Subclinical giant cell arteritis in new onset polymyalgia rheumatica

Hemmig, Andrea K.; Gozzoli, Daniele; Werlen, Laura; Ewald, Hannah; Aschwanden, Markus; Blockmans, Daniel; Brouwer, Elisabeth; Buchanan, Russell R.C.; Camellino, Dario; Campochiaro, Corrado

Published in:
SEMINARS IN ARTHRITIS AND RHEUMATISM

DOI:
10.1016/j.semarthrit.2022.152017

Publication date:
2022

Seminars in Arthritis and Rheumatism 55 (2022) 152017

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Subclinical giant cell arteritis in new onset polymyalgia rheumatica A systematic review and meta-analysis of individual patient data

Andrea K. Hemmig [a,1], Daniele Gozzoli [b,1], Laura Werlen [c], Hannah Ewald [d], Markus Aschwanden [e], Daniel Blockmans [f], Elisabeth Brouwer [g], Russell R.C. Buchanan [h,i], Dario Camellino [j], Corrado Campochiaro [k], Marco A. Cimmino [l], Hector Corominas [m], Viktoria Gloy [c], Liesbet Henckaerts [f], Diego Kyburz [a,n], Patricia Moya-Alvarado [m], Claire E. Owen [h,i], Mihaela Stegert [a], Alessandro Tomelleri [k], Yannick van Sleen [g], Hiroyuki Yamashita [o], Stephan Imfeld [e], Christoph T. Berger [p], Lars G. Hemkens [c,q,r], Thomas Daikeler [a,*]

[a] Department of Rheumatology, University Hospital Basel, Basel, Switzerland
[b] Department of Internal Medicine, University Hospital Basel, Basel, Switzerland
[c] Department of Clinical Research, University Hospital Basel, University of Basel, Basel, Switzerland
[d] University Medical Library Basel, University of Basel, Basel, Switzerland
[e] Department of Angiology, University Hospital Basel, Basel, Switzerland
[f] Department of General Internal Medicine, Department of Microbiology, Immunology and Transplantation, KU Leuven, University Hospitals Leuven, Leuven, Belgium
[g] Department of Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands
[h] Department of Rheumatology, Austin Health, Heidelberg, Victoria, Australia
[i] Department of Medicine, Austin Health, Melbourne Medical School, University of Melbourne, Parkville, Victoria, Australia
[j] Division of Rheumatology, "La Colletta" Hospital, Local Health Trust 3, Arenzano, Italy
[k] Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UniRAR), San Raffaele Scientific Institute, Milan, Italy
[l] Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genoa, Genova, Italy
[m] Department of Rheumatology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
[n] Department of Biomedicine, University of Basel, Basel, Switzerland
[o] Division of Rheumatic Diseases, National Center for Global Health and Medicine, Tokyo, Japan
[p] Departments of Dermatology, Rheumatology and Internal Medicine, University Center for Immunology, University Hospital Basel, Basel, Switzerland
[q] Meta-Research Innovation Center at Stanford (METRICS), Stanford University, Palo Alto, CA, USA
[r] Meta-Research Innovation Center Berlin (METRIC-B), Berlin Institute of Health, Berlin, Germany

ARTICLE INFO

Key words:
Polymyalgia rheumatica
Giant cell arteritis
Subclinical vasculitis
Systematic review
Meta-analysis

ABSTRACT

Objectives: To determine the prevalence and predictors of subclinical giant cell arteritis (GCA) in patients with newly diagnosed polymyalgia rheumatica (PMR).
Methods: PubMed, Embase, and Web of Science Core Collection were systematically searched (date of last search July 14, 2021) for any published information on any consecutively recruited cohort reporting the prevalence of GCA in steroid-naïve patients with PMR without cranial or ischemic symptoms. We combined prevalences across populations in a random-effect meta-analysis. Potential predictors of subclinical GCA were identified by mixed-effect logistic regression using individual patient data (IPD) from cohorts screened with PET/(CT).
Results: We included 13 cohorts with 566 patients from studies published between 1965 to 2020. Subclinical GCA was diagnosed by temporal artery biopsy in three studies, ultrasound in three studies, and PET/(CT) in seven studies. The pooled prevalence of subclinical GCA across all studies was 23% (95% CI 14%-36%, I^2=84%) for any screening method and 29% in the studies using PET/(CT) (95% CI 13%-53%, I^2=85%) (n=266 patients). For seven cohorts we obtained IPD for 243 patients screened with PET/(CT). Inflammatory back pain (OR 2.73, 1.32-

For re-submission to: *Seminars in Arthritis and Rheumatism*

* Corresponding author: Thomas Daikeler, Department of Rheumatology, University Hospital Basel, Basel, Petersgraben 4, CH-4031 Basel, Switzerland, Phone: +41 61 265 27 09.
E-mail address: Thomas.Daikeler@usb.ch (T. Daikeler).

[1] Shared first authorship.

https://doi.org/10.1016/j.semarthrit.2022.152017

Available online 28 April 2022

5.64), absence of lower limb pain (OR 2.35, 1.05-5.26), female sex (OR 2.31, 1.17-4.58), temperature >37° (OR 1.83, 0.90-3.71), weight loss (OR 1.83, 0.96-3.51), thrombocyte count (OR 1.51, 1.05-2.18), and haemoglobin level (OR 0.80, 0.64-1.00) were most strongly associated with subclinical GCA in the univariable analysis but not C-reactive protein (OR 1.00, 1.00-1.01) or erythrocyte sedimentation rate (OR 1.01, 1.00-1.02). A prediction model calculated from these variables had an area under the curve of 0.66 (95% CI 0.55-0.75).
Conclusion: More than a quarter of patients with PMR may have subclinical GCA. The prediction model from the most extensive IPD set has only modest diagnostic accuracy. Hence, a paradigm shift in the assessment of PMR patients in favour of implementing imaging studies should be discussed.

Introduction

Giant cell arteritis (GCA) is the most frequent primary vasculitis. The clinical manifestation is heterogeneous and includes cranial symptoms, peripheral vascular claudication, constitutional symptoms, and polymyalgia. Polymyalgia rheumatica (PMR) is a related inflammatory disorder occurring three to ten times more frequently than GCA [1]. Around half of GCA patients report polymyalgia at diagnosis or during relapse, while others have a history of PMR before the onset of GCA. Moreover, PMR may be the sole manifestation of GCA. These patients present with subclinical vasculitis without specific vasculitic symptoms (subclinical GCA), which can be challenging in the clinical routine [2]. Timely diagnosis and treatment of GCA are essential because, in contrast to PMR, GCA is associated with acute and chronic vascular complications such as vision loss (up to 19% of cases), arterial stenosis (5% to 29%), stroke (2% to 7%) and the development of aortic aneurysms (up to 27%) [3–10]. In PMR patients with undetected subclinical GCA, standard PMR treatment may be inappropriate, with prednisone doses being too low to prevent vascular complications [11]. In a retrospective study, 18 out of 167 patients initially diagnosed with PMR developed typical cranial vasculitic symptoms or signs of vascular insufficiency in the upper extremities during follow-up. Half of these patients experienced severe complications, including permanent vision loss, stroke, and limb claudication [11]. This underscores the relevance of subclinical GCA in PMR patients. Although subclinical GCA in patients with PMR at diagnosis has been recognized, routine screening of PMR patients for subclinical GCA is not considered standard of care in most clinical settings [12].

