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Original article

# Ultrasound of shoulder and knee improves the accuracy of the 2012 EULAR/ACR provisional classification criteria for polymyalgia rheumatica

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## Abstract

**Objective.** Recent studies suggest that the knee is frequently involved in PMR. In this study, we aimed to determine whether the US assessment of the shoulder and knee discriminates between PMR and other differential diagnoses and improves the accuracy of the 2012 EULAR/ACR provisional classification criteria for PMR.

**Methods.** We consecutively enrolled 81 untreated patients who received a diagnosis of PMR. These patients were divided into two groups based on the final diagnosis made at 1-year follow-up: PMR-definite group ($n = 60$) and PMR-mimic group ($n = 21$). We also enrolled age/sex-matched untreated RA patients with shoulder pain from an independent cohort (RA group, $n = 60$). All patients underwent comprehensive US assessment of the shoulder and knee for synovitis, bursitis, tenosynovitis, tendinitis and ligament inflammation at baseline.

**Results.** US scores for tenosynovitis, tendinitis and ligament inflammation better discriminated the PMR-definite group from the PMR-mimic and RA groups than do those for synovitis or bursitis. Among logistic regression models to identify US variables that were associated with the PMR-definite group, the best fitted model included two US variables: the bilateral involvement of the shoulder (long head of biceps, supraspinatus or subscapularis tendon) and the bilateral involvement of the knee (popliteus tendon or medial or lateral collateral ligament). Incorporating these two items into the 2012 EULAR/ACR provisional classification criteria numerically increased the accuracy to classify the PMR-definite group.

**Conclusion.** US assessment of the tendon/ligament-related lesions in the shoulder and knee may improve the accuracy of the 2012 EULAR/ACR provisional classification criteria for PMR.

**Key words:** polymyalgia rheumatica, ultrasound, classification criteria, tenosynovitis, tendinitis, ligament inflammation

CLINICAL SCIENCE

**Rheumatology key messages**

- US findings of the knee discriminated between PMR and the other diseases.
- US findings of the tendon and ligament were sensitive and specific to PMR.
- These US findings increased the accuracy of the 2012 EULAR/ACR classification criteria for PMR.

## Introduction

PMR is an inflammatory rheumatic condition that presents in an acute to subacute manner, particularly in elderly individuals, characterized by aching and morning stiffness in the shoulders, hip girdle and neck [1, 2]. The diagnosis of PMR can be challenging because the pathogenesis of PMR remains largely unknown and there are no specific serologic or imaging biomarkers.

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In 2012, the provisional classification criteria for PMR by the EULAR/ACR initiative was published [3–5]. In the process of their development, candidate criteria were determined by a systematic literature review, expert opinions and larger international surveys. These candidate items were then selected and validated using data from a prospective cohort of patients with PMR and conditions that mimic PMR. The final criteria require age ≥50 years, bilateral shoulder pain, and abnormal CRP and/or ESR, and the scoring part includes four clinical and laboratory items.

In the 2012 EULAR/ACR criteria, US findings were incorporated into the criteria for the first time as an option to improve their accuracy. However, the addition of US items did not substantially improve the diagnostic performance of the criteria. The reasons for the limited benefit of adding US may be that the US assessment was limited to the shoulder and the hip, that the threshold of severity for US abnormalities was not clearly defined and/or that Doppler assessment was not included [4, 5].

Since the development of the 2012 EULAR/ACR criteria, the imaging research on the pathophysiology of PMR has substantially advanced [6–13]. In particular, frequent involvement of the knee has been reported using MRI and PET/CT [7, 8]. Moreover, not only bursitis, synovitis and tenosynovitis but also tendon and muscle lesions have been suggested to be characteristic to PMR [9–14].

In contrast, the limited sensitivity of US to detect abnormalities in the hip has been reported in a recent study that compared US with MRI in PMR [15]. This can be explained by the limited acoustic window and sensitivity to detect Doppler signals in the hip due to its deep location [15–17]. Moreover, US assessment of the hip can be time-consuming and is not always comfortable for either patients or physicians in daily practice. These points can be a hurdle to the hip being assessed and for the US option of the 2012 EULAR/ACR criteria to be utilized in the real world.

