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Clinical science

Prevalence, characteristics, and outcome of subclinical vasculitis in polymyalgia rheumatica: a retrospective cohort study

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Abstract

Objectives: Two recent meta-analyses reported subclinical vasculitis in 22–23% of patients with PMR. We aimed to evaluate the prevalence, characteristics, and outcome of subclinical vasculitis among our PMR patients.

Methods: Consecutive patients with GCA/PMR spectrum disease with isolated PMR symptoms who underwent FDG PET imaging between 2003 and 2020 and who were followed for ≥6 months, were included retrospectively. Vasculitis was defined as FDG uptake ≥grade 2 in any vessel.

Results: We included 337 patients, of whom 31 (9%) with subclinical vasculitis. Among those with subclinical vasculitis, 21 (58%) had isolated large vessel vasculitis, 3 (10%) had isolated cranial vasculitis and 7 (23%) had both cranial and large vessel vasculitis. The glucocorticoid (GC) starting dose and GC doses during follow-up were higher in those with subclinical vasculitis until 12 months after diagnosis ($P < 0.001$). There was no difference in the duration of GC treatment (25 *vs* 20 months, $P = 0.187$). Cox proportional hazard regression analyses showed no difference in the proportion of patients able to stop GC (HR 0.78 [95% CI 0.49–1.25], $P = 0.303$) and in the proportion of patients with relapse (HR 0.82 [95%CI 0.50–1.36], $P = 0.441$).

Conclusion: Only 9% of our PMR patients had subclinical vasculitis with a predilection for large vessel vasculitis. There were no differences in relapse rate and duration of GC treatment, however, those with subclinical vasculitis received higher GC doses until 12 months after diagnosis. Prospective interventional trials are needed to evaluate the outcome of PMR patients with and without subclinical vasculitis treated with a similar GC protocol.

Keywords: polymyalgia rheumatica, PMR, subclinical vasculitis.

Rheumatology key messages

- Only 9% of our PMR patients had subclinical vasculitis with a predilection for large vessel vasculitis.
- There were no differences in relapse rate and duration of glucocorticoid treatment.
- No patients with subclinical vasculitis had arteritic AION or a thoracic aortic aneurysm during follow-up.

Introduction

PMR is a systemic inflammatory disease characterized by pain and morning stiffness in the shoulders, pelvic girdles and neck [1]. GCA is a large vessel vasculitis (LVV) that preferentially affects the cranial arteries, the aorta and its proximal branches [2]. Both are commonly associated with raised inflammatory markers and mainly affect people over 50 years of age [1, 3]. PMR and GCA may be found as isolated conditions or in combination and together form GCA–PMR spectrum disease (GPSD) [4]. Forty to fifty percent of GCA

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patients have PMR symptoms [3, 5]. About 10% of PMR patients will develop GCA during follow-up [6, 7]. In addition, two recent meta-analyses and a recent, large, multicentre study showed that 22–23% of PMR patients have vasculitis without clinical signs typical for GCA, which can only be detected by imaging or pathology [5, 8, 9].

It remains unclear how PMR patients with subclinical vasculitis should be treated. Glucocorticoids (GC) are the mainstay of treatment of both PMR and GCA. However, GCA patients usually require a higher starting dose with slower tapering. De Miguel *et al.* recently found that PMR patients with subclinical vasculitis had higher relapse risk compared with those without [10]. A lower GC starting dose and faster GC tapering were predictors of relapse [10]. In addition, GCA patients have an increased risk of sudden irreversible vision loss at diagnosis or within the first days of initiation of GC treatment and an increased risk of developing thoracic aortic aneurysms during follow-up [11, 12]. It remains unclear if PMR patients with subclinical vasculitis have a similar risk of these complications. These questions are relevant to determine whether screening for subclinical vasculitis in patients with pure PMR symptoms is of added value. Additionally, predictors for subclinical vasculitis have been reported with inconsistent results [8, 9, 13].

The aim of this study was to compare the prevalence, characteristics, and outcome of PMR patients with subclinical vasculitis to those without.