Subclinical GCA can be detected by vessel wall imaging [13] or histology obtained by temporal artery biopsy (TAB) [14]. TAB has limited sensitivity for GCA and was the only screening technique for diagnosing GCA before the introduction of temporal artery ultrasound in 1995 [15]. Ultrasound was later extended to the extra-temporal arteries, thus enhancing diagnostic sensitivity for GCA [16]. Today, PET is the most widely used technique for GCA screening, especially for extracranial large vessel GCA with good diagnostic accuracy (sensitivity of 67% to 77% and specificity of 66% to 100%) [17]. It is mostly used in combination with computed tomography (PET/CT) [13,18].

Amongst publications reporting the prevalence of subclinical GCA at PMR diagnosis, many have considerable biases, such as non-consecutive inclusion of selected patients, and may thus be misleading.

The benefits of a screening program would depend on the true prevalence of subclinical GCA at diagnosis of PMR, the costs, and its availability. Hence, easily assessable predictors of subclinical GCA in PMR patients would be helpful. Our study, therefore, has two objectives: (i) to determine the prevalence of subclinical GCA in patients with new-onset PMR based on a systematic literature review and (ii) to identify predictors of subclinical GCA in PMR patients by performing a meta-analysis of individual patient data (IPD). To this end, we present an example of a prediction model using the identified variables most strongly associated with the outcome.

Methods

We report the systematic literature review and IPD meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and PRISMA-IPD statement [19,20]. The methods were pre-specified in a protocol registered at the Open Science Framework (OSF) (doi: 10.17605/OSF.IO/749RY) [21].

Systematic review

Eligibility criteria

Studies were eligible if they reported the prevalence of subclinical GCA in consecutively recruited, steroid-naïve PMR patients diagnosed according to accepted classification criteria at the time of publication. We excluded patients with ischemic or vascular symptoms consistent with GCA (Supplementary Table S1).

Search strategy and selection process

A medical information specialist (H.E.) systematically searched PubMed, Embase (via Elsevier), and the Web of Science Core Collection using keywords and database-specific subject headings for terms relevant to PMR, GCA, and diagnostic imaging (date of last search July 14, 2021) (Supplementary Table S2).

Three reviewers (D.G., T.D., A.H.) screened titles and abstracts and assessed the full texts of all potentially eligible articles. Disagreements were resolved by discussion. If studies contained overlapping patient cohorts, only the largest study was included. We extracted patient characteristics of the total study population and data on the prevalence of subclinical GCA in PMR patients. If the total study population consisted of multiple patient populations (e.g., PMR, GCA, and GCA with PMR), only data from PMR patients without symptoms suggestive of GCA were used for analysis.

Individual patient data meta-analysis

Eligibility criteria

For the IPD meta-analysis, cohorts were eligible if they included newly diagnosed, steroid-naïve PMR patients who were screened by PET/(CT) at diagnosis. Case reports, IPD of patients with ischemic symptoms consistent with GCA, and patients with a pre-existing diagnosis of GCA were excluded. We restricted this analysis to screening by PET/(CT) to reflect the modern practice in the diagnostic workup for GCA.

Identification of PMR cohorts

We contacted authors of eligible studies identified during an initial search on April 16, 2020 and invited them to share the IPD. We presented the project at the European League Against Rheumatism (EULAR) working group for PMR and GCA web conference in 2020 to invite collaborators and identify additional cohorts.

Data items

We requested IPD for demographical (age, sex), clinical (cardiovascular risk factors; pain localized at the neck, shoulders, lower back, lower limbs, and hip girdle; morning stiffness and its duration; fever; weight loss), and laboratory data (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], IL-6, leukocytes, thrombocytes, haemoglobin level), information on steroid treatment before PET/(CT) (yes/no), GCA

symptoms (headache, scalp tenderness, jaw claudication, visual problems), and imaging data (joint or vascular region involved) at diagnosis.

Definitions of inflammatory back pain and lower limb pain

As has been previously described [22], inflammatory lower back pain was considered present if the patient reported low back pain that improved with exercise, but not with rest, and occurred predominantly at night [22]. Bilateral diffuse lower limb pain was defined as pain in both legs, thighs, or anywhere between the knees and ankles [23].

Individual patient data collection

Collaborating researchers who agreed to share IPD from eligible studies provided data on predefined variables for individual patients. The data were individually reviewed by D.G. and T.D., and checked for discrepancies with published reports, internal consistency, and completeness. Any ambiguities were resolved by discussion with the collaborating researchers.

Risk of bias assessment

We assessed the risk of bias using selected items of the Quality Assessment of Diagnostic Studies (QUADAS)-2 tool [24]. We assessed patient selection and outcome measurement (i.e., the method used to diagnose subclinical GCA). We tailored the tool to our review question and added signalling questions regarding sample frame, patient recruitment, the total number of eligible patients, and participation rate (Supplementary Table S3).

Statistical analysis

We calculated the pooled prevalence of subclinical GCA using a random-effects model and calculated I^2 to quantify the degree of heterogeneity across the studies [25].

For the IPD, we present summary statistics of the included variables by study. We imputed missing data using multilevel joint modelling multiple imputations with the R package jomo [26]. We performed a one-step IPD meta-analysis to compare the odds of having subclinical GCA for characteristics of PMR patients. Using the imputed data sets, we built univariable mixed-effects logistic regression models with vascular involvement (no/yes) as the outcome and each patient characteristic under study as a predictor in turn. We then modelled the outcome including all predictors together in a multivariable model. The characteristics were specified as fixed effects, while the study was included as a random effect. The results for each imputed data set were pooled using Rubin's rules [27]. We included the variables that were significantly associated with subclinical GCA or had confidence intervals slightly overlapping '1' in the univariable model and kept the direction and magnitude of their association with the outcome after adjusting for the other predictors in the multivariable model in a prediction model. We used the R package psfmi [28] to pool the mixed logistic regression models from the multiply imputed data using the median p-values pooling method and evaluating the model's performance using cross-validation. We performed a sensitivity analysis for the univariable analyses using the complete cases from the original study data using the lme4 package [29]. As an additional sensitivity analysis, we redid the analyses, excluding two studies reporting an extreme prevalence of vascular involvement. Statistical significance was defined as $p < 0.05$. All analyses were performed in R version 4.0.3 (2020-10-10) [30].