We hypothesized that the examination of the knee with both greyscale and Doppler US for the pathologies beyond bursitis and synovitis would increase the accuracy of PMR classification and obviate the need for the hip assessment. To address this hypothesis, we compared the US findings of the shoulder and knee between PMR, PMR-mimic and RA patients from prospective cohorts and evaluated the additional benefit of US in the 2012 EULAR/ACR classification criteria for PMR.

## Methods

### Patients

Patients who received a diagnosis of PMR were consecutively recruited in this study at University of Yamanashi Hospital from January 2017 to December 2019. Patients had to be aged ≥50 years and have bilateral shoulder ache, elevated CRP level and/or increased ESR, but the diagnosis was clinically made by the rheumatologist. Patients who had received glucocorticoids or anti-rheumatic/immunosuppresive drugs were excluded. These patients were divided into two groups based on the final diagnosis made by three rheumatologists at 1-year follow-up: PMR-definite and PMR-mimic groups. We also identified untreated RA patients who fulfilled the criteria above (i.e. ≥50 years old, bilateral shoulder ache, elevated CRP/increased ESR) and were age- and sex-matched to the PMR group from an independent, prospective RA cohort (RA group). The diagnosis of RA was made based on the 2010 EULAR/ACR classification criteria [18].

### Clinical assessment

At baseline, we collected information on demographics and clinical items included in the 2012 EULAR/ACR classification criteria [4, 5]. We assessed ESR, the levels of CRP and MMP-3 [19] and the positivity of RF and ACPA. We recorded treatments given for PMR or RA and determined the treatment response and the achievement of remission using the PMR activity score [20].

### US assessment

We performed US examination at baseline in all patients and at the time of remission in those who achieved remission within 1 year. US was performed by two rheumatologists (K.Kobayashi and D.N.), who were trained sonographers certified by Japan College of Rheumatology. Clinical and US assessments of a patient were performed by different individuals who were blinded to each other's information. We used a HITACHI ARIETTA 60 and an L64 multifrequency superficial linear probe (18–5 MHz) (Hitachi Medical Corporation, Tokyo, Japan; the ARIETTA was manufactured in 2017) for US assessment. We always used the same machine with a standardized Doppler setting: pulse repetition frequency 800 Hz, Doppler frequency 7.81 MHz, colour gain 150.

We scanned the bilateral shoulders and knees. For the shoulder, we scanned the long head of biceps tendon (LHBT), subacromial/subdeltoid bursa (SASDB), supraspinatus tendon (SSpT), subscapularis tendon (SScT) and glenohumeral joint (GHJ). For the knee, we scanned the suprapatellar bursa (SPB), medial aspect of knee joint (MKJ), lateral aspect of knee joint (LKJ), medial collateral ligament (MCL), lateral collateral ligament (LCL) and popliteus tendon (PopT) [21–23].

We evaluated the images for synovitis, bursitis, tenosynovitis, tendinitis and ligament inflammation. For synovitis and tenosynovitis, we semiquantitatively graded greyscale abnormality (GS score) and abnormal power Doppler signals (power Doppler score) on a scale of 0–3 as previously reported [24–29]. For bursitis, we subjectively evaluated the GS score as follows: 0, normal; 1, mild synovial thickening or effusion; 2, moderate synovial thickening or effusion; 3, marked synovial thickening or effusion. For bursitis, tendinitis and ligament

inflammation, we graded the power Doppler signals within the synovial thickening, tendon and ligament as follows: 0, none; 1, punctate signals in one to three sites; 2, focal signals in four or more sites; 3, diffuse signals) (supplementary Figs S1–S8, available at *Rheumatology* online). We did not grade GS abnormalities for tendinitis and ligament inflammation in this study in order to focus on the features that represent acute inflammation caused by PMR.

Patients in the independent RA cohort underwent comprehensive US evaluation including all the assessments mentioned above.

### Statistical analyses

We performed statistical analyses using the SPSS software, version 22.0 J (IBM Japan, Tokyo, Japan). Normally distributed continuous data were summarized using mean (S.D.) and were analysed using parametric tests (Student's *t*-test). Non-normally distributed data were summarized using the median and interquartile range and were analysed using non-parametric tests (Mann–Whitney *U* test). Categorical data were summarized with percentages and were analysed using the $\chi^2$, Fisher's exact or McNemar's tests. Multiple regression models were constructed using a forced entry method. Two-sided *P*-values $<0.05$ were considered statistically significant.

