Early Referral of Patients with Suspected Polymyalgia Rheumatica – A Systematic Review

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Abstract

Introduction: Prompt diagnosis and treatment of polymyalgia rheumatica (PMR) is crucial to prevent long-term complications and improve patient outcomes. However, there is currently no standardized approach to referral of suspected PMR patients to rheumatologists, leading to inconsistent management practices. The objective of this systematic review was to clarify the existing evidence regarding the following aspects of early management strategies in patients with suspected PMR: diagnostic strategies, GCA screening, glucocorticoid initiation prior to referral, value of shared care and value of fast track clinic.

Methods: Two authors performed a systematic literature search, data extraction and risk of bias assessment independently. The literature search was conducted in Embase, MEDLINE (PubMed) and Cochrane. Studies were included if they contained cohorts of suspected PMR patients and evaluated the efficacy of different diagnostic strategies for PMR, screening for giant cell arteritis (GCA), starting glucocorticoids before referral to secondary care, shared care, or fast-track clinics.

Results: From 2,437 records excluding duplicates, 14 studies met the inclusion criteria. Among these, 10 studies investigated the diagnostic accuracy of various diagnostic strategies with the majority evaluating different clinical approaches, but none of them showed consistently high performance. However, 4 studies on shared care and fast-track clinics showed promising results, including reduced hospitalization rates, lower starting doses of glucocorticoids, and faster PMR diagnosis.

Conclusion: This review emphasizes the sparse evidence of early management and referral strategies for patients with suspected PMR. Additionally, screening and diagnostic strategies for differentiating PMR from other diseases, including concurrent GCA, require clarification. Fast-track clinics may have potential to aid patients with PMR in the future, but studies will be needed to determine the appropriate pre-referral work-up.

Keywords

Polymyalgia Rheumatica, Early referral, Diagnostic strategy, GCA screening, Shared care, Fast-track clinic

1. Introduction

Polymyalgia rheumatica (PMR) is a common inflammatory disease in people over the age of 50. PMR is characterized by bilateral shoulder and pelvic girdle pain and stiffness, elevated acute phase reactants and constitutional symptoms [1, 2]. Glucocorticoid therapy results in rapid resolution of symptoms and remains the mainstay of treatment [3-5]; but it is associated with a high risk of adverse effects, and efforts should be made to minimize the cumulative dose [6-8]. International consensus recommendations, that include the use of steroid-sparing agents and goals of treatment, exist for the management of people with PMR [9].

In most countries, primary care physicians are responsible for the diagnosis and management of patients with PMR [10]. The non-specific nature of the presenting symptoms, and the lack of a definitive test makes PMR a diagnostic challenge [11, 12]. Therefore, confirmatory evaluation in rheumatology clinics is often required. A recent international survey reported that approximately 25% of patients with suspected PMR were referred to rheumatology clinics, of whom half were on glucocorticoid therapy prior to evaluation, making a subsequent assessment challenging [10]. Thus, an accurate diagnosis of such patients remains problematic, and studies have reported that up to 30% of patients referred for rheumatologic assessment are initially misdiagnosed [12-15]. Incorrectly diagnosing patients as PMR may result in unnecessary long-term glucocorticoid treatment [16]. Furthermore, it has been shown that glucocorticoid dose in primary care is often higher compared to rheumatology practice [10]. Conversely, failing to identify concurrent GCA, which has been reported to be prevalent in approximately 22% of patients with PMR, may result in undertreatment with a risk of subsequent vision loss [17-21]. However, the prognostic benefit of referring patients to secondary care remains unclear. Furthermore, there is currently a lack of evidence or consensus regarding the identification of patients with suspected PMR that may have other rheumatic diseases, cancer, or coexisting GCA. Consequently, recommendations are needed that outline strategies for early referral in patients suspected of PMR [10, 22].

This systematic review was conducted to support the formation of recommendation for the early referral of patients suspected of having PMR. The review aimed to elucidate the existing evidence pertaining to early management strategies including diagnostic strategies for PMR, screening for

GCA, initiation of glucocorticoid treatment before referral, the value of shared care, and the potential benefits of fast-track clinics.

2. Methods

2.1 Framing the research questions

An international research group from Austria, Belgium, Denmark, France, Germany, United Kingdom, The Netherlands, Italy, Portugal, Spain, Switzerland, USA, Brazil, Colombia, Peru and Australia consisting of 28 rheumatologists, 4 general practitioners, 4 patients with PMR and 1 health professional was formed. After engaging in a structured process of discussion, consensus was reached to investigate 6 final research questions. These questions encompass the clinical utility of vital elements needing careful consideration prior to referral. The population, intervention, comparator and outcome (PICO) format was selected to conduct the literature search (Table 1). In brief, these questions considered different aspects of early management in patients suspected with PMR including the role of various diagnostic strategies for diagnosing PMR and GCA; the value of screening for GCA; the value of shared care; the impact of initiating glucocorticoids prior to referral; and the value of fast-track clinics. In the absence of a gold standard diagnostic test, a clear differentiation was made between the diagnostic accuracy and clinical utility of various diagnostic strategies, as certain strategies may have the potential to enhance patient outcomes but not necessarily the diagnostic accuracy. Thus, PICO 1 and PICO 3 were split into an A version, which addressed the diagnostic accuracy, and a B version, which addressed the clinical utility of various strategies. Likewise, all clinical utility outcomes linked to the other identified PICO questions were regarded as important, and no pre-determined outcomes were defined.

Eligible studies were all full-text articles containing cohorts of suspected PMR patients with more than 20 patients and addressing one or more of the 6 research questions. Articles that featured cohorts of verified PMR patients were also included for examining the benefits of shared care. The search was not limited by language, publication date or study type.

2.2 Study selection, data extraction and risk of bias assessment

Prior to conducting the review a study protocol was prepared according to the preferred reporting items for systematic review (PRISMA) principles [23]. The protocol was uploaded and registered in the PROSPERO database on 20th January 2023 (registration number: CRD42023391575). The literature search was conducted on 14th February 2023 in three scientific databases: Embase, MEDLINE (PubMed) and the Cochrane Library. The search term “polymyalgia rheumatica” was used both asfree text and medical subject heading term (*Supplementary Data S1*). The identified records were imported and evaluated in the systematic review screening tool Covidence (Covidence systematic review software, Veritas Health Innovation, Australia).

Two authors (AWN and AH) independently screened all records and subsequently extracted data and performed the risk of bias assessment of the included studies. All titles and abstracts were screened to identify studies that met the eligibility criteria followed by a full-text review for final inclusion. To resolve any disagreements during the screening and inclusion process, CBM and KKK engaged in discussions to determine which articles should proceed to full-text screening or final inclusion. Afterwards, the following data was extracted for all included studies: Author names, publication year, geographical region, study design, time period for study conduction, inclusion criteria, included number of patients, age, sex, diagnostic method(s) for PMR, and number of patients with a final diagnosis of PMR. Additionally, data was extracted for studies evaluating the diagnostic accuracy of different strategies to diagnose PMR or GCA (PICO 1a, 3a), as well as data assessing the clinical utility of different interventions (PICO 2 and PICO 4-6) and for the different diagnostic strategies (PICO 1b, 3b) (Supplementary table S1). Risk of bias in diagnostic studies was appraised utilizing the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool comprising of four domains: patient selection, index test, reference standard, and flow and timing, each of which was graded as having “high”, “low” or “unclear” risk of bias [24]. Furthermore, the applicability of the three first domains was evaluated as high, low or unclear. To assess the risk of bias in cross-sectional studies used for clinical utility outcomes, the Appraisal tool for Cross-Sectional Studies (AXIS) was applied [25]. This tool consists of 20 questions that focus on identifying bias in different key areas. Each question was answered as "yes," "no," or "don't know," corresponding to "low," "high," or "unclear" risk of bias, respectively. Differences of opinion were resolved with the help of CBM and KKK.