Results

Prevalence of subclinical GCA at PMR diagnosis

Study selection

A total of 2362 reports were identified after removing duplicates. Of those, we reviewed 70 full-text articles deemed potentially relevant based on the title and abstract. In total, 13 studies were included for prevalence estimation (Fig. 1) [31–43].

Study characteristics

The 13 included studies were published between 1965 and 2020 [31–43]. Different methods for subclinical GCA screening were used as state-of-the-art diagnostics at the time of publication. The patients were examined by TAB (n=165) (published from 1965 to 1996) [31–33], ultrasound (n=135) (from 1996 to 2020) [34–36], and PET/(CT) (n=266) (from 1999 to 2020) [37–43]. We found no studies that used magnetic resonance tomography or CT for screening.

The aims of the studies were heterogeneous and included the evaluation of possible subclinical GCA in PMR and assessing patterns of articular and periarticular involvement in PMR. Apart from age and sex, patients' characteristics in these studies were mainly not reported (Table 1).

Prevalence of subclinical GCA in newly diagnosed PMR patients

Overall, the 13 included studies reported on 566 PMR patients. Prevalence estimates of vasculitis ranged from 0 to 92%. The combined pooled prevalence was 23% (95% confidence interval [CI] 14%–36%) with high heterogeneity between studies (I^2=84%) (Fig. 2).

The pooled prevalence of subclinical GCA among patients screened by biopsy was 20% (CI, 7%–46%, I^2=86%) [31–33]. Ultrasound signs consistent with vasculitis were found in 15% (CI, 3%–50%, I^2=86%) [34–36]. For the seven PET/(CT) studies, we found a pooled prevalence of 29% (CI, 13%–53%, I^2=85%) [37–43] (Fig. 3). The method used for subclinical GCA screening did not explain the between-study heterogeneity.

Predictors of subclinical GCA

Study selection, IPD obtained, and patient characteristics

We identified ten eligible studies for the IPD meta-analysis: nine PET/(CT) studies were identified during the initial literature search [37–41,44–47]. One unpublished Italian study (Milan study; 24 patients) was identified after the presentation of our study at the EULAR working group meeting. We obtained IPD from seven cohorts [40,41,44–47] for 256 patients, of whom 243 were included in the final analysis (Supplementary Fig. S1 [20]). Three cohorts had no data available (53 patients) [37–39].

Most of the 243 patients were female (n=146; 60.1%), the median age was 72.3 years (interquartile range [IQR] 66.4–78.0 years), median CRP was 46.0 mg/L (IQR 19.0–77.7 mg/L), mean ESR was 65.2 mm/h (standard deviation ± 30.3 mm/h) and 65 patients (27%) were diagnosed with subclinical GCA after PET/CT. Cardiovascular risk factors such as hypertension was found in 29.6%, dyslipidaemia was seen in 15.6%, and 4.9% were smokers. Diabetes was found in 9.5%. Detailed patient characteristics are described in the supplemental material (Supplementary Table S4 and Supplementary Table S5).

Factors associated with subclinical GCA in PMR patients

In the univariable models, the following variables were associated with subclinical GCA: inflammatory back pain (odds ratio [OR], 2.73; CI, 1.32–5.64), absence of lower limb pain (OR, 2.35; CI, 1.05–5.26), female sex (OR, 2.31; CI, 1.17–4.58), and the thrombocyte count (OR, 1.51 for an increase in thrombocyte count of one standard deviation; CI, 1.05–2.18). An increase in haemoglobin level by 1 g (OR, 0.80 per g/dl; CI, 0.64–1.00) was associated with lower odds for subclinical GCA.

In the multivariable analysis, inflammatory back pain (OR, 5.71; CI, 1.41–23.06) and absence of lower limb pain (OR, 3.48; CI, 1.16–10.42) were the only statistically significant predictors (Table 2).

Age, pelvic girdle pain, duration of morning stiffness, and elevation of inflammation markers (ESR, CRP, leukocyte count), were not associated with subclinical GCA, both in the univariable and multivariable models.

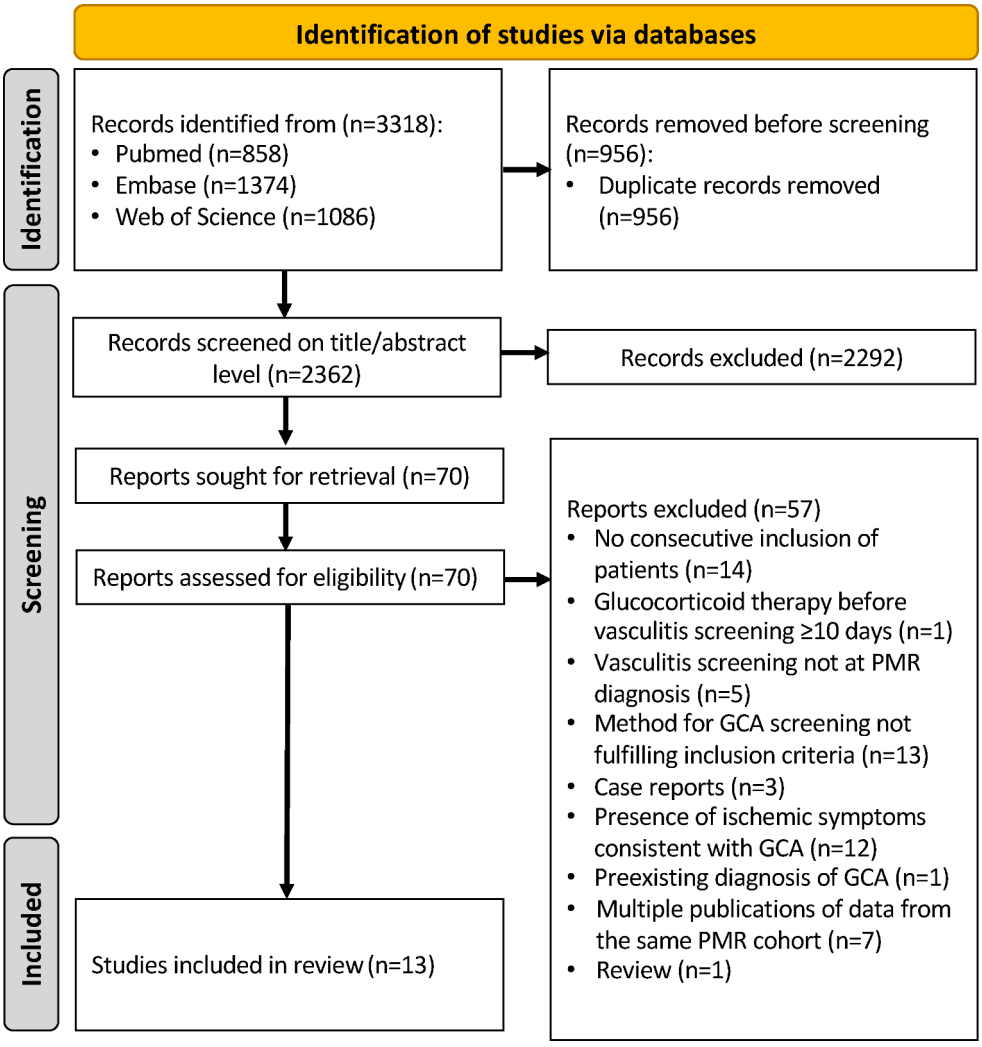

Fig. 1. Flowchart of the study selection process.