Methods

Patient population

We retrospectively included patients with GCA/PMR spectrum disease and isolated PMR symptoms, further called 'PMR patients', evaluated by the Department of General Internal Medicine or Rheumatology of the University Hospitals Leuven between July 2003 and December 2020 who underwent ^{18}F-fluorodeoxyglucose (FDG) PET imaging $\leq$3 days after initiation of GC and who were followed for $\geq$6 months. In the Department of General Internal Medicine, a PET scan was performed in the majority of patients during the diagnostic workup of suspected PMR. Patients with cranial symptoms or limb claudication were excluded. The final diagnosis of GCA/PMR spectrum disease with isolated PMR symptoms was based on the judgment of the treating clinicians after at least 6 months of follow-up, considering all available information (clinical data, biochemical and radiological results, PET images and evolution during follow-up).

The study was conducted in accordance with the Declaration of Helsinki and approved by the ethical committee of the University Hospitals 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: age, sex, date of diagnosis, symptom duration until diagnosis, Charlson Comorbidity Index, symptoms, laboratory results and temporal artery biopsy (TAB) result at diagnosis, duration of follow-up, dose (in equivalents of methylprednisolone) and duration of GC treatment, use of GC-sparing agents, relapses and vascular complications 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 need to fast for at least 6 h 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 intravenous injection of 4–5 MBq/kg of ^{18}F-FDG. PET scans were performed between 2003 and 2020, 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. Prior to PET acquisition on PET/CT systems, either a low-dose CT scan or a diagnostic, high-dose CT scan was performed. The CT scan was used for attenuation correction and anatomical localization. In the older HR+ acquisitions, no attenuation correction was performed, but this will only impact the most central body areas. Attenuation-corrected PET images were thus only available for the patients scanned on a PET/CT system ($n = 151$, 45%). PET data were corrected for scatter and randoms. Data were reconstructed using iterative OSEM reconstruction, with image quality parameters optimized over the years.

Reconstructed PET images were rescored visually by a specialist in nuclear medicine (L.B.), who was unaware of any other patient data. FDG PET uptake was visually assessed at seven vascular regions (thoracic and abdominal aorta, subclavian, axillary, carotid, iliac, and femoral arteries) on a scale of 0 (no FDG uptake), 1 (minimal but not negligible FDG uptake), 2 (clearly increased FDG uptake), or 3 (very marked FDG uptake). FDG uptake $\geq$grade 2 was considered indicative of vasculitis. In addition, a total vascular score was calculated ranging from 0 (no vascular FDG uptake in any of the seven vascular regions) to 21 (vascular FDG uptake scored 3 in all seven segments) [14]. Subclavian, axillary, carotid, iliac and femoral arteries were counted as one vascular region each with the highest score taken when the score differed from right to left artery. Furthermore, to evaluate cranial vasculitis, the vertebral, maxillary, occipital and temporal arteries were scored similarly.

In addition, FDG PET uptake was also visually assessed 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) on a scale of 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 determined by summing the scores from the 12 skeletal regions [15].

Statistical analysis

Categorical and continuous variables were expressed as count (percentage) and as mean ± S.D. or median ± interquartile range (IQR) as appropriate. Comparison of the characteristics in PMR patients with and without subclinical vasculitis was performed by χ^2 test, Fisher's exact test, Mann–Whitney U test or unpaired t test as appropriate. 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. Cox proportional hazard models were used to estimate the association between the presence of subclinical vasculitis on the one hand and the proportion of patients able to stop GC and the proportion of patients with relapse on the other hand. 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 2023.10.31, The R Foundation for Statistical Computing) and SAS OnDemand for Academics.

Results

A total of 337 patients were included in this study, of whom 31 (9%) with and 306 (91%) without subclinical vasculitis. 12 (7%) of the 186 patients scanned with a standalone PET scan had subclinical vasculitis compared with 19 (13%) of the 151 patients scanned with a PET/CT system ($P = 0.053$). Eight (2%) patients received GC for less than three days prior to PET imaging; 329 (98%) were steroid-naïve. 255 (76%) patients were evaluated and followed by the Department of General Internal Medicine, 79 (23%) by the Department of Rheumatology and 3 (1%) by both departments. The median duration of follow-up was 26 months (IQR 15–49).

Baseline characteristics are presented in Table 1. Patients with subclinical vasculitis had a longer median symptom duration until diagnosis (18 *vs* 9 weeks, $P = 0.036$). Sex and age were not significantly different. Patients with subclinical vasculitis more frequently reported constitutional symptoms (71% *vs* 52%, $P = 0.047$), weight loss (45% *vs* 27%, $P = 0.039$) and neck pain (40% *vs* 21%, $P = 0.021$). They had lower haemoglobin (11.4 *vs* 12.5 g/dl, $P = 0.013$), white blood cell count (8.0 *vs* 8.7×10^9/l, $P = 0.007$) and neutrophils (5.3 *vs* 5.8×10^9/l, $P = 0.031$).