### Ethics

This study was approved by the ethics committee of the University of Yamanashi (reference number: 1928). All subjects enrolled provided written informed consent according to the declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.

## Results

### Patient characteristics

Eighty-one patients with an initial diagnosis of PMR were enrolled in this study. Of these, 60 patients received a final diagnosis of PMR at 1 year (PMR-definite group), whereas 21 patients received a different diagnosis (PMR-mimic group). The major final diagnoses in the PMR-mimic group were RA ($n=6$), AS ($n=1$), PsA ($n=3$), OA ($n=3$), undifferentiated arthritis ($n=7$) and tendon rupture ($n=1$). Sixty matched RA patients were identified from an independent cohort (RA group).

Patient demographics, clinical, laboratory and treatment data at baseline are shown in Table 1. In the PMR-definite and the age/sex-matched RA groups, mean age was 74 years and 58% were women. Patients in the PMR-mimic group were younger than those in the others. Mean CRP level was the highest in the PMR-definite group (PMR-definite, PMR-mimic and RA: 6.52, 1.26 and 2.97 mg/dl, respectively; $P<0.001$). Similarly, median ESR was the highest in the PMR group (PMR-definite, PMR-mimic and RA: 90, 31 and 32 mm/h, respectively; $P=0.01$).

Among the clinical items in the 2012 EULAR/ACR classification criteria, 'morning stiffness duration >45 min', 'hip pain or limited range of motion' and 'absence of other joint pain' were most frequently present in the PMR-definite group. Without US, 87% of the patients in the PMR group, 67% in the PMR-mimic group and 20% in the RA group were classified as PMR based on the 2012 EULAR/ACR classification criteria.

### Treatment and response

All patients in the PMR group received glucocorticoids. The initial dose of glucocorticoids was also the highest in the PMR group (PMR-definite, PMR-mimic and RA: 15.0, 0 and 0 mg/day, respectively; $P<0.0001$). On the other hand, the highest proportion of patients received any DMARDs in the RA group. All patients in the PMR-definite group achieved remission in a median of 1 month, whereas 15 (71%) of those in the PMR-mimic group did in a median of 4 months.

### US finding and definition of abnormal score

The baseline US findings at each joint region are summarized in Fig. 1. GS scores for the LHBT, SASDB, SPB and PopT were most frequently positive in the PMR-definite group (Fig. 1A). The positivity was particularly high for tenosynovitis (LHBT and PopT) and the difference between the PMR-definite and RA groups was also larger for tenosynovitis than for bursitis (SASDB, SPB) (Fig. 1A). In contrast, GS scores for synovitis (GHJ, MKJ and LKJ) were most frequently positive in the RA group and were all negative in the PMR-definite group (Fig. 1A). These positivity and differences in joint regions were similar for power Doppler scores (Fig. 1B). Power Doppler scores for the tendons/ligaments (SSpT, SScT, MCL, LCL), which were not assessed with GS scores, were most frequently positive in the PMR-definite group (Fig. 1B). These data indicate that US scores for tenosynovitis (LHBT, PopT), tendinitis (SSpT, SScT) and ligament inflammation (MCL, LCL) better discriminate between PMR-definite, PMR-mimic and RA than do those for synovitis (GHJ, MKJ, LKJ) or bursitis (SASDB, SPB); therefore, we exclusively assessed tenosynovitis, tendinitis and ligament inflammation in the subsequent analyses.

We next focused on the differences between grades (0–3) of US scores to determine the optimal cut-offs. GS score $\geq$1 for LHBT and PopT was likely to be less specific to PMR-definite than GS score $\geq$2 (Fig. 1A). On the other hand, power Doppler score $\geq$1 for SSpT and SScT seemed to provide additional sensitivity and specificity for the discrimination (Fig. 1B). Given these data and to keep consistency with the previous definition for RA [27], we defined the cut-off for abnormal US scores for tenosynovitis (LHBT, PopT) as GS score $\geq$2 or power Doppler score $\geq$1, and that for tendinitis