Prediction model with candidate predictors

We included the variables that had the strongest associations with subclinical GCA from the univariable and multivariable models in a prediction model and used cross-validation to assess model performance. Those variables were inflammatory back pain, lower limb pain, female sex, temperature > 37°, weight loss, thrombocyte count, and haemoglobin level. The prediction model's ORs and 95% CIs can be found in the supplementary material (Supplementary Table S6). The cross-validation procedure calculated an area under the curve (AUC) of 0.66 (95% CI: 0.55-0.75) and a pseudo-R^2 of 0.178.

Sensitivity analyses

The results of the univariable analyses using the complete cases from the original study data were similar to those obtained from the imputed data (Supplementary Table S7). In the multivariable analyses excluding the two studies that reported extreme prevalence of subclinical GCA (Owen et al. [44] with 0% and the Milan study with 71%), inflammatory back pain and lower limb pain were no longer statistically significant (for details see Supplementary Table S8–S10).

Risk of bias and applicability concerns

Patient selection was a main source of potential bias in most studies since most patients were recruited from specialized centres or the description of recruitment was incomplete (overall summary in Supplementary Table S11 and S12), but we deemed this to have limited impact on applicability in most cases. The studies using TAB for screening are potentially biased due to the lack of clear-cut definitions of PMR and GCA at that time.

Discussion

In this systematic review of 13 studies reporting on 566 steroid-naive patients with PMR about one in four patients were judged to have subclinical GCA. The pooled prevalence of subclinical GCA among patients screened by PET/(CT), the standard nowadays, was even higher, as expected due to the high sensitivity of PET/(CT) in this setting. Evaluation of the temporal artery during routine scanning with advanced PET/CT scanners is now possible, which might further increase the sensitivity of PET/CT for GCA in the future [48].

The cumulative lifetime risk of patients with PMR developing GCA may be even higher and has not yet been systematically studied.

Altogether, this supports the 'one disease' hypothesis that was already postulated 57 years earlier by Hamrin, i.e. that GCA and isolated PMR represent a different spectrum of the same disease [49].

We retrieved IPD from seven cohorts using PET/(CT) for screening. This enabled us to study characteristics of PMR patients with and without subclinical GCA at diagnosis in the largest existing dataset. In the univariable analysis, potential predictors of subclinical GCA were female sex and weight loss and variables indirectly associated with inflammation. These were thrombocytosis, anaemia, and temperature

Table 1
Study and patient characteristics.

Study	Location	Patients screened for GCA, *n*	Patients diagnosed with GCA, *n (%)*	Females, *n* (%)	Mean age (yrs ± SD)	Diagnostic procedure	Vascular area examined
Hamrin 1965 [31]	Sweden	30	11 (37)	NA	NA	TAB	TA
Bengtsson 1981 [32]	Sweden	67	21 (31)	50 (75)	NA	TAB	TA
Myklebust 1996 [33]	Norway	68	3 (4)	NA	NA	TAB	TA
Kraft 1996 [34]	Germany	8	0 (0)	7 (88)	70	Ultrasound	TA
Schmidt 2002 [35]	Germany	102	8 (8)	71 (70)	69	Ultrasound	TA
Burg 2020 [36]	Germany	25	10 (40)	NA	NA	Ultrasound	TA, Occ, CRA, Carot, Vert, Ax
Blockmans 1999 [37]	Belgium	5	4 (80)	5 (100)	63 ± 6	PET (4P-VS)	Ao, Sub, Carot, Pop, Fem, Tib
Moosig 2004 [38]	Germany	13	12 (92)	11 (85)	65.5	PET (Vasc-ROI)	Ao, Sub, ext Carot, Iliac
Blockmans 2007 [39]	Belgium	35	11 (31)	20 (57)	68.5 ± 7.2	PET (TVS)	Ao, Sub, Carot, Ax, Iliac, Fem
Camellino 2012 [40]	Italy	64	25 (39)	NA	NA	PET/CT (4P-VS*)	Ao, Sub, Carot, Iliac, Fem
Corica 2019 [41]	Spain	52	6 (12)	NA	NA	PET/CT (qualitative)	NA
Owen 2020 [42]	Australia	33	0 (0)	15 (45)	68.6 ± 7.4	PET/CT (4P-VS* + semi-quantitative)	NA
Emamifar 2020 [43]	Denmark	64	6 (9)	NA	NA	PET/CT (4P-VS*)	TA, MA, BA, Ao, Sub, ext Carot, Vert, Iliac, Fem

Abbreviations: Ao, aorta; Ax, axillary artery; BA, basilar artery; n, number; Carot, carotid artery; CRA, central retinal artery; CT, computed tomography; ext Carot, external carotid artery; Fem, femoral artery; GCA, giant cell arteritis; Iliac, iliac arteries; NA, not available; MA, maxillary artery; Occ, occipital artery; PET, positron emission tomography; PET/CT, positron emission tomography/computed tomography; Pop, popliteal artery; SD, standard deviation; Sub, subclavian artery; TA, temporal artery; TAB, temporal artery biopsy; Tib, tibial artery; TVS, total vascular score (seven vascular regions were scored as negative (0) or positive (1, 2, or 3), and scores were summed (max score: 21), TVS of ≥1 were regarded as positive for vascular uptake); Vasc-ROI, vascular region of interest divided by individual background value (peripheral region of the lung); Vert, vertebral artery; 4P-VS, four-point visual score ranging from 0 (no visualization of blood vessels) to 3 (intense FDG uptake), scores of ≥2 were regarded as positive for vascular uptake; 4P-VS*, four-point visual score relative to liver uptake (0=no uptake, 1=lower than liver uptake, 2=similar to liver uptake, 3=higher than liver uptake, with scores of ≥2 regarded as positive for vascular uptake).

above 37°C, but unexpectedly, classical inflammatory markers such as ESR and CRP were not amongst them. After multivariable analysis, only inflammatory low back pain and absence of lower limb pain remained significantly associated with subclinical GCA in PMR patients. However, the presence of these two pain symptoms only identifies a minority of patients with subclinical GCA. Although lower limb and inflammatory back pain have been reported in the context of newly diagnosed PMR, non-inflammatory musculoskeletal pains are frequent in elderly patients. Therefore, these two symptoms have to be interpreted with caution. The presence of inflammatory back pain showed no statistical correlation with the FDG uptake in the abdominal aorta or in the bursae of the spinous processes of the lumbar spine (data not shown).