Among the 31 patients with subclinical vasculitis, 21 (68%) patients had isolated large vessel vasculitis, 3 (10%) had isolated cranial vasculitis and 7 (23%) had both cranial and large vessel vasculitis on PET imaging. The median total vascular score was 6 (IQR 2–13). FDG uptake ≥grade 2 was most frequently observed in the thoracic aorta (74%), followed by subclavian arteries (65%), axillary arteries (52%), abdominal aorta (48%), carotid arteries (45%), vertebral arteries (32%), maxillary arteries (13%), iliac arteries (10%) and femoral arteries (6%). None of the patients had FDG uptake ≥grade 2 in the temporal or occipital arteries. Five (16%) patients had only FDG uptake in the aorta. Among the 306 patients without FDG uptake ≥grade 2 in at least one vessel, 71 (23%) patients had FDG uptake grade 1 in one vessel, 27 (9%) in two vessels and 8 (3%) in three vessels. None of the 306 patients without FDG uptake ≥ grade 2 had FDG uptake grade 1 in four or more vessels. Two hundred (65%) patients had no FDG uptake in any vessel. Among the patients without subclinical vasculitis, the median total vascular score was 0 (IQR 0–1). So, in our total cohort, 137 (41%) patients had FDG uptake ≥grade 1 in at least one vessel. The Leuven score was not significantly different between patients with and without subclinical vasculitis (18 [IQR 13–21] *vs* 19 [IQR 16–22], $P = 0.078$). Five of the 10 (50%) TABs performed in patients with subclinical vasculitis were positive, whereas all 51 TABs performed in patients without subclinical vasculitis were negative.

The GC starting dose was significantly higher in patients with subclinical vasculitis (24.3 mg *vs* 14.6 mg, $P < 0.001$). There was no difference in the proportion of patients who required escalation of the GC starting dose to achieve remission (7% *vs* 4%, $P = 0.638$). GC doses during follow-up were significantly higher in patients with subclinical vasculitis until 12 months after diagnosis (Fig. 1). The median duration of GC treatment was not significantly different (25 *vs* 20 months, $P = 0.187$). Cox proportional hazard regression analysis showed no difference in the proportion of patients able to stop GC (HR 0.78 [95% CI 0.49–1.25], $P = 0.303$) (Fig. 2). In addition, disease-modifying antirheumatic drugs were equally frequently used in patients with and without vasculitis (10% *vs* 10%, $P = 1.000$).

There was no difference in the proportion of patients with relapse (HR 0.82 [95%CI 0.50–1.36], $P = 0.441$) (Fig. 3). The number of relapses was also similar. 19% of the patients with vasculitis *vs* 22% of those without had one relapse, 13% *vs* 11% had two relapses and 23% *vs* 19% had more than two relapses ($P = 0.911$). Among patients who relapsed, those with subclinical vasculitis had a longer median time to first relapse (14 *vs* 11 months, $P = 0.027$) without difference in the median daily dose of methylprednisolone at that time (both 1 mg, $P = 0.943$). There were no differences in the median time to second relapse (18 *vs* 20 months, $P = 0.885$) and the median daily dose of methylprednisolone at that time (both 2 mg, $P = 0.554$). In patients with subclinical vasculitis, the relapse rate was not significantly different in patients who were treated with a starting dose of methylprednisolone 16 mg or less compared with those treated with higher starting doses (33% *vs* 68%, $P = 0.056$).

0/17 (0%) patients with and 7/158 (4%) patients without subclinical vasculitis had cranial symptoms at first relapse ($P = 1.000$). Two patients developed a thoracic aortic aneurysm during follow-up; both patients did not have large vessel vasculitis at diagnosis. No patients had acute vision loss due to vasculitis.

Discussion

In this study, we found that only 9% of our PMR patients had subclinical vasculitis with a predilection for large vessel vasculitis. Patients with subclinical vasculitis had a longer symptom duration until diagnosis and more frequently reported constitutional symptoms. There were no significant differences in relapse rate and duration of GC treatment, however, patients with subclinical vasculitis were treated with higher GC doses until 12 months after diagnosis.