TABLE 1 Patient demographics and clinical and laboratory data at baseline, and comparison between patients in the PMR-definite, PMR-mimic and RA groups

| | PMR-definite | PMR-mimic | RA | *P*-value | |
|---|---|---|---|---|---|
| | *n* = 60 | *n* = 21 | *n* = 60 | *vs* PMR-mimic | *vs* RA |
| Demographics and laboratory data | | | | | |
| Age, mean (S.D.), years | 74 (8.1) | 53 (27.1) | 74 (8.1) | <0.0001[a] | 1[a] |
| Female, *n* (%) | 35 (58) | 12 (57) | 35 (58) | 0.924[b] | 1[b] |
| CRP level, mean (S.D.), mg/dl | 6.52 (4.51) | 1.26 (2.02) | 2.97 (3.58) | <0.0001[a] | <0.0001[a] |
| ESR, median (IQR), mm/h | 90 (70–102) | 31 (20–54) | 32 (17–86) | 0.006[c] | <0.0001[c] |
| MMP-3, median (IQR), ng/ml | 185 (119–432) | 94 (30–152) | 72 (72–370) | 0.001[c] | 0.084[c] |
| 2012 EULAR/ACR classification criteria | | | | | |
| Morning stiffness duration >45 min, *n* (%) | 57 (95) | 14 (67) | 23 (38) | 0.002[b] | <0.0001[b] |
| Hip pain or limited range of motion, *n* (%) | 29 (48) | 4 (19) | 14 (23) | 0.019[b] | 0.004[b] |
| Absence of RF or ACPA, *n* (%) | 57 (95) | 21 (100) | 22 (37) | 0.401[b] | <0.0001[b] |
| Absence of other joint pain, *n* (%) | 40 (67) | 1 (5) | 0 (0) | <0.0001[b] | <0.0001[b] |
| Fulfilment of 4 or more criteria, *n* (%) | 52 (87) | 14 (67) | 12 (20) | 0.048[b] | <0.0001[b] |
| Treatment for PMR or RA | | | | | |
| Glucocorticoids ever, *n* (%) | 60 (100) | 10 (48) | 27 (45) | <0.0001[b] | <0.0001[b] |
| Initial dose of glucocorticoids, median (IQR) [range], mg/day (prednisolone equivalent) | 15 (10–15) [5–40] | 0 (0–5) [0–10] | 0 (0–10) [0–20] | <0.0001[c] | <0.0001[c] |
| Any DMARDS ever, *n* (%) | 20 (33) | 14 (67) | 57 (95) | 0.008[b] | <0.0001[b] |
| csDMARDS ever, *n* (%) | 15 (25) | 7 (33) | 41 (68) | 0.46[b] | <0.0001[b] |
| MTX ever, *n* (%) | 9 (15) | 11 (52) | 48 (80) | 0.001[b] | <0.0001[b] |
| bDMARDS ever, *n* (%) | 4 (7) | 3 (14) | 25 (42) | 0.257[b] | <0.0001[b] |
| tsDMARDS ever, *n* (%) | 1 (2) | 0 (0) | 0 (0) | 0.741[b] | 0.5[b] |

[a]*t*-test. [b]$\chi^2$ test, or Fisher's exact test with Bonferroni correction. [c]Mann–Whitney *U* test. IQR: interquartile range; csDMARD: conventional synthetic DMARD; bDMARD: biological DMARD; tsDMARD: targeted synthetic DMARD. *P*-values were calculated for the difference between PMR-definite *vs* PMR-mimic or RA.

(SSpT, SScT) and ligament inflammation (MCL, LCL) as power Doppler score ≥1.