To create a tool to predict subclinical GCA, we included all variables that showed an association with subclinical GCA in the univariable model and maintained this relationship in the multivariable model. However, the discriminatory ability of this prediction model was modest, with an AUC of 0.66%.

Strengths of the study include the large number of analysed IPD sets and the strict inclusion criteria, which led to the exclusion of several large cohorts that had reported subclinical GCA in patients with PMR but had not included patients consecutively. Thus, although struggling with potential biases, the prevalence derived from our meta-analysis is to date the most reliable estimation.

Limitations to the study include the considerable heterogeneity across the included studies. This was not statistically explained by diagnostic methodology which evolved over the decades (TAB, ultrasound, PET/(CT)). Possible explanations include different diagnostic criteria, but we would need much more data to investigate this. In addition, study focus and population selection were not identical for all studies.

Second, as GCA is primarily a disease treated by specialists/rheumatologists, most studies included patients referred to specialist care, whereas the majority of PMR patients are usually treated by their primary care physician. Consequently, it is unclear whether the prevalence estimates apply to a broader population in primary care settings.

Third, the collected parameters for the IPD data were, in part, incomplete. While we imputed missing values, this led to more statistical uncertainty and weakened the statistical power to detect relevant factors.

Fourth, our study only analysed routinely collected laboratory markers. However, the recent study by van Sleen et al. has shown that nonroutine biomarkers such as angiopoietin-2 are associated with large vessel vasculitis in PMR [46]. Further studies are needed to identify new potential biomarkers of subclinical GCA.

In conclusion, this systematic review and meta-analysis indicated that subclinical GCA might affect more than one in four patients with PMR when screened by PET/(CT) at diagnosis. Although we identified factors associated with subclinical GCA, the development of a helpful prediction model to systematically screen patients with PMR requires more data and the subsequent assessment. Due to the high prevalence of subclinical GCA at PMR diagnosis, the role of routine imaging for GCA warrants discussion. Although PET/CT has been most often used, other modalities such as CT, ultrasound, or MRI, each with its specific advantages and disadvantages, are available for this purpose [13]. Carefully designed prospective, longitudinal cohort studies, taking the potential biases in account would be needed to confirm the presented data. These studies should also assess the long-term damage caused by subclinical GCA, the diagnostic accuracy and the cost effectiveness of the employed imaging techniques.

Author contributions

DG and AH contributed equally to this work as joint first authors. TD, DG, AH, LGH, LW, and HE were responsible for the study conception and design. HE provided the search strategy and execution. Screening of the studies was conducted by DG, TD, and AH. DG, TD, and AH contributed

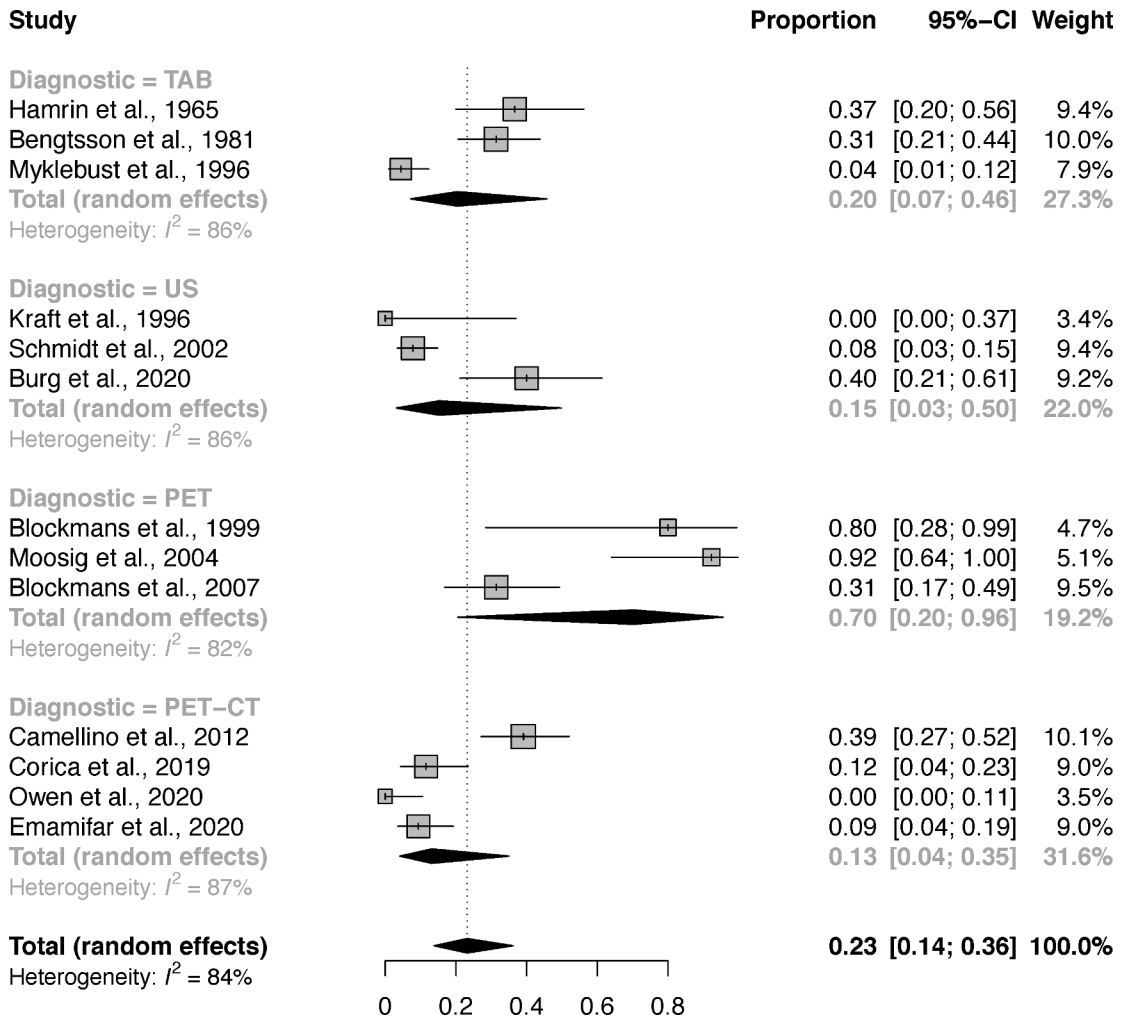

Fig. 2. Forest plot of the prevalence of subclinical GCA in all studies, stratified by the method used for subclinical GCA screening. Abbreviations: CI, confidence interval; CT, computed tomography; PET, positron emission tomography; TAB, temporal artery biopsy; US, ultrasound.