2.3 Statistics

Results of the diagnostic accuracy studies were depicted in a forest plot and sub-grouped according to diagnostic methods. The sensitivity and specificity were computed with 95% confidence intervals for each study. Relative risks of clinical utility outcomes were calculated if relevant with 95% confidence intervals. Otherwise, differences between the intervention and comparator groups were reported with p-value, if stated in the original article. A p-value less than 0.05 was considered as statistically significant. All analyses were conducted using STATA software (Version 17, StataCorp, USA).

3. Results

3.1 Literature search

The search identified 2,437 records excluding duplicates, of which 14 studies were included in this review (*Figure 1*). *Table 2* summarizes the main study and patient characteristics of the included studies. Among the studies that addressed the diagnostic accuracy of various strategies, 10 studies assessed different strategies for diagnosing PMR (PICO 1a) [26-35]; one study assessed the diagnostic accuracy of Positron Emission Tomography and Computed Tomography (PET/CT) for diagnosing GCA (PICO 3a) [29]. Clinical utility of different interventions were investigated in four studies, of which two studies reported outcomes of shared care (PICO 4) [8, 36], and two studies assessed the utility of fast-track clinics (PICO 6) [37, 38]. Only one study was included for two objectives including the diagnostic accuracy of using PET/CT to diagnose PMR as well as GCA in patients suspected of PMR [29]. We did not identify studies reporting clinical utility outcomes for the remaining research question (*Table 2*).

3.2 Diagnostic strategies for diagnosing PMR (PICO 1)

Studies examining the diagnostic accuracy of various strategies for diagnosing PMR had a female population ranging from 48% to 77%, with mean ages ranging from 65 to 75 years [26-35]. All patients were suspected of having PMR at the time of diagnosis, although the inclusion and exclusion criteria differed across studies. The proportion of patients ultimately diagnosed with PMR

ranged from 48% to 80%. The final diagnosis of PMR was usually confirmed at long-term clinical follow-up, but Horikoshi et al. did not report this information (*Supplementary table S2*) [30].

Most studies evaluated the diagnostic accuracy of a clinical PMR diagnosis at baseline or by assessment of pre-specified clinical classification criteria (*Figure 2 / Supplementary table S2*) [26-28, 30, 31]. The two studies conducted by Lee et al. and Ozen et al. specifically aimed to compare the diagnostic performance of different clinical classification criteria including the 2012 EULAR/ACR criteria, Jones and Hazleman criteria, Bird criteria, Chuang and colleagues criteria, Healey criteria and Nobunga criteria [1, 28, 31, 39-43]. Considerable differences in diagnostic accuracy were observed within the same study when using different classification criteria, and even when comparing specific criteria across the two studies. A clinical diagnosis of PMR at baseline showed the highest sensitivity ranging from 0.67-1 with a specificity between 0.41-0.92. Heterogeneity in the study designs could not be fully assessed since the criteria used to diagnose the patients were not defined. Among studies comparing established classification criteria for diagnosing PMR, the Bird criteria exhibited the highest sensitivity (0.94-0.97), but the specificity was poor (0.18-0.50). Conversely, the Jones and Hazleman criteria had the highest specificity (0.50-0.97), but with a lower sensitivity (0.42-1).

Four studies investigated the diagnostic performance of PET/CT for diagnosing patients with PMR (*Figure 2*) [29, 32, 33, 35]. Three studies based the diagnosis of PMR on composite-scores and/or algorithms, relying on fluorodeoxyglucose (FDG) uptake in regions typically affected in patients with PMR [29, 33, 35, 44, 45]. However, a study by Emamifar et al. assessed PET/CT scans as positive for PMR if there was FDG-uptake in any pre-specified articular or periarticular sites around in the shoulder and pelvic girdle or along the interspinous ligament. In this study, two cut-offs for a PET/CT diagnosis of PMR were applied depending on if the FDG-uptake was equal to (cut-off 2) or above liver-uptake (cut-off 3) [32]. Of the different scoring tools, the Leuven and the Leuven-Groningen score seemed to have the best diagnostic accuracy.

The quality assessment demonstrated that all studies had potential high risk of bias (*Supplementary table S3*). The primary issues identified were bias in the selection of participants and bias in the assessment of the reference standard.

3.3 Diagnostic strategies for diagnosing GCA (PICO 3)

Henckaerts et al. performed the only study eligible for inclusion regarding diagnostic strategies for diagnosing GCA in patients suspected of PMR (*Figure 2 / supplementary table S2*) [29]. High-grade vascular FDG-uptake on PET/CT (equal to or above liver-uptake) was deemed suggestive of GCA and the final diagnosis was confirmed by a temporal artery biopsy (TAB). This imaging modality showed a high sensitivity/specificity (1.0/0.90) but several risks of bias were identified regarding the selection, index test, reference standard as well as flow and timing (*Supplementary table S3*).

3.4 Clinical utility of shared care (PICO 4)

Two cross-sectional studies reported a single outcome each for the utility of shared care in patients diagnosed with PMR (*Table 3 / supplementary table S2*). Shared care outcomes were not reported for patients suspected of PMR. Gabriel et al. found that patients referred to and assessed by rheumatologists were administered a prednisolone starting dose that was 9.5 mg lower compared to standard care (not referred patients) [8]. Helliwell et al. reported that patients seen in shared care were more likely to be started on osteoporosis prophylaxis [36]. However, risk of bias was identified in both studies including unsuitable main objectives, inappropriate selection processes, and insufficient presentation of results regarding our research question (*Supplementary table S4*).

3.5 Clinical utility of fast-track clinics (PICO 6)

Two Danish studies compared outcomes between fast-track clinics and standard care in patients with a final diagnosis of PMR [37, 38]. In both studies, a historical cohort was used as a comparator after the introduction of the fast-track clinic. The cohorts assessed in the fast-track clinics demonstrated faster diagnosis of PMR, decreased days of hospitalizations, and Frølund et al. reported a reduced starting dose of prednisolone in their fast-track cohort (*Table 3 / supplementary table S2*) [37]. However, the risk of bias assessment revealed high risk of selection bias in both studies (*Supplementary table S4*).

4. Discussion

An international survey on early referral and management practices for suspected PMR patients has highlighted the inconsistencies in present approaches towards early referral and management strategies in PMR [10]. We report the current evidence of various management strategies with the goal of providing evidence-based recommendations for appropriate early management and referral of patients with suspected PMR for secondary care evaluation. This systematic review demonstrates the paucity of evidence concerning clinical utility outcomes regarding application of different diagnostic methods, screening approaches for GCA, and early management strategies in primary care for patients suspected of PMR.

The most relevant studies in this review were those that examined the diagnostic accuracy of different methods for diagnosing PMR [26-35]. However, due to methodological differences and limited data availability, a meaningful meta-analysis was not allowed. A general concern of the included studies was the lack of clinician blinding to initial index test, which may have produced a systematic bias in favor of the index test. Moreover, questions arose about the validity of the final diagnosis of PMR since the baseline clinical diagnosis exhibited a sensitivity of 100% in three out of four studies. This suggests that a change in diagnosis was unlikely once glucocorticoid treatment had been initiated. Consequently, it was challenging to determine which clinical criteria had the best diagnostic performance. Nonetheless, the ACR/EULAR criteria demonstrated a good sensitivity across studies, while the Chuang and Colleagues criteria exhibited the highest specificity. However, it is important to acknowledge that classification criteria are not designed to achieve flawless diagnostic accuracy. Instead, their development serves specific purposes within a scientific context.

