)	26 (38%)	0.108
▪ **Night sweats**	62 (26%)	46 (27%)	16 (23%)	0.520
○ **Cranial symptoms**	162 (68%)	106 (63%)	56 (81%)	**0.006**
▪ **Headache**	141 (59%)	91 (54%)	50 (72%)	**0.008**
▪ **Scalp tenderness**	37 (16%)	19 (11%)	18 (26%)	**0.004**
▪ **Jaw claudication**	66 (28%)	41 (24%)	25 (36%)	0.061
▪ **Permanent visual loss**	24 (10%)	12 (7%)	12 (17%)	**0.017**
▪ **Transient visual loss**	31 (13%)	24 (14%)	7 (10%)	0.399
▪ **Diplopia**	9 (4%)	4 (2%)	5 (7%)	0.126
▪ **CVA**	2 (1%)	2 (1%)	0 (%)	1.000
▪ **TIA**	5 (2%)	4 (2%)	1 (1%)	1.000
○ **PMR**	119 (50%)	83 (49%)	36 (52%)	0.668
○ **Limb claudication**	5 (2%)	5 (3%)	0 (0%)	0.325
Laboratory tests, median (IQR)				
○ **ESR, mm/h**	67 (45-102)[31]	70 (46-105)[22]	66 (45-93)[9]	0.249
○ **CRP, mg/L**	79 (41-128)	77 (38-116)	99 (50-151)	**0.041**
○ **Hemoglobin, g/dL**	11.6 (10.6-12.6)[1]	11.4 (10.4-12.2)[1]	12.4 (11.2-13.1)	**<0.001**
○ **Platelets, *10⁹/L**	405 (314-509)[3]	413 (322-514)[2]	373 (298-484)[1]	0.239
○ **White blood cell count, *10⁹/L**	8.9 (7.6-10.9)	8.5 (7.2-10.3)	9.9 (8.2-12.2)	**<0.001**
○ **Neutrophils, *10⁹/L**	6.2 (5.1-8.0)[18]	5.8 (4.8-7.4)[13]	7.3 (5.9-9.4)[5]	**<0.001**
○ **Albumin, g/L**	38.1 (34-.5-41.4)[72]	37.9 (34.3-41.4)[57]	38.4 (34.7-41.1)[15]	0.904
○ **Alkaline phosphatase, U/L**	121 (81-206)[17]	123 (90-198)[16]	103 (75-208)[1]	0.226
Positive temporal artery biopsy, n (%)	113 (59%)[48]	76 (61%)[45]	37 (56%)[3]	0.484
PET results				
○ **FDG uptake in the cranial vessels, n (%)**	112 (47%)[1]	87 (51%)	25 (37%)[1]	**0.040**
○ **Total vascular score, median (IQR)**	7 (1-15)	12 (5-17)	0 (0-0)	**<0.001**
○ **Leuven score, median (IQR)**	7 (3-15)	7 (2-15)	7 (2-15)	0.866
Duration of follow-up, months, median (IQR)	46 (25-86)	49 (27-89)	36 (22-72)	**0.026**

Abbreviations: ACR, American College of Rheumatology; CRP, C-reactive protein; CVA, cerebrovascular accident; ESR, erythrocyte sedimentation rate; EULAR, European Alliance of Associations for Rheumatology; FDG, fluorodeoxyglucose; GCA, giant cell arteritis; IQR, interquartile range; LVV, large vessel vasculitis; no., number; PET, positron emission tomography; PMR, polymyalgia rheumatica; SD, standard deviation; TIA, transient ischemic attack

Number of missing values are reported in superscript.