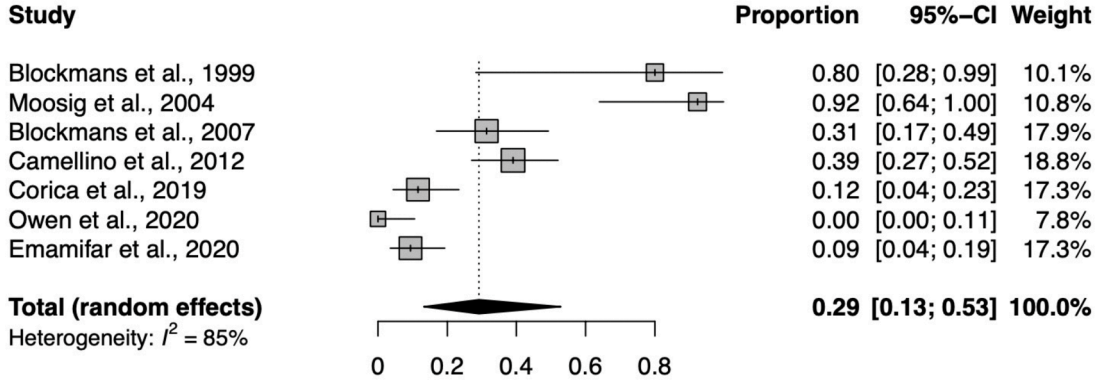

Fig. 3. Forest plot of the prevalence of subclinical GCA in PET/(CT) studies.
Abbreviations: CI, confidence interval; GCA, giant cell arteritis; PET/(CT), positron emission tomography with or without computed tomography.

to data extraction, and evaluation of the included studies. IPD was collected and provided by AT, CC, CO, DC, DB, EB, HC, HY, LH, MAC, PMA, RRCB, YvS. LGH and LW contributed to data synthesis. All authors were involved in data analysis and interpretation. DG, TD, AH, LW, LGH drafted the manuscript and all authors revised it critically. All authors had the final responsibility for the decision to submit for publication. The corresponding author (TD) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Role of funding source

AH is supported by a grant from the Swiss Foundation for Research on Muscle Diseases (FSRMM). The funding source had no role in the

Table 2
Association of patient characteristics and subclinical GCA in univariable and multivariable analysis.

Predictor	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (in years)	0.99 (0.96, 1.03)	0.700	0.97 (0.93, 1.03)	0.326
Sex (female vs. male)	2.31 (1.17, 4.58)	0.016	1.43 (0.60, 3.45)	0.428
Hypertension	0.63 (0.26, 1.49)	0.294	[a]	[a]
Dyslipidaemia	0.61 (0.22, 1.70)	0.349	[a]	[a]
Diabetes mellitus	0.36 (0.08, 1.59)	0.179	0.36 (0.06, 2.13)	0.260
Current smoking status	2.20 (0.40, 12.23)	0.373	2.22 (0.24, 20.72)	0.493
Shoulder girdle pain	0.65 (0.10, 4.13)	0.662	0.35 (0.04, 2.92)	0.339
Pelvic girdle pain	1.01 (0.48, 2.16)	0.971	0.71 (0.26, 1.96)	0.520
Inflammatory back pain	2.73 (1.32, 5.64)	0.007	5.71 (1.41, 23.06)	0.014
Neck pain	1.45 (0.68, 3.09)	0.338	0.38 (0.09, 1.51)	0.169
Absence of lower limb pain	2.35 (1.05, 5.26)	0.038	3.48 (1.16, 10.42)	0.025
Morning stiffness	1.11 (0.42, 2.97)	0.843	[a]	[a]
Duration of morning stiffness	1.00 (1.00, 1.00)	0.640	1.00 (0.99, 1.00)	0.848
Temperature > 37°	1.83 (0.90, 3.71)	0.095	1.29 (0.53, 3.15)	0.590
Weight loss	1.83 (0.96, 3.51)	0.067	1.38 (0.63, 3.04)	0.432
Weight loss (in kg)	1.10 (0.99, 1.22)	0.085	[a]	[a]
ESR (in mm/h)	1.01 (1.00, 1.02)	0.135	[a]	[a]
CRP (in mg/l)	1.00 (1.00, 1.01)	0.365	1.00 (0.99, 1.01)	0.886
Haemoglobin (in g/dl)	0.80 (0.64, 1.00)	0.051	0.81 (0.59, 1.11)	0.195
Leukocyte count (in G/l)	1.02 (0.87, 1.19)	0.838	[a]	[a]
Scaled Thrombocyte count (per SD)[b]	1.51 (1.05, 2.18)	0.027	1.37 (0.80, 2.33)	0.249

Abbreviations: CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis, OR, odds ratio.

[a] To fit the multivariable model, we excluded variables that were hypothesized to have less medical relevance for the outcome (hypertension and dyslipidaemia) as well as highly correlated inflammation markers (ESR and leukocyte count).

[b] We scaled the variable thrombocyte count to improve model fit.

study design, in the collection, analysis and interpretation of data, in the writing of the report, and in the decision to submit the article for publication.

Data availability statement

The data used and analysed during this study are available from the corresponding author upon request.

Declaration of competing interest

AH is funded by a grant from the Swiss Foundation for Research on Muscle Diseases (FSRMM) for her Ph.D. thesis. CC has received honorariums for lectures and educational events from Roche. CO has received speaking honoraria from Roche and Novartis and meeting sponsorship from Roche. DK has received honorariums from Abbvie, Gilead, Lilly, Novartis, Janssen, and Pfizer. EB as an employee of the UMCG, received speaker fees and consulting fees from Roche in 2017, 2018 which were paid to the UMCG. HC has received honorariums from Abbvie, Gilead, Lilly, Novartis, Janssen and Pfizer. LW has received a research grant from the Swiss National Science Foundation. CTB received funding from the FSRMM and the Swiss National Science Foundation. TD received funding from the FSRMM. No other disclosures were reported.

Acknowledgements

The authors would like to thank the patient and public involvement representative Chasper Knapp for his contribution to the study. We would also like to thank Christian Appenzeller-Herzog, University Medical Library, University of Basel, Basel, Switzerland, for peer-reviewing the final search strategy and PD Dr. Michael Mayr for supporting the doctoral thesis of Daniele Gozzoli as well as the Swiss Foundation for Research on Muscle Diseases (FSRMM) for supporting the Ph.D. of Andrea Hemmig.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2022.152017.