The PET/CT studies included in the review showed promising results in terms of the diagnostic accuracy of PET/CT for the diagnosis of PMR [29, 32, 33, 35]. Especially, the Leuven and Leuven/Groningen composite-scores exhibited remarkable sensitivity and specificities across studies, surpassing the performance of the clinical classification criteria [29, 33]. These two composite scores are very similar as they both assess the FDG-uptake intensity in numerous typically FDG-uptaking PMR sites surrounding the shoulder and hip girdle, as well as interspinous region. However, a major concern was that the three studies utilizing these composite scores had a high risk of information bias, as the PET/CT was included at the follow-up assessment for the final

diagnosis of PMR. Moreover, selection bias could not be ruled out since all cohorts were enrolled at hospital departments. Nonetheless, these composite scores might be the best diagnostic tools for distinguishing PMR from non-PMR but more prospective studies of suspected PMR patients are needed before it can be implemented in routine care. Furthermore, the clinical utility of applying PET/CT needs to be addressed, given the array of concerns associated with this imaging modality. These concerns include substantial operating costs, uneven availability of PET/CT, radiation exposure, and risk of additional tests as a consequence of unspecific findings. Such unintended consequences could potentially be counterproductive. A careful evaluation of the utility of PET/CT is warranted, taking into account the various drawbacks and challenges associated with its application.

We were not able to identify any studies comparing the clinical utility of screening for GCA in patients suspected of PMR compared to not screening. During the full-text screening, one study reported a 2% prevalence of GCA in a subgroup suspected of PMR who underwent vascular ultrasound examination and had a TAB performed [46]. However, this study was not included because patients suspected of having PMR as well as PMR with GCA were included and subgroup analysis were not available.

Henckaerts et al. conducted the only study that was included regarding the diagnostic accuracy of using different strategies for diagnosing GCA in patients suspected of PMR [29]. Using PET/CT the study identified 12 patients with vascular FDG uptake equal to or above the uptake of FDG in the liver, of which 2 were diagnosed with GCA based on TAB. However, this study had several potential biases (*Supplementary table S3*), including whether all patients had a TAB and its timing in relation to PET/CT. The site of vascular uptake was not stated, which may have underestimated the prevalence of GCA since TAB negativity does not exclude extra-cranial involvement [47, 48]. The primary objective of the Henckaert et al. study was to assess the diagnostic accuracy of PET/CT for diagnosing PMR, therefore clinical outcomes data of the patients with GCA were not reported. The reason that only one study was eligible for inclusion was that most studies focused on evaluating the presence of GCA in patients who have already been diagnosed with PMR. In these studies, the patients were screened for GCA subsequent to the PMR diagnosis, which may reflect the standard practice in most clinics. Studies have reported a prevalence of GCA among PMR patients without

any symptoms of GCA of approximately 10-20% [32, 49-51]. However, such screening is typically conducted on a selected cohort of patients who have been referred to hospital departments.

Gabriel et al. and Helliwell et al. demonstrated that patients assessed by shared care had improved outcomes regarding prescription of osteoporosis prophylaxis and initial prednisolone dosage compared to standard care [8, 36]. However, neither of these studies were specifically designed to answer our research question (*Table 1 – PICO 4*). The retrospective nature of the two epidemiologic studies may have introduced selection bias since patient identification relied on records with sufficient reported data.

Fast-track clinics appeared to improve the time to PMR diagnosis, initial prednisolone dosage and inpatient days at hospitals [37, 38]. Another interesting result reported by Chrysidis et al. was a reduced annual cost for patients assessed by fast-track clinics compared to standard care [38]. This may greatly influence the willingness to introduce fast-track clinics, but a more thorough cost-effectiveness analysis will be needed. Unfortunately, the studies did not report the consequence of starting glucocorticoids prior to referral. Frølund et al. stated that there was no increased risk of initial misdiagnosis in the historic cohort compared to the fast-track cohort, despite that patients in the historic cohort were more likely to be on prednisolone treatment prior to referral. This may reflect that patients who were initiated on prednisolone treatment prior to being assessed by a rheumatologist were less likely to experience a change in diagnosis if the PMR symptoms resolved. Thus, it may be worth considering whether patients in this situation should be tapered off prednisolone to verify the PMR diagnosis. A significant limitation of the fast-track pathway studies was their use of historical cohorts as a comparator. These comparator cohorts may partly represent a cohort of patients referred specifically because of refractoriness to prednisolone in primary care. Additionally, the two fast-track studies were conducted in Denmark and the transferability of the results to other countries needs to be investigated. Therefore, to evaluate the true efficacy of fast-track clinics, international multicenter studies will be necessary.

Conclusion

This is the first systematic literature review pertaining to the evidence basis of early management strategies in patients with suspected PMR. This review elucidates the challenges in diagnosing PMR due to the absence of consistently reliable clinical criteria, although imaging has the potential to

assist an early diagnosis. Additionally, screening and diagnostic strategies for identifying patients at risk of GCA requires clarification. Fast-track clinics may have potential to aid patients with PMR in the future, but studies will be needed to determine the appropriate pre-referral work-up.

This review emphasizes the need for further research into the benefits of early referral strategies of patients suspected of PMR ideally comparing usual care to early referral.

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Conflicts of interest

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Figure

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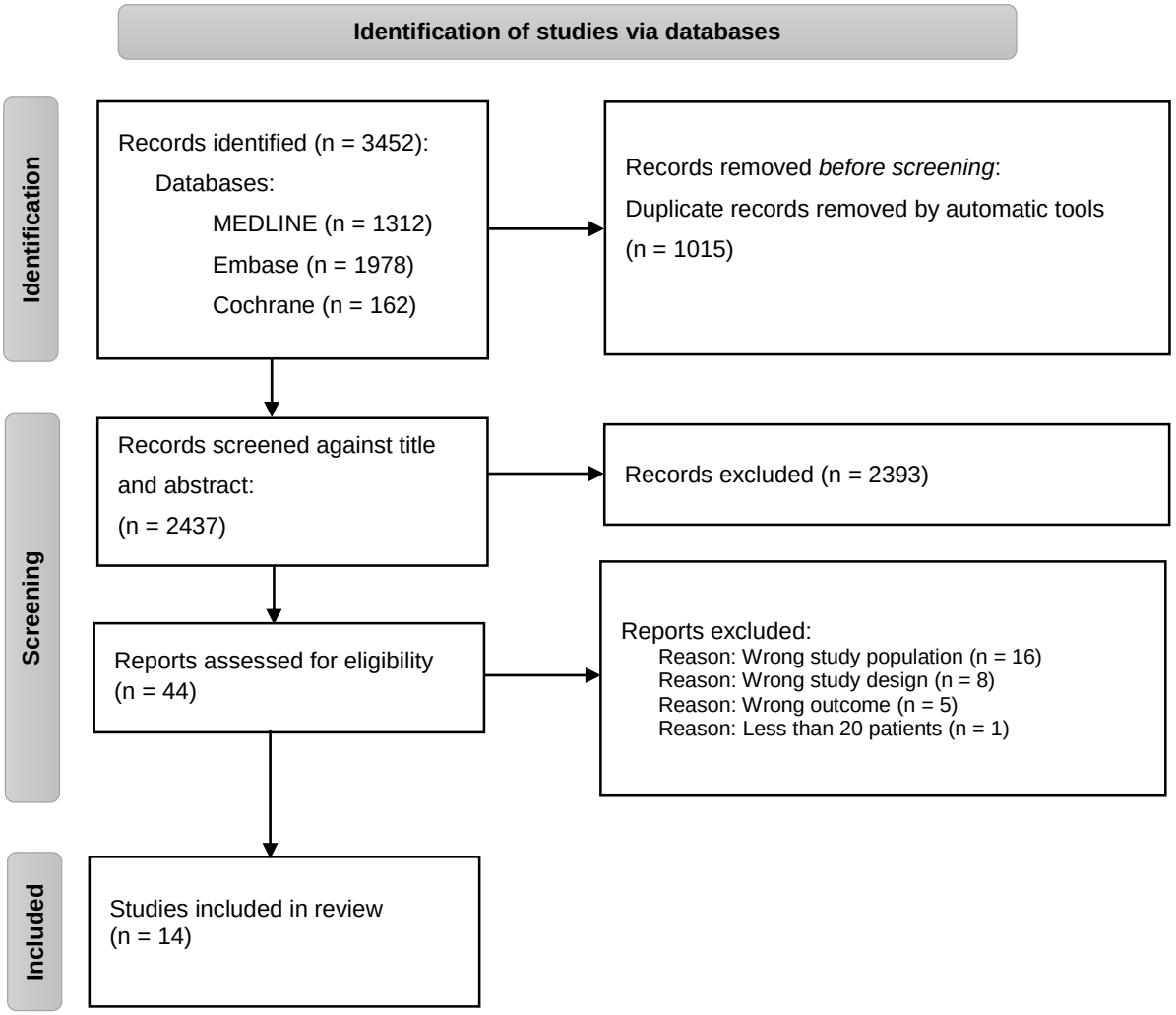