Two recent meta-analyses showed that 22–23% of PMR patients have subclinical vasculitis [5, 8]. The included studies used different imaging techniques and different criteria for the diagnosis of PMR and GCA. In addition, in most of the studies imaging or TAB was only performed in a proportion of patients. In a recent study, which systematically performed ultrasound of the temporal, common carotid, subclavian and axillary arteries, subclinical vasculitis was also found in 23% of PMR patients [9]. We found a much lower prevalence of subclinical vasculitis compared with earlier published studies. However, our definition of vasculitis, namely FDG uptake ≥grade 2, was more stringent than we used in our previous prospective cohort, where the prevalence of subclinical vasculitis was 31% [16]. If we consider FDG uptake ≥grade 1 in at least one vessel as indicative of vasculitis, we found a prevalence of 41%. A second possible explanation is the exclusion of patients with very mild or transient cranial symptoms in

Table 1. Baseline characteristics of patients with and without subclinical vasculitis

Characteristics	Total ($n = 337$)	Subclinical vasculitis ($n = 31$)	No subclinical vasculitis ($n = 306$)	*P*-value
Age at inclusion, years, mean (S.D.)	70 (10)	70 (8)	70 (10)	0.961
Sex, no. of females, *n* (%)	180 (53)	19 (61)	161 (53)	0.356
Charlson Comorbidity Index, median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	0.982
Symptom duration until diagnosis, weeks, median (IQR)	9 (5–18)[23]	18 (7–29)[5]	9 (5–17)[18]	**0.036**
Symptoms at diagnosis, *n* (%)				
Constitutional symptoms	182 (54)	22 (71)	160 (52)	**0.047**
Fever	22 (7)	0 (0)	22 (7)	0.243
Fatigue	127 (38)	16 (52)	111 (36)	0.093
Anorexia	56 (17)	6 (19)	50 (16)	0.667
Weight loss	98 (29)	14 (45)	84 (27)	**0.039**
Night sweats	32 (10)	4 (13)	28 (9)	0.517
Dyspnoea	17 (5)	3 (10)	14 (5)	0.198
Dry cough	11 (3)	1 (3)	10 (3)	1.000
PMR				
Morning stiffness	239 (92)[76]	22 (96)[8]	217 (91)[68]	0.704
Shoulder pain	327 (97)	31 (100)	296 (97)	0.608
Pelvic girdle pain	262 (78)	24 (77)	238 (78)	0.964
Neck pain	75 (22)	12 (39)	63 (21)	**0.021**
Lower back pain	64 (19)	5 (16)	59 (19)	0.670
Pain in peripheral joints	166 (49)	11 (35)	155 (51)	0.107
Laboratory tests, median (IQR)				
ESR, mm/h	50 (33–68)[39]	37 (24–62)[6]	50 (34–68)[33]	0.150
CRP, mg/l	42 (19–73)[1]	44 (19–78)	42 (19–72)[1]	0.951
Haemoglobin, g/dl	12.4 (11.5–13.5)[1]	11.4 (10.7–12.8)	12.5 (11.7–13.5)[1]	**0.013**
Platelets, $*10^9$/l	343 (281–406)[5]	334 (283–422)	343 (281–406)[5]	0.756
White blood cell count, $*10^9$/l	8.6 (7.4–10.4)[1]	7.9 (6.9–8.4)	8.7 (7.5–10.4)[1]	**0.007**
Neutrophils, $*10^9$/l	5.8 (4.7–7.4)[20]	5.3 (4.2–6.1)[5]	5.8 (4.8–7.5)[15]	**0.031**
Albumin, g/l	40.9 (38.5–43.6)[135]	41.8 (38.8–44.4)[15]	40.9 (38.5–43.6)[120]	0.400
Alkaline phosphatase, U/l	115 (76–197)[38]	121 (88–190)[6]	115 (76–198)[32]	0.686
Duration of follow-up, months, median (IQR)	26 (15-49)	31 (20-59)	26 (15-49)	0.159

A number of missing values are reported in superscript. *P*-values < 0.05 are indicated in bold.
FDG: fluorodeoxyglucose; IQR: interquartile range; no.: number.