### Identification of significant US component and combination

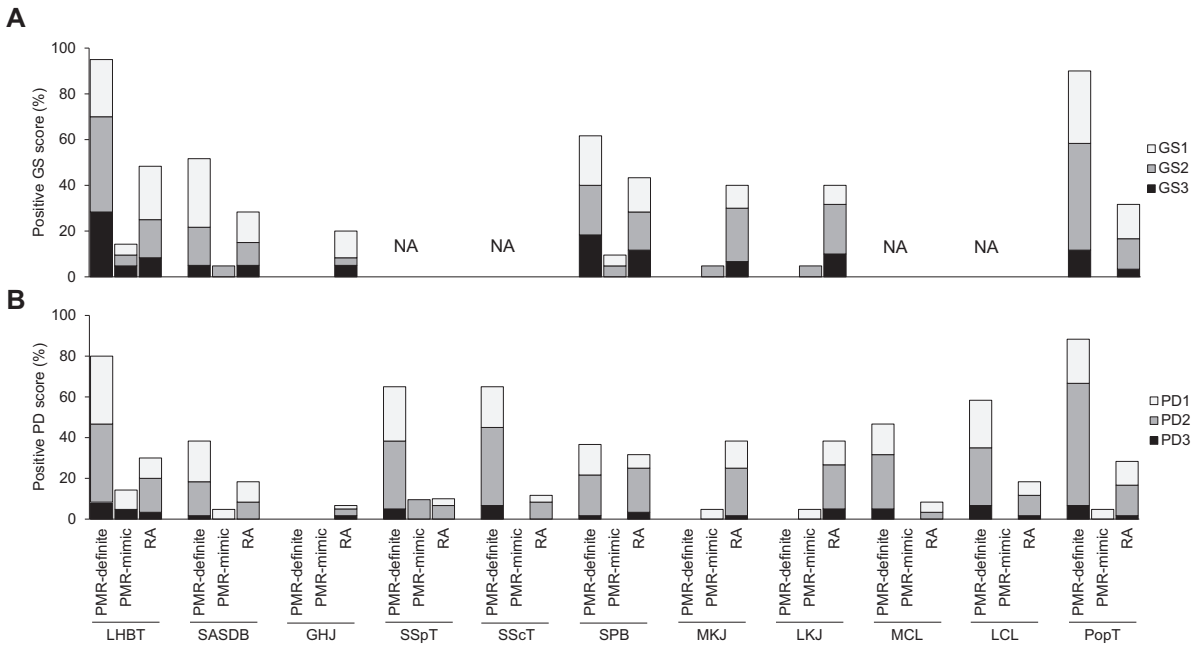
Next, we compared the prevalence of abnormal scores (GS score ≥2 or power Doppler score ≥1) for tenosynovitis, tendinitis and ligament inflammation in the PMR-definite group with the other two groups. We calculated the prevalence for each component and combinations and also for whether the bilaterality is required or not (Table 2). The prevalence of tenosynovitis, tendinitis, ligament inflammation and any of their combinations with or without bilaterality was significantly higher in the PMR-definite group than that in the PMR-mimic group or in the RA group.

We performed logistic regression analyses with belonging to the PMR-definite group as the dependent variable and all US components or combinations (Table 2) as the independent variables to identify independent US factors that contribute to the diagnosis of the definite PMR. As a result, a model with two factors best fitted the data (Cox & Snell's $R^2$ 0.495). These factors are the bilateral shoulder involvement (LHBT, SSpT, SScT) and the bilateral knee involvement (MCL, LCL, PopT) (supplementary Table S1, available at *Rheumatology* online). In our definition, 'bilateral involvement' did not require the involvement of the same component. For example, the combination of an abnormal LHBT in the right shoulder and an abnormal left SScT on the left shoulder was considered 'bilateral shoulder involvement'.

### Improved accuracy of 2012 EULAR/ACR classification criteria

Finally, we replaced the original US items in the 2012 EULAR/ACR classification criteria [4, 5] with the two US items newly identified in our regression model (shoulder-knee US criteria) (Table 3). Given the similar odds ratios for these US items in our regression model, and to keep consistency with the original criteria, we gave one point to each US item. Using a total of 141 patients in our study, the area under the curve of receiver operator characteristic analysis to classify patients in the PMR-definite group were 0.876 (95% CI 0.820, 0.933) for the 2012 EULAR/ACR criteria without US and 0.942 (95% CI 0.905, 0.979) for the shoulder-knee US criteria, respectively (Fig. 2, Table 4).

FIG. 1 Prevalence of positive US scores at each joint site in PMR-definite, PMR-mimic and RA patients




Shown are the frequencies of positive GS scores (**A**) and power Doppler scores (**B**) at each joint site in patients in the PMR-definite, PMR-mimic and RA groups. GS score: greyscale score; PD score: power Doppler score; NA: not applicable; LHBT: long head of biceps tendon; SASDB: subacromial/subdeltoid bursa; GHJ: glenohumeral joint; SScT: subscapularis tendon; SSpT: supraspinatus tendon; SPB: suprapatellar bursa; MKJ: medial aspect of knee joint; LKJ: lateral aspect of knee joint; MCL: medial collateral ligament; LCL: lateral collateral ligament; PopT: popliteus tendon.