Figure 1. Prisma flow diagram of study selection

Figure

Click here to access/download;Figure;Figure 2 - Forest plot 090523.docx

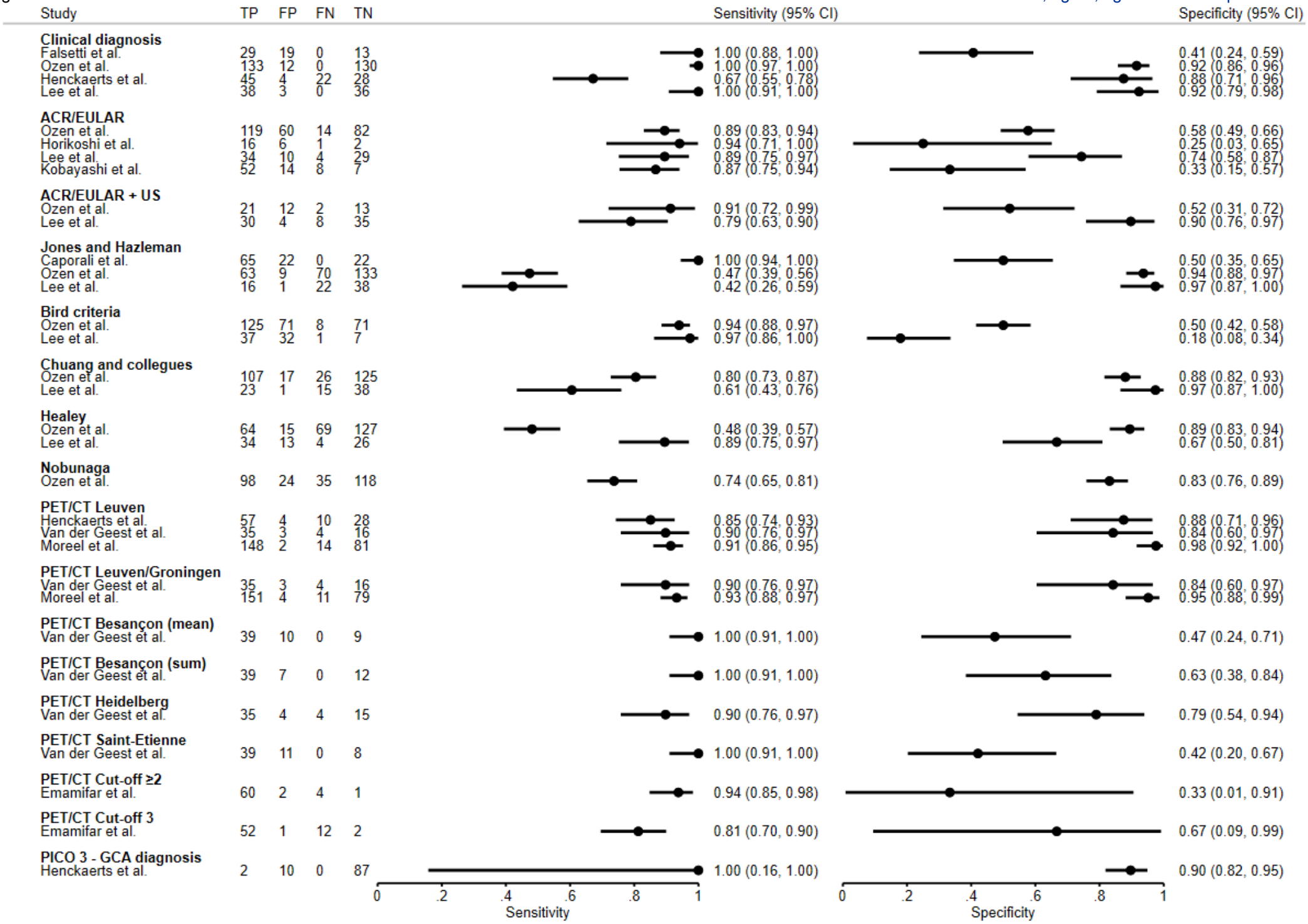

Figure 2. Forest plot of diagnostic accuracy of different methods to diagnose PMR/GCA. US: ultrasound. TP: true positive. FP: false positive. FN: false negative. TN: true negative. GCA: Giant cell arteritis

Table 1 - Final PICO questions framed after the PICO format in a tabular layout

Review question	Patients/population (P)	Intervention (I)	Comparator (C)	Outcome (O)
PICO 1a: DA	Suspected PMR	PMR diagnosed after following diagnostic strategy A	PMR excluded after following diagnostic strategy A	Diagnostic strategy B (reference standard diagnosis of PMR[1])
PICO 1b: CU	Suspected PMR	Diagnostic strategy A for diagnosing PMR	Diagnostic strategy B for diagnosing PMR	Clinical outcomes[2]
PICO 2: CU	Suspected PMR	Screening for GCA (imaging or biopsy)	No screening for GCA	Clinical outcomes[2]
PICO 3a: DA	Suspected PMR	GCA diagnosed after following diagnostic strategy A	GCA excluded after following diagnostic strategy A	Diagnostic strategy B: (reference standard diagnosis of GCA)[3]
PICO 3b: CU	Suspected PMR	Diagnostic strategy A for diagnosing GCA	Diagnostic strategy B for diagnosing GCA	Clinical outcomes[2]
PICO 4: CU – suspected PMR	Suspected PMR (without GCA)	Care shared between primary and secondary care	Care in primary care alone	Clinical outcomes[2]
PICO 4: CU – already diagnosed with PMR	Already diagnosed with PMR (without GCA)	Care shared between primary and secondary care	Care in primary care alone	Clinical outcomes[2]
PICO 5: CU	Suspected PMR, referred to secondary care	Initiation of glucocorticoids prior to referral to secondary care	No initiation of glucocorticoids prior to referral to secondary care	Proportion of patients with misdiagnosis (diagnostic error) and clinical outcomes[2]
PICO 6: CU	Suspected PMR, referred to secondary care	Short waiting time (fast track clinic)	Long waiting time (standard care clinic)	Proportion of patients with misdiagnosis (diagnostic error) and clinical outcomes[2]

DA: diagnostic accuracy PICO. CU: clinical utility PICO. 1: The reference standard in the included studies was mainly a confirmed PMR diagnosis through clinical follow-up 2. Clinical outcomes needed to be measured in both intervention and control group for inclusion. 3. One PET/CT study was included using temporal artery biopsy as reference standard.

