Ultrasound imaging for the rheumatologist XLIII. Ultrasonographic evaluation of shoulders and hips in patients with polymyalgia rheumatica: a systematic literature review

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ABSTRACT

Objective. *Musculoskeletal ultrasonography (US) has lately been applied to patients with polymyalgia rheumatica for the examination of shoulders and hip, and included in the 2012 PMR classification criteria. We aimed to perform a comprehensive overview of the literature on this topic with a systematic review.*

Methods. *We searched PubMed, Embase, the Cochrane library and the proceedings from EULAR and ACR congresses (2011–2012). We included studies evaluating patients with confirmed or suspected PMR, undergoing US of shoulders and/or hips. The diagnosis of PMR could be based on expert opinion or diagnostic criteria. Cohort, case-control, diagnostic accuracy studies and case-series were eligible for inclusion. The features of the included studies were presented. When available, sensitivities and specificities were calculated for primary studies.*

Results. *Out of 1736 papers identified by our search, 13 articles and 1 abstract were finally included in the review. Eight studies focused on shoulder US, 1 on hip US, 4 on both. Studies were extremely variable in terms of population, US examination, reference standard and control population. In general, at the shoulder, pathological bilateral US findings in most studies were more prevalent in patients with PMR compared to controls. When sensitivity and specificity could be calculated, bilateral findings were more sensitive. Notably, less information was available on hip US.*

Conclusion. *US (especially in shoulder examination) is confirmed to be a potentially useful instrument to integrate clinical information in the management of patients with PMR. Its additional value in conjunction with the new classification criteria should be further tested.*

Introduction

Polymyalgia rheumatica (PMR) is a relatively frequent inflammatory disease (1) involving elderly patients that determines inflammatory pain at scapular and pelvic girdles (2). The disease has a characteristic clinical presentation, however, diagnosis is not always straightforward at the first evaluation, with elderly-onset rheumatoid arthritis (EORA) representing the most difficult differential diagnosis (3), but also with possible secondary forms (4). Several markers (5-7) have been proposed for differential diagnosis, without satisfactory results, and this has remained an unresolved issue.

In fact, a single reliable reference standard for the diagnosis of PMR has not been found, and often a definite diagnosis can emerge only after a period of follow-up, also evaluating the response to corticosteroids (8-10).

Due to the subsequent difficulties in including patients in clinical trials, in 2012 the ACR and EULAR proposed new classification criteria for PMR (11, 12). The new criteria were developed based on expert opinion, but they were afterwards tested in an observational study performed *ad hoc*. Patients were included if they presented with new onset bilateral shoulder pain, they were over 50 years old and they had not been previously treated with corticosteroids; the diagnosis of PMR had to be confirmed by the physician. Patients were

treated according to a standardised corticosteroid-based therapeutic protocol. The prospective study also included a control population of patients without PMR but with similar presentation. Patients were followed for 26 weeks and at each visit the response to corticosteroids was evaluated.

In the last decade musculoskeletal ultrasonography (US) has been increasingly used in rheumatology (13-17), and several studies have tested its value also in cohorts of PMR patients, focusing in particular on hip and shoulder assessment (18-20). US has been used for both diagnostic purposes and follow-up (21).

For this reason, patients enrolled in the observational study for the development of the criteria underwent shoulder and hip US. All the examined US abnormalities were helpful to distinguish between patients with PMR and controls without rheumatoid arthritis (RA), while only the involvement of at least one shoulder and one hip was taken to be a distinction between PMR and RA (9).

US was finally included in the criteria therefore included in the final set of classification criteria; the criteria can be applied using only clinical features, however, the addition of US slightly improves their performance.

Recently, a systematic review on the application of all imaging modalities in PMR has been published (22). This review also took into account US, but was not specifically focused on that and the search was last carried in 2010, before the presentation of the new criteria.

We wanted therefore to perform a systematic literature search specifically focused on shoulder and hip US in PMR, evaluating the prevalence of US abnormalities in patients with PMR and their diagnostic value. We also aimed to evaluate the usefulness of US for the follow-up of PMR patients.

Methods

A search strategy based on terms related to PMR, EORA and US was developed. The search was meant to be quite broad, in order to be as sensitive rather than specific (Table I). We searched MEDLINE (PubMed), Embase and Cochrane Central, the search was last carried out on October 9th 2012. Furthermore, we manually screened the proceedings from the ACR and EULAR congresses (2011–2012) and the references of the included studies to look for additional studies. The search was limited to humans, but no language or publication restrictions were applied. Data were extracted using a standardised form. The risk of bias of the studies was evaluated by the Newcastle-Ottawa scale for case-control or observational studies, when appropriate (23).

Table I. Search strategy.