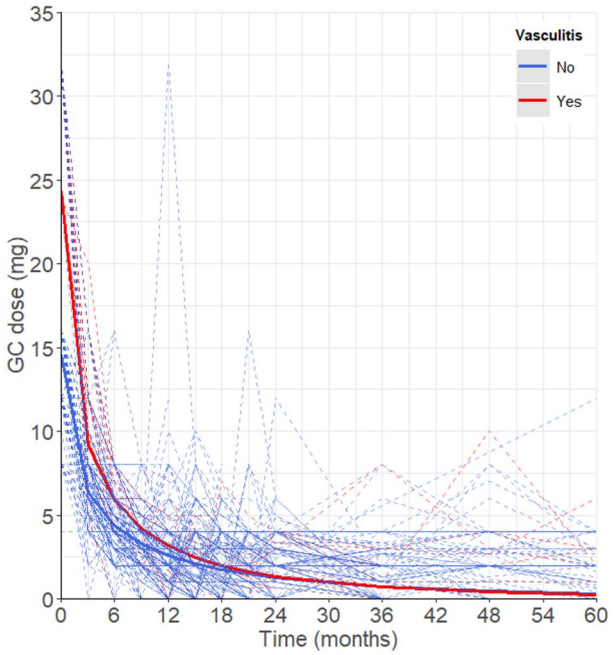

Figure 1. Non-linear mixed model estimates for the change in GC dose (expressed in methylprednisolone equivalents) in PMR patients with and without subclinical vasculitis. GC: glucocorticoids

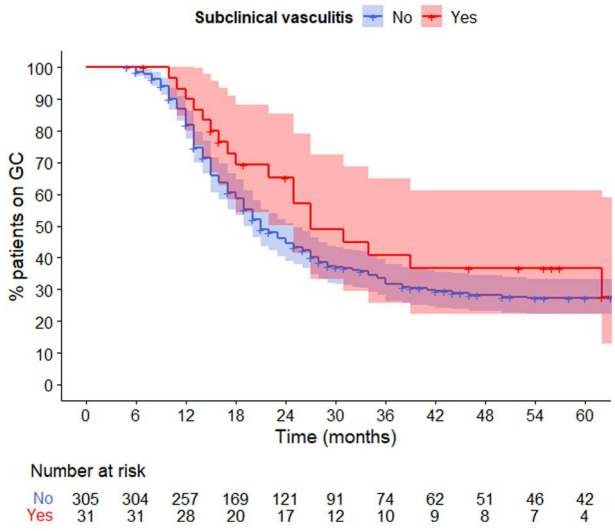

Figure 2. Kaplan-Meier estimates for the proportion of patients on GC treatment comparing PMR patients with and without subclinical vasculitis. GC: glucocorticoids

our cohort. In addition, discrepancies between ultrasound and PET results are common [17–20], which can be explained by differences in imaging technique: PET detects increased glucose metabolism due to inflammation, while ultrasound visualizes morphologic changes. It is unclear if a positive ultrasound and PET scan represent the same stage of the disease.

This is the largest study evaluating the outcome of PMR patients with and without subclinical vasculitis. Similar to the findings of De Miguel *et al.* [10], patients with subclinical

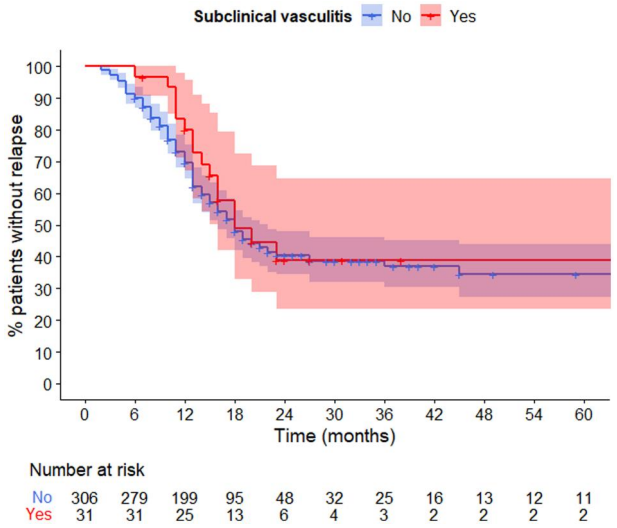

Figure 3. Kaplan-Meier estimates for the proportion of patients without relapse comparing PMR patients with and without subclinical vasculitis