Table 2 - Characteristics of included studies

Study ID (Publication year)	Country, region	Study design	Time period	Included patients, N	Age (SD)	Female, N, (%)	PMR, N (%)	Inclusion criteria	Diagnostic method for assessing PMR	Research Question
Gabriel et al. (1997)	USA, Olmsted county, Minnesota	Retrospective cohort study	1970-1992	232	72.9	163 (70%)	232 (100%)	Identified PMR	Chuang and colleagues criteria at baseline	PICO 4
Caporali et al. (2001)	Italy, Pavia	Prospective case-control study	N/A	109	70.1**	45 (69%)**	65 (60%)	Suspected PMR	Jones and Hazleman criteria at baseline and at 12 months	PICO 1a
Falsetti et al. (2011)	Italy, Arezzo	Prospective case-control study	2006-2008	61	74 (±7.4)**	35 (57%)	29 (48%)	Suspected PMR	Clinical using US + clinical diagnosis at 12 months	PICO 1a
Helliwell et al. (2013)	UK, Staffordshire	Retrospective cohort study	1999-2006	304	73 (66-80)^	229 (75%)	304 (100%)	Identified PMR	N/A	PICO 4
Ozen et al. (2016)	Turkey	Prospective case-control study	N/A	275	64.9 (±8.9)	212 (77%)	133 (48%)	Suspected PMR	Various clinical criteria at baseline + clinical diagnosis at 12 months	PICO 1a
Henckaerts et al. (2018)	Belgium, Leuven	Prospective case-control study	2012-2015	99	71 (65-77)**,^	58 (59%)	67 (68%)	Suspected PMR	PET/CT + Clinical diagnosis at 6 months	PICO 1a +3a
Horikoshi et al. (2020)	Japan, Saitama	Retrospective case-control study	2008-2013	25	75 (±2)**	12 (48%)	17 (68%)	Suspected PMR	N/A	PICO 1a
Lee et al. (2020)	Korea, Seoul	Prospective case-control study	2016-2019	77	72.8 (±10.3)**	57 (74%)	38 (49%)	Suspected PMR	Various clinical criteria at baseline + clinical diagnosis at 12 months	PICO 1a
Emamifar et al. (2020)	Denmark, Svendborg	Prospective case-control study	2018-2019	80*	72.0 (±7.9)*	50 (63%)*	64 (80%)	Suspected PMR or GCA	PET/CT + Clinical diagnosis at 40 weeks	PICO 1a
Frølund et al. (2021)	Denmark, Silkeborg	Retrospective cohort study	2014-2019	I: 113 C: 97	I: 72.7 (±7.6) C: 71 (±7.8)	I: 47 (57%)** C: 43 (44%)	I: 83 (73%) C: 97 (100%)	Suspected PMR	Clinical diagnosis at baseline and at 12 months	PICO 6
Chrysidis et al. (2021)	Denmark, Esbjerg	Retrospective cohort study	2013-2018	I: 56 C: 254	I: 71.8 (±6.6)** C: 71.6 (±8.8)**	I: 27 (48%) C: 147 (56%)	I: 56 (100%) C: 254 (100%)	Suspected PMR	Clinical diagnosis of PMR	PICO 6
Van der Geest et al. (2022)	The Netherlands, Groningen	Retrospective case-control study	2010-2020	58	71 (54-82)**,^	39 (67%)	39 (67%)	Suspected PMR	PET/CT + Clinical diagnosis at 6 months	PICO 1a
Kobayashi et al. (2022)	Japan, Yamanashi	Prospective case-control study	2017-2019	81	74 (±8.1)**	35 (58%)**	60 (74%)	Suspected PMR	ACR/EULAR criteria at baseline + clinical diagnosis at 12 months	PICO 1a
Moreel et al. (2022)	Belgium, Leuven	Retrospective case-control study	2003-2020	245	70 (60-76)^	131 (53%)	162 (66%)	Suspected PMR	PET/CT + Clinical diagnosis at 6 months	PICO 1a

*PMR: Polymyalgia rheumatica. SD: Standard deviation. PET/CT: Positron emission tomography and computed tomography. US: Ultrasound. Results will be reported separately for each group if possible. N/A: Not applicable. I: Intervention group. C: Comparator group. *Pooled data of suspected PMR and GCA group. **Only data from the patients with a final diagnosis of PMR. ^Results presented as median (interquartile range).*

Table 3 – Patient outcomes according to early management strategies

PICO 1b – Clinical utility for using different diagnostic strategies to diagnose PMR

Based on our search criteria and selection process, we were unable to find any studies that met the eligibility requirements for inclusion in our analysis.

PICO 2 – Clinical utility of screening for GCA in patients suspected of PMR

Based on our search criteria and selection process, we were unable to find any studies that met the eligibility requirements for inclusion in our analysis.

PICO 3b - Clinical utility for using different diagnostic strategies for diagnosing GCA in patients suspected of PMR

Based on our search criteria and selection process, we were unable to find any studies that met the eligibility requirements for inclusion in our analysis

PICO 4 – Clinical utility of shared care in treating PMR

	Patients	**Intervention**	**Controls**	**Outcome**
Gabriel et al.	Diagnosed with PMR (**n=232**)	Patients treated in shared care: **N/A**	Patients treated in primary care alone: **N/A**	Patients that were assessed by a rheumatologist at PMR diagnosis were administered a **9.5 mg** lower initial prednisolone dose compared to standard treated patients (**p-value <0.001**)
Helliwell et al.	Diagnosed with PMR (**n=304**)	Patients treated in shared care (**n=135**)	Patients treated in primary care alone (**n=169**)	Osteoporosis prophylaxis (**n=183**). Significantly more where started on osteoporosis prophylaxis in shared care group but numbers not reported (**p-value <0.001**).

PICO 5 – Clinical utility of delaying glucocorticoid treatment until secondary care assessment in patients suspected of PMR

Based on our search criteria and selection process, we were unable to find any studies that met the eligibility requirements for inclusion in our analysis