PubMed	#1"Ultrasonography"[Mesh] #2 "ultrasonography" #3 "ultrasonograph*" #4 "ultrasound" #5 #1 OR #2 OR #3 OR #4 #6 "Polymyalgia Rheumatica"[Mesh] #7 "polymyalgia" #8 "polymyalgia rheumatica" #9 "polymyalg*" #10 #6 OR #7 OR #8 OR #9 #11 "Arthritis, Rheumatoid"[Mesh] #12 "Arthritis, Rheumatoid"[Mesh] #13 "rheumatoid" #14 #11 OR #12 OR #13 #15 "Aged, 80 and over"[Mesh] #16 "Middle Aged"[Mesh] #17 #15 OR #16 #18 #14 AND #17 #19 #10 AND #18
Embase	1'polymyalgia rheumatica'/de OR 'polymyalgia rheumatica' OR 'polymyalgia' OR 'polymyalgic' AND [embase]/lim 2'rheumatoid arthritis'/exp OR 'rheumatiod arthritis' OR 'rheumatoid' AND [embase]/lim 3'middle aged'/exp OR 'aged'/exp 4 AND/2-3 5 OR/1-4 6 'echography'/exp OR 'ecography' OR 'ultrasonography' OR 'ultrasound' OR 'ultrasonographic' 7 AND/5-6
Cochrane	#1 MeSH descriptor: [Ultrasonography] this term only #2 "ultrasonography":ti,ab,kw #3 "ultrasound":ti,ab,kw #4 ultrasonograph*:ti,ab,kw #5 #1 or #2 or #3 or #4 #6 MeSH descriptor: [Arthritis, Rheumatoid] this term only #7 rheumatoid arthritis":ti,ab,kw #8 "rheumatoid" #9 MeSH descriptor: [Aged] this term only #10 AGED, 80 and OVER:ti,ab,kw #11 #9 or #10 #12 #6 or #7 or #8 #13 #11 and #12 #14 MeSH descriptor: [Polymyalgia Rheumatica] this term only #15 "polymyalgia rheumatica":ti,ab,kw #16 polymyalg*:ti,ab,kw #17 "polymyalgia":ti,ab,kw #18 #14 or #15 or # 16 or #17 #19 #18 or #13 #20 #5 and #19

The target population was patients with a diagnosis or suspicion of PMR; the index test was US of the shoulders and/or of the hips. To test diagnostic accuracy, the pre-specified reference standards were expert opinion, definite diagnostic/classificative criteria or response to glucocorticoids (24); diagnostic accuracy, retrospective or prospective cohort studies, case-control studies and case series were eligible for inclusion. When available, data on diagnostic accuracy were extracted in 2x2 tables to estimate sensitivity and specificity of

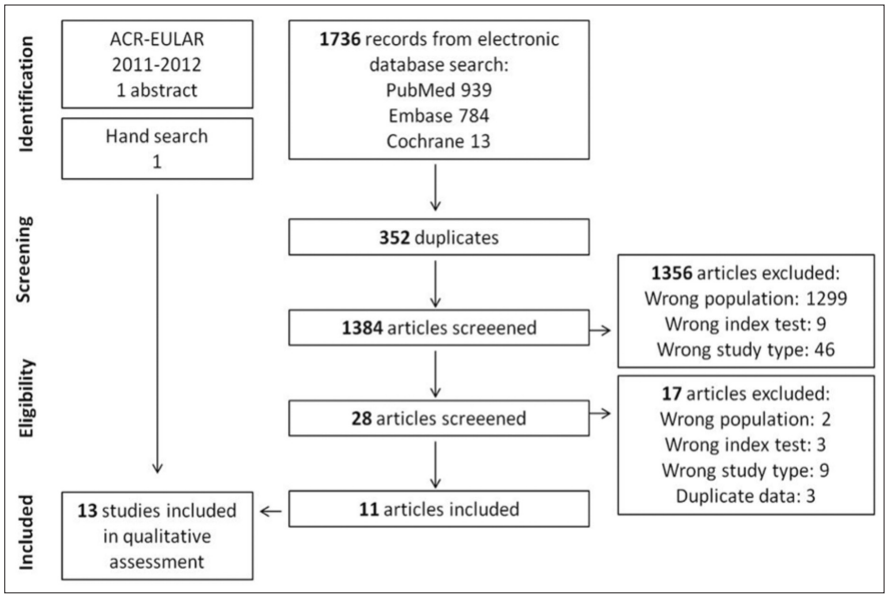

Fig. 1. Flow chart showing the selection process.

each US finding in primary studies. We focused on the diagnostic accuracy of the US findings that were included in the classification criteria: glenohumeral (GH) and coxofemoral (CF) synovitis, tenosynovitis of the long head of the biceps tendon (LHBT) and subacromial/subdeltoid (SAD) bursitis, trochanteric bursitis. When sufficient data to calculate sensitivity and specificity were presented, forest plots showing sensitivities and specificities for single US abnormalities of the primary studies were constructed using Review Manager 5 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen).