The receiver operator characteristic analysis provided the optimal cut-point of 4 for the 2012 EULAR/ACR criteria without US and 5 for the shoulder-knee US criteria. Using these cut-points, the shoulder-knee criteria provided numerically higher sensitivity (90% *vs* 87%), specificity (83% *vs* 68%), positive predictive value (79% *vs* 67%) and negative predictive value (92% *vs* 87%) compared with the 2012 EULAR/ACR criteria without US (Table 4).

### Change in US score after treatment

Forty patients in the PMR-definite group underwent second US assessment within 1 month after achieving remission. All GS and power Doppler scores markedly decreased with statistical significance (supplementary Fig. S9, available at *Rheumatology* online).

## Discussion

In this study, we comprehensively performed US on the shoulder and the knee in patients with definite PMR, those with clinical manifestations that mimicked PMR and age/sex-matched patients with RA with shoulder pain and elevated CRP/ESR. We identified US features that are independently associated with the definite PMR diagnosis and demonstrated that the presence of US tenosynovitis, tendinitis and ligament inflammation in the shoulder and the knee numerically increases the accuracy of the 2012 EULAR/ACR classification criteria for PMR. To our knowledge, this is the first study to assess the value of US of both shoulder and knee in the diagnosis of PMR using a prospective cohort.

Our data revealed that not only the shoulder but also the knee is the joint where US abnormalities are frequently detected (Fig. 1). Collectively, 95% of patients with definite PMR had some US abnormalities in the knee, whereas 77% and 10% had tenderness and swelling, respectively (data not shown). This prevalence of knee involvement detected by US was even higher than those previously reported with PET/CT (84%) and PET/CT/MRI (76%) [7, 8]. The previous US studies that showed a lower frequency of knee involvement were different from ours in that they mostly focused on synovitis or bursitis, and did not assess the popliteus tendon or collateral ligaments [30, 31]. These data indicate that knee is frequently involved in PMR and that US is a sensitive, inexpensive tool to detect various types of inflammation in this joint.

Our data also revealed that tendon- and ligament-related lesions are more specific to PMR than are synovium- or bursa-related lesions. Indeed, synovitis in glenohumeral and knee joints was infrequent in patients with PMR in our study (Fig. 1). Although subacromial/subdeltoid bursitis were frequently identified in PMR as previously reported, they were also prevalent in age/sex-matched RA with shoulder symptoms and elevated

**Table 2** Prevalence of baseline abnormal US findings for tenosynovitis, tendinitis and ligament inflammation in PMR-definite, PMR-mimic and RA groups

| | Present either unilaterally or bilaterally | | | | | Present bilaterally | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | PMR-definite | PMR-mimic | RA | *P*-value | | PMR-definite | PMR-mimic | RA | *P*-value | |
| | | | | *vs* PMR-mimic | *vs* RA | | | | *vs* PMR-mimic | *vs* RA |
| Shoulder component, *n* (%) | | | | | | | | | | |
| LHBT | 53 (88) | 3 (14) | 22 (37) | <0.001 | <0.001 | 42 (70) | 1 (5) | 10 (17) | <0.001 | <0.001 |
| SScT | 39 (65) | 0 (0) | 7 (12) | <0.001 | <0.001 | 18 (30) | 0 (0) | 1 (2) | 0.002 | <0.001 |
| SSpT | 39 (65) | 2 (10) | 6 (10) | <0.001 | <0.001 | 20 (33) | 0 (0) | 3 (5) | 0.002 | <0.001 |
| Shoulder combination, *n* (%) | | | | | | | | | | |
| Tendinitis (SScT and/or SSpT) | 50 (83) | 2 (10) | 12 (20) | <0.001 | <0.001 | 28 (47) | 0 (0) | 4 (7) | <0.001 | <0.001 |
| Any (LHBT, SScT and/or SSpT) | 58 (97) | 5 (24) | 27 (45) | <0.001 | <0.001 | 50 (83) | 1 (5) | 11 (18) | <0.001 | <0.001 |
| Knee component, *n* (%) | | | | | | | | | | |
| MCL | 29 (48) | 0 (0) | 5 (8) | <0.001 | <0.001 | 18 (30) | 0 (0) | 1 (2) | 0.002 | <0.001 |
| LCL | 35 (58) | 0 (0) | 11 (18) | <0.001 | <0.001 | 19 (32) | 0 (0) | 6 (10) | 0.001 | 0.003 |
| PopT | 53 (88) | 1 (5) | 19 (32) | <0.001 | <0.001 | 40 (67) | 0 (0) | 10 (17) | <0.001 | <0.001 |
| Knee combination, *n* (%) | | | | | | | | | | |
| Ligament (MCL and/or LCL) | 42 (70) | 0 (0) | 13 (22) | <0.001 | <0.001 | 28 (47) | 0 (0) | 6 (10) | <0.001 | <0.001 |
| Any (MCL, LCL and/or PopT) | 54 (90) | 1 (5) | 23 (38) | <0.001 | <0.001 | 47 (78) | 0 (0) | 11 (18) | <0.001 | <0.001 |
| All combinations, *n* (%) | | | | | | | | | | |
| Any shoulder (LHBT, SScT, SSpT) or any knee (MCL, LCL, PopT) | 58 (97) | 6 (29) | 36 (60) | <0.001 | <0.001 | 57 (95) | 1 (5) | 18 (30) | <0.001 | <0.001 |
| Any shoulder (LHBT, SScT, SSpT) and any knee (MCL, LCL, PopT) | 54 (90) | 0 | 14 (23) | <0.001 | <0.001 | 40 (67) | 0 (0) | 4 (7) | <0.001 | <0.001 |