PICO 6 – Clinical utility of fast track PMR clinics

	Patients	**Intervention**	**Controls**	**Outcome**
Frølund et al.	Suspected PMR patients (**n=210**)	Patients with PMR assessed in fast-track clinic (**n=83**)	Patient with PMR assessed according to standard care (**n=97**)	1. Diagnosis of PMR after 1 year, n (%): **80 (96%) in FTC vs 94 (97%) in historical cohort**. RR between groups: **1.17 (95% CI: 0.24-5.64)** 2. Time to PMR diagnosis, median days (IQR): **52 (31-83) in FTC vs 80 (58-132) in historical cohort**. Between group difference: **p-value <0.001** 3. Prednisolone starting dose (mg), median (IQR): **15 (15-15) in FTC vs 15 (15-20) in historical cohort**. Between group difference: **p-value <0.001** 4. Prednisolone prescription prior to rheumatologic assessment, n (%): **9 (11%) in FTC vs 41 (42%) in historical cohort**. RR between groups: **0.26 (95% CI: 0.13-0.50)** 5. Number of contacts with hospitals from referral to diagnosis, median (range): **0 (0-8) in FTC vs 1 (0-17) in historical cohort**. Between group difference: **p-value <0.001**
Chrysidis et al.	Suspected non-hospitalized PMR patients (**n=310**)	Patients with PMR assessed in fast-track clinic (**n=56**)	Patient with PMR assessed according to standard care (**n=254**)	1. Duration of symptoms before PMR diagnosis, mean weeks (SD): **6.8 (±0.7) in FTC vs 12.3 (±12.3) in historical cohort**. Between group difference: **p-value = 0.001** 2. Initial prednisolone dose (mg), mean (SD): **18.4 (±8.3) in FTC vs 19.2 (±9.25) in historical cohort**. Between group difference: **p-value = 0.55** 3. Patients hospitalized during the disease course, n (%): **2 (3.6%) in FTC vs 52 (20.5%) in historical cohort**. RR between groups: **0.20 (95% CI: 0.05-0.82)** 4. Inpatients days of care, mean days (SD): **1 (±0) in FTC vs 4.2 (±3.1) in historical cohort**. Between group difference: **p-value <0.001** 5. Annual cost for patients assessed in fast-track clinic was reduced by **65%.** Between group difference: **N/A**

PMR: Polymyalgia Rheumatica. GCA: Giant Cell Arteritis. SD: Standard deviation. RR: Relative risk. 95% CI: 95% confidence interval. IQR: Interquartile range. N/A: Not applicable. FTC: Fast track cohort. HC: Historical cohort.

Supplementary data S1

EMBASE:

('rheumatic polymyalgia'/exp OR 'rheumatic polymyalgia') NOT 'case report'/exp NOT 'conference paper'/exp NOT 'review'/exp AND [abstracts]/lim NOT 'chapter'/it NOT 'conference abstract'/it NOT 'conference review'/it NOT 'editorial'/it NOT 'letter'/it NOT 'review'/it

MEDLINE (PubMed):

(("Polymyalgia Rheumatica"[Mesh] OR "Polymyalgia Rheumatica"[all fields]) NOT ("Review"[pt] or "Case reports"[pt]) AND (fha[Filter]) NOT (systematicreview[Filter])) NOT (booksdocs[Filter]))

Cochrane:

#1	("polymyalgia rheumatica"):ti,ab,kw (Word variations have been searched)
#2	MeSH descriptor: [Polymyalgia Rheumatica] explode all trees
#3	#1 OR #2

Supplementary Table S1 – Data extracted from diagnostic accuracy studies as well as clinical utility of different interventions/diagnostic strategies

Review question	**Harvested data**	**Calculated data**
Diagnostic accuracy studies - PICO 1a, 3a	• Diagnostic method(s) at baseline • Number of patients diagnosed with PMR/GCA using diagnostic method(s) at baseline • Number of patients excluded of PMR/GCA using diagnostic method(s) at baseline • Diagnostic method to confirm final PMR/GCA diagnosis • Number of patients with a final diagnosis of PMR/GCA	• Sensitivity/specificity of diagnostic method(s) used at baseline • Positive likelihood ratio/negative likelihood ratio of diagnostic method(s) used at baseline • Positive predictive value/negative predictive value of diagnostic method(s) used at baseline
Clinical utility studies - PICO 1b, 2, 3b, 4-6	• Number of patients diagnosed/suspected of PMR • Number of patients receiving the intervention (e.g. managed by shared care or assessed in fast-track clinic) • Number of patients in comparator group (e.g. managed solely in primary care or assessed according to standard care) • All clinical utility outcomes • Relevant statistics related to outcomes.	• Relative risk of different outcomes between intervention and comparator group

Supplementary table S2 – Characteristics of diagnostic studies

PICO 1a – Diagnostic accuracy of different diagnostic strategies for diagnosing PMR

Study ID	Patients	Intervention	Controls	Outcome	Sens/spec	+LH/-LH	PPV/NPV
Caporali et al.	Suspected PMR patients (**n=109**)	Jones and Hazleman criteria (**n=87**)	Diagnosis of PMR excluded using Jones and Hazleman criteria (**n=22**)	Final diagnosis of PMR using clinical diagnosis after 12 months as reference standard (**n=65**)	**100/50.0**	**2.0/0**	**74.7/100**
Falsetti et al.	Suspected PMR patients (**n=61**)	Clinical diagnosis of PMR at baseline using US (**n=48**)	Clinical diagnosis of PMR excluded at baseline using US (**n=13**)	Final diagnosis of PMR using clinical diagnosis after 12 months as reference standard (**n=29**)	**100/40.6**	**1.7/0**	**60.4/100**
Ozen et al.	Suspected PMR patients (**n=275**) Subgroup of suspected PMR evaluated using US (**n=48**)	Diagnosis of PMR using different criteria: Clinical (**n=145**) ACR/EULAR (**n=179**) Bird (**n=196**) Jones and Hazleman (**n=72**) Chuang and colleagues (**n=124**) Healey (**n=79**) Nobunaga (**n=122**) ACR/EULAR with US (**n=33**)	Diagnosis of PMR excluded using different criteria: Clinical (**n=130**) ACR/EULAR (**n=96**) Bird (**n=79**) Jones and Hazleman (**n=203**) Chuang and colleagues (**n=151**) Healey (**n=196**) Nobunaga (**n=153**) ACR/EULAR with US (**n=15**)	Final diagnosis of PMR using clinical diagnosis after 12 months as reference standard (**n=133**) Final diagnosis of PMR using clinical diagnosis after 12 months as reference standard for subgroup evaluated with US (**n=23**)	Clinical: **100/91.6** ACR/EULAR: **89.5/57.7** Bird: **94.0/50.0** Jones and Hazleman: **47.4/93.7** Healey: **48.1/89.4** Nobunaga: **73.7/83.1** ACR/EULAR with US **91.3/52.0**	Clinical: **11.8/0.0** ACR/EULAR: **2.1/0.2** Bird: **1.9/0.1** Jones and Hazleman: **7.5/0.6** Chuang and colleagues: **6.7/0.2** Healey: **4.6/0.6** Nobunaga: **4.4/0.3**	Clinical: **91.7/100** ACR/EULAR: **66.5/85.4** Bird: **63.8/89.9** Jones and Hazleman: **87.5/65.5** Chuang and colleagues: **86.3/82.8** Healey: **81.0/64.8** Nobunaga: **80.3/77.1**