References

[1] Buttgereit F, Dejaco C, Matteson EL, Dasgupta B. Polymyalgia Rheumatica and Giant Cell Arteritis: A Systematic Review. JAMA 2016 Jun 14;315(22):2442–58. https://doi.org/10.1001/jama.2016.5444.
[2] de Boysson H, Liozon E, Ly KH, Dumont A, Delmas C, Aouba A. The different clinical patterns of giant cell arteritis. Clin Exp Rheumatol 2019 Apr;37(Suppl 117):57–60 (2).
[3] Salvarani C, Cimino L, Macchioni P, et al. Risk factors for visual loss in an Italian population-based cohort of patients with giant cell arteritis. Arthritis Care & Research 2005;53(2):293–7. https://doi.org/10.1002/art.21075.
[4] González-Gay MA, García-Porrúa C, Llorca J, et al. Visual manifestations of giant cell arteritis. Trends and clinical spectrum in 161 patients. Medicine (Baltimore) 2000;79(5):283–92. https://doi.org/10.1097/00005792-200009000-00001.
[5] Schmidt WA, Seifert A, Gromnica-Ihle E, Krause A, Natusch A. Ultrasound of proximal upper extremity arteries to increase the diagnostic yield in large-vessel giant cell arteritis. *Rheumatology (Oxford)*. 2008 Jan;47(1):96–101. https://doi.org/10.1093/rheumatology/kem322.
[6] Gonzalez-Gay MA, Vazquez-Rodriguez TR, Gomez-Acebo I, et al. Strokes at time of disease diagnosis in a series of 287 patients with biopsy-proven giant cell arteritis. Medicine (Baltimore) 2009;88(4):227–35. https://doi.org/10.1097/MD.0b013e3181af4518.
[7] Caselli RJ, Hunder GG, Whisnant JP. Neurologic disease in biopsy-proven giant cell (temporal) arteritis. Neurology 1988 Mar;38(3):352–9. https://doi.org/10.1212/wnl.38.3.352.
[8] Nuenninghoff DM, Hunder GG, Christianson TJH, McClelland RL, Matteson EL. Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. Arthritis Rheum. 2003 Dec;48(12):3522–31. https://doi.org/10.1002/art.11353.
[9] García-Martínez A, Hernández-Rodríguez J, Arguis P, et al. Development of aortic aneurysm/dilatation during the followup of patients with giant cell arteritis: a cross-sectional screening of fifty-four prospectively followed patients. Arthritis Rheum 2008;59(3):422–30. https://doi.org/10.1002/art.23315.
[10] Berger CT, Wolbers M, Meyer P, Daikeler T, Hess C. High incidence of severe ischaemic complications in patients with giant cell arteritis irrespective of platelet count and size, and platelet inhibition. Rheumatology (Oxford). 2009 Mar;48(3):258–61. https://doi.org/10.1093/rheumatology/ken480.
[11] Narváez J, Estrada P, López-Vives L, et al. Prevalence of ischemic complications in patients with giant cell arteritis presenting with apparently isolated polymyalgia rheumatica. *Seminars in Arthritis and Rheumatism.*2015;45(3):328–33. https://doi.org/10.1016/j.semarthrit.2015.06.009.
[12] Dejaco C, Singh YP, Perel P, et al. 2015 Recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Ann Rheum Dis 2015;74(10):1799–807. https://doi.org/10.1136/annrheumdis-2015-207492.
[13] Berger CT, Sommer G, Aschwanden M, Staub D, Rottenburger C, Daikeler T. The clinical benefit of imaging in the diagnosis and treatment of giant cell arteritis. Swiss Med Wkly 2018 Aug 13;148:w14661. https://doi.org/10.4414/smw.2018.14661.
[14] Luqmani R, Lee E, Singh S, et al. The Role of Ultrasound Compared to Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis (TABUL): a diagnostic accuracy and cost-effectiveness study. Health Technol Assess 2016;20(90):1–238. https://doi.org/10.3310/hta20900.

[15] Ball EL, Walsh SR, Tang TY, Gohil R, Clarke JMF. Role of ultrasonography in the diagnosis of temporal arteritis. Br J Surg 2010 Dec;97(12):1765–71. https://doi.org/10.1002/bjs.7252.

[16] Aschwanden M, Kesten F, Stern M, et al. Vascular involvement in patients with giant cell arteritis determined by duplex sonography of 2×11 arterial regions. Ann Rheum Dis 2010 Jul;69(7):1356–9. https://doi.org/10.1136/ard.2009.122135.

[17] Duftner C, Dejaco C, Sepriano A, Falzon L, Schmidt WA, Ramiro S. Imaging in diagnosis, outcome prediction and monitoring of large vessel vasculitis: a systematic literature review and meta-analysis informing the EULAR recommendations. RMD Open 2018;4(1):e000612. https://doi.org/10.1136/rmdopen-2017-000612.

[18] Imfeld S, Rottenburger C, Schegk E, et al. [18F]FDG positron emission tomography in patients presenting with suspicion of giant cell arteritis-lessons from a vasculitis clinic. Eur Heart J Cardiovasc Imaging 2018 Aug 1;19(8):933–40. https://doi.org/10.1093/ehjci/jex259.

[19] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71.

[20] Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. JAMA 2015;313(16):1657–65. https://doi.org/10.1001/jama.2015.3656.

[21] Gozzoli, D. S., Hemmig, A., Hemkens, et al. (2021, August 3). Findings consistent with subclinical vasculitis in patients with new onset polymyalgia: a systematic literature review and a meta-analysis of cohort data. https://doi.org/10.17605/OSF.IO/749RY.

[22] Sieper J, van der Heijde D, Landewé R, et al. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). Ann Rheum Dis 2009;68(6):784–8. https://doi.org/10.1136/ard.2008.101501.

[23] Prieto-Peña D, Martínez-Rodríguez I, Loricera J, et al. Predictors of positive 18F-FDG PET/CT-scan for large vessel vasculitis in patients with persistent polymyalgia rheumatica. Semin Arthritis Rheum 2019;48(4):720–7. https://doi.org/10.1016/j.semarthrit.2018.05.007.

[24] Whiting PF, Rutjes AWS, Westwood ME, et al. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. Ann Intern Med 2011;155(8):529–36. https://doi.org/10.7326/0003-4819-155-8-201110180-00009.

[25] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003 Sep 6;327(7414):557–60. https://doi.org/10.1136/bmj.327.7414.557.

[26] Carpenter JR, Kenward MG. Multiple imputation and its application. Chichester, West Sussex: John Wiley & Sons; 2013.

[27] Little RJA, Rubin DB. Statistical Analysis with Missing Data. 2nd edition. New York: John Wiley & Sons; 2002.