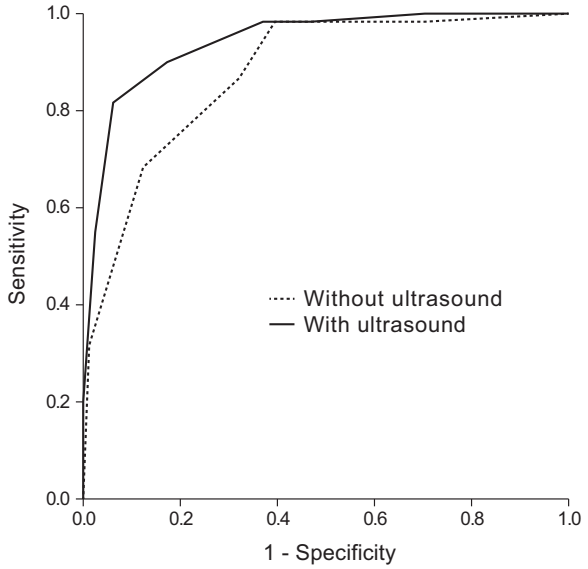
*P*-values were calculated by $\chi^2$ test or Fisher's exact test for the difference between PMR-definite *vs* PMR-mimic or RA with Bonferroni correction. LHBT: long head of biceps tendon; SScT: subscapularis tendon; SSpT: supraspinatus tendon; MCL: medial collateral ligament; LCL: lateral collateral ligament; PopT: popliteus tendon.

TABLE 3 Modified classification criteria for PMR incorporating US findings in shoulder and knee

| Criteria | 2012 ACR/EULAR clinical classification criteria without US[a] | 2012 ACR/EULAR classification criteria including shoulder and knee US[b] |
|---|---|---|
| Morning stiffness duration >45 min | 2 | 2 |
| Hip pain or limited range of motion | 1 | 1 |
| Absence of RF or ACPA | 2 | 2 |
| Absence of other joint involvement | 1 | 1 |
| Bilateral shoulder involvement (biceps tenosynovitis[c], supraspinatus or subscapularis tendinitis[d] in each shoulder) | | 1 |
| Bilateral knee involvement (popliteus tenosynovitis[c], medial or lateral collateral ligament inflammation[d] in each knee) | | 1 |

[a]The optimal cut point is 4. A patient with a score of ≥4 is categorized as having PMR. [b]The optimal cut point is 5. A patient with a score of ≥5 is categorized as having PMR. [c]Moderate or severe greyscale tenosynovitis and/or any tenosynovial Doppler signals. [d]Any Doppler signals in the tendon or ligament.