						ACR/EULAR with US: **1.9/0.2**	ACR/EULAR with US: **63.6/86.7**
Henckaerts et al.	Suspected PMR patients (**n=99)**	Diagnosis of PMR using PET/CT Leuven-score (cut-off score ≥16) (**n=61**) Diagnosis of PMR using clinical probability score (cut-off ≥4) (**n=49**)	Diagnosis of PMR excluded using PET/CT Leuven-score (cut-off score ≥16) (**n=38**) Diagnosis of PMR excluded using clinical probability score (cut-off ≥4) (**n=50**)	Final diagnosis of PMR using clinical diagnosis after 6 months as reference standard (**n=67**)	PET/CT Leuven-score (cut-off ≥16): **85.1/87.5** Clinical probability score: **67.2/87.5**	PET/CT Leuven-score (cut-off ≥16): **6.8/0.8** Clinical probability score: **5.4/0.4**	PET/CT Leuven-score (cut-off ≥16): **93.4/73.7** Clinical probability score: **91.8/56.0**
Horikoshi et al.	Suspected PMR patients (**n=25**)	Diagnosis of PMR using ACR/EULAR criteria (**n=22**)	Diagnosis of PMR excluded using ACR/EULAR criteria (**n=3**)	Final diagnosis of PMR (diagnostic method not accounted for) (**n=17**)	**94.1/25.0**	**1.25/0.24**	**72.7/66.7**
Lee et al.	Suspected PMR patients (**n=77**)	Diagnosis of PMR using different criteria: Clinical (**n=41**) ACR/EULAR (**n=44**) Bird (**n=69**) Jones and Hazleman (**n=17**) Chuang and colleagues (**n=24**) Healey (**n=47**) ACR/EULAR with US (**n=34**)	Diagnosis of PMR excluded using different criteria: Clinical (**n=36**) ACR/EULAR (**n=33**) Bird (**n=8**) Jones and Hazleman (**n=60**) Chuang and colleagues (**n=53**) Healey (**n=30**) ACR/EULAR with US (**n=43**)	Final diagnosis of PMR using clinical diagnosis after 12 months as reference standard (**n=38**)	Clinical: **100/92.3** ACR/EULAR: **89.5/74.4** Bird: **97.4/18.0** Jones and Hazleman: **42.1/97.4** Chuang and colleagues: **60.5/97.4** Healey: **89.5/66.7** ACR/EULAR with US: **79.0/89.7**	Clinical: **13/0.0** ACR/EULAR: **3.5/0.1** Bird: **1.2/0.2** Jones and Hazleman: **16.4/0.6** Chuang and colleagues: **23.6/0.4** Healey: **2.7/0.2** ACR/EULAR with US: **7.7/0.2**	Clinical: **92.7/100** ACR/EULAR: **77.8/87.9** Bird: **53.6/87.5** Jones and Hazleman: **94.1/63.3** Chuang and colleagues: **95.8/71.7** Healey: **72.3/86.7** ACR/EULAR with US: **88.2/81.4**

Emamifar et al.	Suspected PMR patients (**n=67**)	Diagnosis of PMR using PET/CT: Pathologic cut-off ≥3 (**n=53**) Pathologic cut-off ≥2 (**n=62**)	Diagnosis of PMR excluded using PET/CT Pathologic cut-off ≥3 (**n=14**) Pathologic cut-off ≥2 (**n=5**)	Final diagnosis of PMR using clinical diagnosis after 40 weeks as reference standard (**n=64**)	Pathologic cut-off ≥3: **81.2/66.7** Pathologic cut-off ≥2: **93.8/33.3**	Pathologic cut-off ≥3: **2.4/0.28** Pathologic cut-off ≥2: **1.4/0.2**	Pathologic cut-off ≥3: **98.1/14.3** Pathologic cut-off ≥2: **96.8/20.0**
Van der Geest et al.	Suspected PMR patients (**n=58)**	Diagnosis of PMR using PET/CT Leuven-score (cut-off score ≥16) (**n=38**) Diagnosis of PMR using PET/CT Leuven/Groningen-score (cut-off score ≥8) (**n=38**) Diagnosis of PMR using PET/CT Besançon-score (sum) (cut-off ≥3) (**n=46**) Diagnosis of PMR using PET/CT Besançon-score (mean) (cut-off ≥0.53) (**n=49**) Diagnosis of PMR using PET/CT Saint-Etienne algorithm (**n=50**) Diagnosis of PMR using PET/CT Heidelberg algorithm (**n=39**)	Diagnosis of PMR excluded using PET/CT Leuven-score (cut-off score ≥16) (**n=20**) Diagnosis of PMR excluded using PET/CT Leuven/Groningen-score (cut-off score ≥8) (**n=20**) Diagnosis of PMR excluded using PET/CT Besançon-score (cut-off ≥3) (sum) (**n=12**) Diagnosis of PMR excluded using PET/CT Besançon-score (mean) (cut-off ≥0.53) (**n=9**) Diagnosis of PMR excluded using PET/CT Saint-Etienne algorithm (**n=8**) Diagnosis of PMR excluded using PET/CT Heidelberg algorithm (**n=19**)	Final diagnosis of PMR using clinical diagnosis after 6 months as reference standard (**n=39**)	Leuven-score (cut-off ≥16): **89.7/84.2** Leuven/Groningen-score (cut-off ≥8): **89.7/84.2** Besançon-score (sum) (cut-off ≥3): **100/63.2** Besançon-score (mean) (cut-off ≥0.53): **100/47.4** Saint-Etienne algorithm: **100/42.1** Heidelberg algorithm: **89.7/78.9**	Leuven-score (cut-off ≥16): **5.7/0.1** Leuven/Groningen-score (cut-off ≥8): **5.7/0.1** Besançon-score (sum) (cut-off ≥3): **2.7/0** Besançon-score (mean) (cut-off ≥0.53): **1.9/0** Saint-Etienne algorithm: **1.7/0** Heidelberg algorithm: **4.3/0.1**	Leuven-score (cut-off ≥16): **92.1/80.0** Leuven/Groningen-score (cut-off ≥8): **92.1/80.0** Besançon-score (sum) (cut-off ≥3): **84.8/100** Besançon-score (mean) (cut-off ≥0.53): **79.6/100** Saint-Etienne algorithm: **78.0/100** Heidelberg algorithm: **89.7/78.9**

Kobayashi et al.	Suspected PMR patients (**n=81**)	Diagnosis of PMR using ACR/EULAR criteria (**n=66**)	Diagnosis of PMR excluded using ACR/EULAR criteria (**n=15**)	Final diagnosis of PMR (diagnostic method not accounted for) (**n=60**)	**86.7/33.3**	**1.3/0.4**	**78.8/46.7**
Moreel et al.	Suspected PMR patients (**n=245)**	Diagnosis of PMR using PET/CT Leuven-score (cut-off score ≥16) (**n=150**) Diagnosis of PMR using PET/CT Leuven/Groningen-score (cut-off score ≥8) (**n=155**)	Diagnosis of PMR excluded using PET/CT Leuven-score (cut-off score ≥16) (**n=95**) Diagnosis of PMR excluded using PET/CT Leuven/Groningen-score (cut-off score ≥8) (**n=90**)	Final diagnosis of PMR using clinical diagnosis after 6 months as reference standard (**n=162**)	Leuven-score (cut-off ≥16): **91.4/97.6** Leuven/Groningen-score (cut-off ≥8): **93.2/95.2**	Leuven-score (cut-off ≥16): **37.9/0.1** Leuven/Groningen-score (cut-off ≥8): **19.3/0.1**	Leuven-score (cut-off ≥16): **98.7/85.3** Leuven/Groningen-score (cut-off ≥8): **97.4/87.8**

PICO 1b – Clinical utility for using different diagnostic strategies to diagnose PMR

Based on our search criteria and selection process, we were unable to find any studies that met the eligibility requirements for inclusion in our analysis.

PICO 2 – Clinical utility of screening for GCA in patients suspected of PMR

Based on our search criteria and selection process, we were unable to find any studies that met the eligibility requirements for inclusion in our analysis.