vasculitis were treated with higher GC doses until 12 months after diagnosis, which is caused by the lack of blinding of the treating physicians to the imaging results in both studies. However, there was no difference in the median duration of GC treatment and in the proportion of patients able to stop GC. In strong contrast with the study of De Miguel *et al.* [10], which reported a much higher relapse rate in PMR patients with subclinical vasculitis compared with those without, we did not find a difference in relapse rate with a longer time to first relapse in patients with subclinical vasculitis and a similar daily dose of methylprednisolone at time of first relapse. In comparison to the relapse rate of 43% 1 year after diagnosis in a meta-analysis [21] and taken into account the prevalence of subclinical vasculitis of 23% [9], the relapse rate of 27% in the total cohort of the study of De Miguel *et al.* was rather low [10]. In addition, we observed a numerically lower relapse rate in patients with subclinical vasculitis treated with a starting dose of methylprednisolone of 16 mg or less, while De Miguel *et al.* found a relapse rate of 100% with this starting dose. Interestingly, no PMR patients with subclinical vasculitis experienced an ischemic event due to vasculitis or developed a thoracic aortic aneurysm during follow-up. Hence, based on the available evidence, it remains unclear if PMR patients with subclinical vasculitis should be treated with higher GC doses and a slower tapering protocol. This should be further investigated in a prospective trial.

Predictors for subclinical vasculitis remain unclear with very inconsistent reports. The symptom duration before diagnosis was twice as long in patients with subclinical vasculitis compared with those without. This finding was significant but unexpected and may suggest that ongoing inflammation in patients presenting with PMR may progressively affect the arteries. This hypothesis, however, remains to be proven. In addition, we observed that patients with subclinical vasculitis more frequently reported constitutional symptoms and neck pain and had lower haemoglobin, white blood cell and neutrophil counts. In a meta-analysis of individual patient data, inflammatory back pain and the absence of lower limb pain were predictive symptoms for subclinical vasculitis [8]. De Miguel *et al.* reported that patients with subclinical vasculitis were older, had a longer duration of morning stiffness and more frequently had hip pain [9]. Prieto-Peña *et al.* found bilateral diffuse lower limb pain, pelvic girdle pain and inflammatory low back pain as predictive factors for subclinical vasculitis [13]. Hence, it remains unclear which PMR patients should be screened for subclinical vasculitis.

Our study has several limitations. First, we only included patients with PET imaging at diagnosis, which could have introduced selection bias. However, in the Department of General Internal Medicine, which included 76% of patients, performing a PET scan has been part of the standard diagnostic workup of suspected PMR during the entire period. In addition, contrary to what we expected, the prevalence of subclinical vasculitis was lower compared with previous studies. Second, since follow-up and treatment were part of routine clinical practice, the treatment was at the discretion of the physician who was not blinded by the PET images. As a result, patients with subclinical vasculitis were treated with higher GC doses and we could not assess whether treatment with a similar GC tapering protocol would be associated with a higher relapse rate in this population. Third, 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 the detection of vasculitis in smaller vessels and thus increase the sensitivity of FDG PET over time. Fourth, this was a single-centre study in a tertiary care hospital, limiting the overall generalizability. In addition, the exclusion of patients with mild cranial symptoms could have lowered the representativeness of this cohort for a real-life PMR population. Sixth, the sample size and follow-up duration may have been too limited to detect thoracic aortic aneurysms. Finally, the retrospective design may be associated with information bias.

In conclusion, only 9% of our PMR patients had subclinical vasculitis with a predilection for large vessel vasculitis. The occurrence of subclinical vasculitis in patients with isolated PMR symptoms supports the concept of a GCA–PMR spectrum. There were no consistent predictors for subclinical vasculitis. We observed no difference in relapse rate and duration of GC treatment, but patients with subclinical vasculitis were treated with higher GC doses until 12 months after diagnosis. Interventional trials are needed to compare the outcomes of PMR patients with and without subclinical vasculitis treated with the same GC tapering protocol.

Data availability

All relevant data are reported in the article. Additional details can be provided by the corresponding author upon reasonable request.

Contribution statement

L.M.: Conceptualization, Methodology, Validation, Investigation, Formal analysis, Writing—original draft, Writing—review & editing, Visualization; L.B.: Investigation, Writing—review & editing; A.B.: Conceptualization, Methodology, Writing—review & editing; T.M.: Investigation, Writing—review & editing; G.M.: Methodology, Formal analysis, Writing—review & editing; K.V.L.: Writing—review & editing, supervision; E.D.L.: Investigation, Writing—review & editing; S.V.: Conceptualization, Methodology, Investigation, Writing—

review & editing, Supervision; D.B.: Conceptualization, Methodology, Investigation, Writing—review & editing, Supervision.

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