FIG. 2 Receiver operator characteristic curves for the 2012 EULAR/ACR criteria without and with shoulder-knee US to classify patients in PMR-definite group




ESR/CRP. Instead, tenosynovitis of LHBT and PopT, tendinitis of SSpT and SScT, and inflammation of medial and lateral collateral ligaments in the knee were more specific to PMR (Fig. 1) and contributed to the improved accuracy of classification (Tables 3 and 4, Fig. 2). There has been only one report on the histopathological findings in PMR [32], which showed inflammation in biopsied tissues from bursa, deep fascia and deltoid muscle. However, recently accumulated evidence with imaging indicates that 'musculotendinous' inflammation plays an important role in the pathophysiology of PMR [9–14, 19, 33–35]. Our data are consistent with this view and further support it.

Of note, the tenosynovitis of LHBT and that of PopT are the two most frequently detected US lesions and 85% of patients had both in the PMR-definite group. This frequent coexistence of spatially distant lesions may be related to the anatomical similarities between LHBT and PopT. Both tendons have a surrounding synovial sheath that directly connects to the articular synovium, reducing the friction [21, 36–41]. Our data and this anatomical resemblance may add to the musculotendinous hypothesis and could be a clue to further understanding of the pathogenesis of PMR.

Given the sample size, our data on the responsiveness of US scores to treatment are inconclusive. Nevertheless, our data demonstrate that US scores can be very responsive to treatment in patients with PMR who achieve remission (supplementary Fig. S9, available at *Rheumatology* online). US scores markedly decreased not only in the shoulder but also in the knee, including PopT. These data indicate the inflammatory nature of these US elements and further support the importance of assessing the knee in PMR.

In the 2012 EULAR/ACR classification criteria dataset, the additional benefit of US in the classification performance was not substantial [4, 5]. In their dataset, the sensitivity without and with US were 68% and 66%; the specificity without and with US were 78% and 81%. In our study, the sensitivity without and with US were 87% and 90%; the specificity without and with US were 68% and 83% (Table 4). Although direct comparison is inappropriate and fewer sonographers in a single institute might have an advantage in standardized scanning, these data indicate that the US of the shoulder and knee would add a benefit that is at least equivalent to that added by the shoulder and hip in the classification of PMR. This also suggests that the US assessment of the hip, which is not a patient- or physician-friendly joint to scan, can be replaced by that of the knee in daily practice.

The current study has some limitations. First, this is a single-centre study in Japan and the results may not be

TABLE 4 Accuracy of classification criteria for diagnosis of PMR with shoulder and knee US

| | 2012 ACR/EULAR clinical classification criteria without US | 2012 ACR/EULAR classification criteria with shoulder and knee US |
|---|---|---|
| Area under the ROC curve (95% CI) | 0.876 (0.820, 0.933) | 0.942 (0.905, 0.979) |
| Sensitivity, % (95% CI) | 87 (79, 96) | 90 (82, 98) |
| Specificity, % (95% CI) | 68 (58, 78) | 83 (75, 91) |
| Positive predictive value, % (95% CI) | 67 (57, 77) | 79 (74, 84) |
| Negative predictive value, % (95% CI) | 87 (79, 95) | 92 (86, 98) |

ROC: receiver operating characteristic.

generalizable to other countries. Second, the sample size was limited and we could not show the statistical significance. The sample size was especially small for the PMR-mimic group; however, patients in the PMR-mimic group were those who were tentatively diagnosed as having PMR that later turned out to be different diseases in prospective observation. This control group is more likely to reflect conditions to be differentiated in real-world than the control groups with pre-determined conditions in previous reports. Third, the lack of the hip assessment in our study made the direct comparisons between knee and hip and between studies more difficult. A study including the shoulder, hip and knee needs to be done to confirm our hypothesis. Fourth, GS abnormalities for tendon and ligament were not evaluated and their roles in PMR classification and the association with power Doppler signals remain unknown. In addition, our Doppler-dependent US evaluation could be influenced by the US equipment.

Nevertheless, our data highlight the importance of assessing the knee and the tendon/ligament-related lesions in PMR. Moreover, our study suggests an alternative US option to improve the accuracy of PMR classification without scanning the hip, which would merit further validation in a larger scale.

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## Data availability statement

Most of the data underlying this article are available in the article and in its online supplementary material.

## Supplementary data

Supplementary data are available at *Rheumatology* online.

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