PICO 3a – Diagnostic accuracy of different diagnostic strategies for diagnosing GCA in patient suspected of PMR

	Patients	**Intervention**	**Controls**	**Outcome**	**Sens/spec**	**+LH/-LH**	**PPV/NPV**
Henckaerts et al.	Suspected PMR patients (**n=99**)	Patients with high-grade vascular uptake on PET/CT (**n=12**)	Patients without high vascular uptake on PET/CT (**n=87**)	Final diagnosis of GCA using TAB reference standard (**n=2**)	**100/89.7**	**9.7/0**	**16.7/100**

PICO 3b - Clinical utility for using different diagnostic strategies for diagnosing GCA in patients suspected of PMR

Based on our search criteria and selection process, we were unable to find any studies that met the eligibility requirements for inclusion in our analysis

PICO 4 – Clinical utility of shared care in treating PMR

Patients	**Intervention**	**Controls**	**Outcome**

Gabriel et al.	Diagnosed with PMR (**n=232**)	Patients treated in shared care: **N/A**	Patients treated in primary care alone: **N/A**	Patients that were assessed by a rheumatologist at PMR diagnosis were administered a **9.5 mg** lower initial prednisolone dose compared to standard treated patients (**p-value <0.001**)
Helliwell et al.	Diagnosed with PMR (**n=304**)	Patients treated in shared care (**n=135**)	Patients treated in primary care alone (**n=169**)	Osteoporosis prophylaxis (**n=183**). Significantly more where started on osteoporosis prophylaxis in shared care group but numbers not reported (**p-value <0.001**).

PICO 5 – Clinical utility of delaying glucocorticoid treatment until secondary care assessment in patients suspected of PMR

Based on our search criteria and selection process, we were unable to find any studies that met the eligibility requirements for inclusion in our analysis

PICO 6 – Clinical utility of fast track PMR clinics

	Patients	**Intervention**	**Controls**	**Outcome**
Frølund et al.	Suspected PMR patients (**n=210**)	Patients with PMR assessed in fast-track clinic (**n=83**)	Patient with PMR assessed according to standard care (**n=97**)	1. Diagnosis of PMR after 1 year, n (%): **80 (96%) in FTC vs 94 (97%) in historical cohort**. RR between groups: **1.17 (95% CI: 0.24-5.64)** 2. Time to PMR diagnosis, median days (IQR): **52 (31-83) in FTC vs 80 (58-132) in historical cohort**. Between group difference: **p-value <0.001** 3. Prednisolone starting dose (mg), median (IQR): **15 (15-15) in FTC vs 15 (15-20) in historical cohort**. Between group difference: **p-value <0.001** 4. Prednisolone prescription prior to rheumatologic assessment, n (%): **9** (**11%) in FTC vs 41 (42%) in historical cohort**. RR between groups: **0.26 (95% CI: 0.13-0.50)** Number of contacts with hospitals from referral to diagnosis, median (range): **0 (0-8) in FTC vs 1 (0-17) in historical cohort**. Between group difference: **p-value <0.001**
Chrysidis et al.	Suspected non-hospitalized PMR patients (**n=310**)	Patients with PMR assessed in fast-track clinic (**n=56**)	Patient with PMR assessed according to standard care (**n=254**)	1. Duration of symptoms before PMR diagnosis, mean weeks (SD): **6.8 (±0.7) in FTC vs 12.3 (±12.3) in historical cohort**. Between group difference: **p-value = 0.001** 2. Initial prednisolone dose (mg), mean (SD): **18.4 (±8.3) in FTC vs 19.2 (±9.25) in historical cohort**. Between group difference: **p-value = 0.55** 3. Patients hospitalized during the disease course, n (%): **2 (3.6%) in FTC vs 52 (20.5%) in historical cohort**. RR between groups: **0.20 (95% CI: 0.05-0.82)** 4. Inpatients days of care, mean days (SD): **1 (±0) in FTC vs 4.2 (±3.1) in historical cohort**. Between group difference: **p-value <0.001** Annual cost for patients assessed in fast-track clinic was reduced by **65%.** Between group difference: **N/A**

PMR: Polymyalgia Rheumatica. GCA: Giant Cell Arteritis. Sens/spec: Sensitivity/specificity. +LH/-LH: Positive and negative likelihood ratios. PPV/NPV: Positive and negative predictive values. PET/CT: Positron emission tomography and computed tomography. N/A: Not applicable. US: Ultrasound. SD: Standard deviation. RR: Relative risk. 95% CI: 95% confidence interval. IQR: Interquartile range. FTC: Fast track cohort. HC: Historical cohort.

Supplementary table S3 - Risk of Bias assessment of diagnostic accuracy studies in patients suspected of PMR

☺ Low risk of bias
☹ High risk of bias
? Unclear risk of bias

Risk of Bias assessment of diagnostic accuracy studies for diagnosing PMR

	RISK OF BIAS				APPLICABILITY CONCERNS		
Study	**PATIENT SELECTION**	**INDEX TEST**	**REFERENCE STANDARD**	**FLOW AND TIMING**	**PATIENT SELECTION**	**INDEX TEST**	**REFERENCE STANDARD**
Caporali et al.	☹	☺	☹	☹	☺	☺	☺
Falsetti et al.	☹	?	☹	☺	☹	?	☺
Ozen et al.	☹	☺	☹	☺	☹	☺	☺
Henckaerts et al.	☹	☺	☹	☺	☺	☹	☺
Horikoshi et al.	☹	☹	☹	?	☹	☺	?
Lee et al.	☹	☺	☹	☺	☺	☺	☺
Emamifar et al.	☹	☹	☺	☺	☹	☹	☺
Van der Geest et al.	☹	☺	☹	☺	☹	☹	☺
Kobayashi et al.	☹	☺	☹	☹	☹	☺	☹
Moreel et al.	☹	☺	☹	☺	☹	☹	☺

Risk of Bias assessment of diagnostic accuracy studies for diagnosing GCA

Study	**PATIENT SELECTION**	**INDEX TEST**	**REFERENCE STANDARD**	**FLOW AND TIMING**	**PATIENT SELECTION**	**INDEX TEST**	**REFERENCE STANDARD**
Henckaerts et al.	☹	☹	☹	☹	☺	☹	☺

Risk of bias assessment using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool

Supplementary table S4 - Risk of Bias in studies assessing utility of shared care and fast-track

☺ Low risk of bias
☹ High risk of bias
? Unclear risk of bias

	Gabriel et al.	Helliwell et al.	Frølund et al.	Chrysidis et al.
1 – Did the aim fit our research question?	☹	☹	☺	☺
2 – Were the study design appropriate?	☹	☹	☹	☹
3 – Was the sample size justified?	☹	☹	☹	☹
4 – Was the target/reference population defined?	☺	☺	☹	☹
5 – Was the sample frame appropriate?	☺	☹	☹	☹
6 – Was the selection process done appropriately?	☹	☹	☹	☹
7 - Categorization of non-responders	N/A	N/A	N/A	N/A
8 – Were outcome variables measured appropriately regarding our research question?	?	☺	☺	☺
9 – Were outcome variables measured using validated methods?	☺	☹	☺	☺
10 – Was it clear what was used to determine statistical significance and/or precision estimates?	☹	☺	☺	☺
11 – Were the methods sufficiently described?	☺	☹	☺	☺
12 – Was description of basic data sufficient?	☺	☹	☺	☺
13 - Non-response bias	N/A	N/A	N/A	N/A
14 - Information about non-responders	N/A	N/A	N/A	N/A
15 – Were the results internally consistence?	☺	☺	☺	☺
16 – Were results sufficiently presented for all included analyses?	☹	☹	☺	☺
17 – Were the discussion/conclusion of the included results justified?	☺	☺	☺	☺
18 – Were the limitations of the study discussed?	☺	☺	☺	☺
19 – Were there any funding/conflict of interest affecting interpretation of the results?	?	☺	☺	☺
20 – Was ethical approval/consent of participants attained?	?	☺	☺	☺

clinics

Risk of bias in cross-sectional studies using the Appraisal tool for Cross-Sectional Studies (AXIS)