[28] Heymans Martijn W. psfmi: *Prediction Model Pooling, Selection and Performance Evaluation, Across Multiply Imputed Datasets*. 2021. R package version 1.0.0. https://mwheymans.github.io/psfmi/.

[29] Bates, D, Maechler, M, Bolker, B, Walker, S. 2015: lme4: Linear mixed-effects models using Eigen and S4. R package version 1.1-8.

[30] R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2020. http://www.r-project.org/index.html [accessed August 29, 2021].

[31] Hamrin B, Jonsson N, Landberg T. Involvement of large vessels in polymyalgia arteritica. Lancet 1965;1(7397):1193–6. https://doi.org/10.1016/s0140-6736(65)92723-6.

[32] Bengtsson BA, Malmvall BE. The epidemiology of giant cell arteritis including temporal arteritis and polymyalgia rheumatica. Incidences of different clinical presentations and eye complications Arthritis Rheum 1981 Jul;24(7):899–904. https://doi.org/10.1002/art.1780240706.

[33] Myklebust G, Gran JT. A prospective study of 287 patients with polymyalgia rheumatica and temporal arteritis: clinical and laboratory manifestations at onset of disease and at the time of diagnosis. Br J Rheumatol 1996 Nov;35(11):1161–8. https://doi.org/10.1093/rheumatology/35.11.1161.

[34] Kraft HE, Möller DE, Völker L, Schmidt WA. Color Doppler ultrasound of the temporal arteries–a new method for diagnosing temporal arteritis. Klin Monbl Augenheilkd 1996;208(2):93–5. https://doi.org/10.1055/s-2008-1035176.

[35] Schmidt WA, Gromnica-Ihle E. Incidence of temporal arteritis in patients with polymyalgia rheumatica: a prospective study using colour Doppler ultrasonography of the temporal arteries. Rheumatology (Oxford) 2002 Jan;41(1):46–52. https://doi.org/10.1093/rheumatology/41.1.46.

[36] Burg L, Brossart P, Behning C, Schaefer V. Prospective Analysis of the Prevalence of Giant Cell Arteritis in Consecutive Newly Diagnosed Patients with Polymyalgia Rheumatica [abstract]. Arthritis Rheumatol 2020;72(suppl 10)). https://acrabstracts.org/abstract/prospective-analysis-of-the-prevalence-of-giant-cell-arteritis-in-consecutive-newly-diagnosed-patients-with-polymyalgia-rheumatica/.

[37] Blockmans D, Maes A, Stroobants S, et al. New arguments for a vasculitic nature of polymyalgia rheumatica using positron emission tomography. Rheumatology (Oxford) 1999;38(5):444–7. https://doi.org/10.1093/rheumatology/38.5.444.

[38] Moosig F, Czech N, Mehl C, et al. Correlation between 18-fluorodeoxyglucose accumulation in large vessels and serological markers of inflammation in polymyalgia rheumatica: a quantitative PET study. Ann Rheum Dis 2004;63(7):870–3. https://doi.org/10.1136/ard.2003.011692.

[39] Blockmans D, De Ceuninck L, Vanderschueren S, Knockaert D, Mortelmans L, Bobbaers H. Repetitive 18-fluorodeoxyglucose positron emission tomography in isolated polymyalgia rheumatica: a prospective study in 35 patients. Rheumatology (Oxford). 2007 Apr;46(4):672–7. https://doi.org/10.1093/rheumatology/kel376.

[40] Camellino D, Morbelli S, Paparo F, Massollo M, Sambuceti G, Cimmino MA. Similarities exceeds differences in the pattern of joint and vascular positron emission/computed tomography uptake in polymyalgia rheumatica and giant cell arteritis. Arthritis Rheum 2012. https://acrabstracts.org/abstract/similarities-exceeds-differences-in-the-pattern-of-joint-and-vascular-positron-emissioncomputed-tomography-uptake-in-polymyalgia-rheumatica-and-giant-cell-arteritis/.

[41] Corica ME, Moya P, Fernandez A, et al. THU0603 Suitability of PET-CT in refractory polymyalgia rheumatica. Ann Rheum Dis 2019;78:593–5. https://doi.org/10.1136/annrheumdis-2019-eular.6162.

[42] Owen CE, Poon AMT, Yang V, et al. Abnormalities at three musculoskeletal sites on whole-body positron emission tomography/computed tomography can diagnose polymyalgia rheumatica with high sensitivity and specificity. Eur J Nucl Med Mol Imaging 2020;47(10):2461–8. https://doi.org/10.1007/s00259-020-04731-z.

[43] Emamifar A, Ellingsen T, Hess S, et al. The Utility of 18F-FDG PET/CT in Patients With Clinical Suspicion of Polymyalgia Rheumatica and Giant Cell Arteritis: A Prospective, Observational, and Cross-sectional Study. ACR Open Rheumatol 2020;2(8):478–90. https://doi.org/10.1002/acr2.11163.

[44] Owen C, Poon A, Lee S, et al. Fusion of positron emission tomography/computed tomography with magnetic resonance imaging reveals hamstring peritendonitis in polymyalgia rheumatica. Rheumatology (Oxford) 2018;57(2):345–53. https://doi.org/10.1093/rheumatology/kex411.

[45] Yamashita H, Kubota K, Takahashi Y, et al. Whole-body fluorodeoxyglucose positron emission tomography/computed tomography in patients with active polymyalgia rheumatica: evidence for distinctive bursitis and large-vessel vasculitis. Mod Rheumatol 2012;22(5):705–11. https://doi.org/10.1007/s10165-011-0581-x.

[46] van Sleen Y, Boots AMH, Abdulahad WH, et al. High angiopoietin-2 levels associate with arterial inflammation and long-term glucocorticoid requirement in polymyalgia rheumatica. Rheumatology (Oxford) 2020;59(1):176–84. https://doi.org/10.1093/rheumatology/kez261.

[47] Henckaerts L, Gheysens O, Vanderschueren S, Goffin K, Blockmans D. Use of 18F-fluorodeoxyglucose positron emission tomography in the diagnosis of polymyalgia rheumatica-A prospective study of 99 patients. Rheumatology (Oxford) 2018 Nov 1;57(11):1908–16. https://doi.org/10.1093/rheumatology/kex376.

[48] Rottenburger C, Mensch N, Imfeld S, et al. 18F-FDG PET/CT compared with ultrasound and biopsy for detection of vasculitis of the temporal artery branches. Swiss Med Wkly 2021;151:w20512. https://doi.org/10.4414/smw.2021.20512.

[49] Hamrin B, Jonsson N, Landberg T. Arteritis in 'polymyalgia rheumatica. Lancet 1964;1(7330):397–401. https://doi.org/10.1016/s0140-6736(64)92784-9.