Table 2: Spearman correlation and logistic regression analyses between TVS and outcomes of interest in the subgroup of patients with LVV, defined as FDG uptake ≥ grade 2 in any large vessel

Characteristics	Total (n = 169)	Spearman's correlation coefficient r_s	Odds ratio (95%CI)	P-value
Age at inclusion, years, mean (SD)	69 (8)	0.01		0.908
Sex, no. of females, n (%)	121 (72%)		1.10 (1.04-1.17)	**<0.001**
Symptom duration until diagnosis, weeks, median (IQR)				
○ **Any symptom**	10 (5-23)[17]	0.09		0.276
○ **PMR symptoms**	17 (8-26)[97]	0.06		0.602
○ **Cranial symptoms**	8 (4-17)[74]	0.36		**<0.001**
○ **Constitutional symptoms**	9 (4-22)[43]	0.17		0.057
Symptoms at diagnosis, n (%)				
○ **Constitutional symptoms**	142 (84%)		1.09 (1.02-1.18)	**0.017**
▪ **Fever**	44 (26%)		0.99 (0.92-1.05)	0.697
▪ **Fatigue**	114 (67%)		1.10 (1.04-1.16)	**<0.001**
▪ **Anorexia**	85 (50%)		1.02 (0.97-1.08)	0.355
▪ **Weight loss**	83 (49%)		1.09 (1.03-1.15)	**0.002**
▪ **Night sweats**	46 (27%)		1.04 (0.99-1.11)	0.145
○ **Cranial symptoms**	106 (63%)		0.98 (0.92-1.03)	0.344
▪ **Headache**	91 (54%)		0.98 (0.92-1.03)	0.522
▪ **Scalp tenderness**	19 (11%)		0.98 (0.90-1.06)	0.628
▪ **Jaw claudication**	41 (24%)		0.96 (0.90-1.02)	0.148
▪ **Permanent visual loss**	12 (7%)		1.02 (0.92-1.13)	0.723
▪ **Transient visual loss**	24 (14%)		0.91 (0.84-0.98)	**0.018**
▪ **Diplopia**	4 (2%)		0.81 (0.59-0.99)	0.036
▪ **CVA**	2 (1%)		0.99 (0.77-1.28)	0.921
▪ **TIA**	4 (2%)		0.89 (0.71-1.05)	0.179
○ **PMR**	83 (49%)		0.93 (0.88-0.98)	**0.007**
○ **Limb claudication**	5 (3%)		1.21 (1.01-1.56)	**0.042**
Laboratory tests, median (IQR)				
○ **ESR, mm/h**	70 (46-105)[22]	0.21		**0.013**
○ **CRP, mg/L**	77 (38-116)	0.18		**0.018**
○ **Hemoglobin, g/dL**	11.4 (10.4-12.2)[1]	-0.30		**<0.001**
○ **Platelets, *10⁹/L**	413 (322-514)[2]	0.14		0.076
○ **White blood cell count, *10⁹/L**	8.5 (7.2-10.3)	-0.10		0.175
○ **Neutrophils, *10⁹/L**	5.8 (4.8-7.4)[13]	-0.13		0.106
○ **Albumin, g/L**	37.9 (34.3-41.4)[57]	-0.10		0.316
○ **Alkaline phosphatase, U/L**	123 (90-198)[16]	-0.05		0.556
Positive temporal artery biopsy, n (%)	76 (61%)[45]		1.13 (1.06-1.21)	**<0.001**
PET results				
○ **FDG uptake in the cranial vessels, n (%)**	87 (51%)		1.11 (1.06-1.18)	**<0.001**
○ **FDG uptake in the large vessels, n (%)**	/		/	
○ **Total vascular score, median (IQR)**	12 (5-17)	/		
○ **Leuven score, median (IQR)**	7 (2-15)	-0.16		**0.044**
Duration of follow-up, months, median (IQR)	49 (27-89)	-0.00		0.988

Abbreviations: CRP, C-reactive protein; CVA, cerebrovascular accident; ESR, erythrocyte sedimentation rate; FDG, fluorodeoxyglucose; GCA, giant cell arteritis; IQR, interquartile range; LVV, large vessel vasculitis; no., number; PET, positron emission tomography; PMR, polymyalgia rheumatica; SD, standard deviation; TIA, transient ischemic attack
Number of missing values are reported in superscript.