Results

The search strategy identified 1736 records. Figure 1 shows the selection process that finally led to the inclusion of 13 studies (12 full-text papers (18-21, 25-32) and 1 abstract (33)), in accordance with the selection criteria described in the methods section. The search retrieved also the systematic review we mentioned above (19). One study was excluded because, although based on shoulder US, the attention was focused on the deltoid fascia, that was found to be thicker in patients with PMR compared to healthy controls and to decrease after corticosteroid treatment (34). The median (interquartile range, IQR) value of the Newcastle Ottawa Scale was 6 (5, 6). In particular, items related to comparability were unsatisfactory in most studies.

At first sight, there was a relevant degree of variability among the studies. They were performed in periods ranging from 1992 to 2012, the adopted scanning techniques were not the same and the US machines and probes were different because of the relevant technological advances made in the last twenty years. The criteria for the inclusion of patients and even more the selection of controls in case-control studies were very heterogeneous.

The features of the included studies are shown in Table II. Eight studies evaluated shoulder US, 1 study hip US, and 4 studies both. Four studies adopted a case-control design, 3 studies were prospective. The reference standard applied for diagnosis is reported for the studies for which sensitivity and specificity have been calculated; only expert opinion or recognised diagnostic criteria were used (35, 36). Tables III and IV report the prevalence of US abnormalities among cases and controls; the prevalence over the total number of cases and controls has been reported for all findings, and where they were not directly reported in the paper they were calculated by the reviewers, although not all papers reported sufficient data.

Two studies (28, 29) were not included in Table III, since there was insufficient data to evaluate the prevalence of single findings. In a 1998 study, Lange and colleagues evaluated 13 PMR patients and 19 EORA controls. Patients with PMR had inflammatory involvement in articular and periarticular shoulder structures in 61.5% of cases, while EORA patients in 63.2%. The same authors in 2000 reported a prevalence of GH synovitis in 40.9% of PMR patients, compared to 65.5% in EORA patients.

When sensitivities and specificities of single findings, detected cross-sectionally, of the primary studies were calculated (Fig. 2), we found that there was a great variability in their values, and the findings were not always consistent across studies. What seemed to emerge quite uniformly is that when single features were taken into account, bilateral involvement tends to be more specific for a diagnosis of PMR.

Some studies evaluated the value of prospective US evaluation in PMR, the focus of all of them being shoulder US.

In 2009 Macchioni evaluated 57 PMR patients for a 12-month period performing shoulder US, examining SAD bursa, LHBT and GH joint. At the time of diagnosis, 98.2% of patients had inflammatory signs detected by US, and 45.8% by power Doppler (PD) signal. After corticosteroid treatment, the only inflammatory sign that significantly and consistently decreased was SAD bursitis. LHBT tenosynovitis and GH synovitis were not less prevalent. However, the thickness of the examined structures decreased, together with the prevalence of PD. Moreover, a relevant proportion of patients that were in clinical remission showed US signs of involvement of extra-articular structures (30).

Jiménez-Palop prospectively followed 59 PMR patients in order to investigate the sensitivity to change of shoulder and hip US after the beginning of corticosteroid treatment. The standardised response mean for US was similar to that of the main clinical and laboratory variables (27).

One study used US for the follow-up of 6 corticosteroid-refractory PMR patients treated with etanercept. US demonstrated a reduction of GH and periarticular inflammatory signs at the end of follow-up (21).

Table II. Features of the included studies. Reference standard is reported when data from the study have been used to estimate sensitivity and specificity.

Study	n	Study design	Population	Index test	Examined structures	Equipment	Control group	Reference standard
Balser 2012	35	Cross-sectional	PMR (expert opinion)	Shoulder and hip US	Glenohumeral joint Long head of the biceps tendon Subacromial bursa Coxofemoral joint	–	–	–
Cantini 2001 (19)	18	case-control cross-sectional study (controls were patients with PMR and normal ESR)	PMR diagnosed based on typical symptoms, morning stiffness, response to prednisone, differential diagnosis. Median age 72, M/F 8/10	Shoulder US	Glenohumeral joint Long head of the biceps tendon Subacromial bursa	SSA 340A (Toshiba), 7.5-MHz linear transducer	–	–
Cantini 2001 (25)	57 PMR, 114 controls	case-control cross-sectional study	PMR diagnosed base on typical symptoms, morning stiffness, response to prednisone, differential diagnosis, ESR>40 mm/h. Median age 71, M/F 32/68.	Shoulder US	Glenohumeral joint Long head of the biceps tendon Subacromial bursa	SSA 340A (Toshiba), 7.5-MHz linear transducer	patients >50 with bilateral shoulder pain (rheumatoid arthritis, inflammatory arthritis, fibromyalgia).	Expert opinion
Cantini 2005	20 PMR, 40 controls	cross-sectional	PMR with pelvic girdle symptoms	Hip US	Coxofemoral joint, Trochanteric, iliopsoas and ischiogluteal bursa	–	Mixed rheumatic diseases	–
Catanoso 2007	6	prospective case series	PMR (Healey's criteria) with steroid refractory disease	Shoulder US	Glenohumeral joint Long head of the biceps tendon Subacromial bursa	multiple high-frequency probes (5–13 MHz)	–	–
Coari 1999	16 PMR, 66 ED, 45 RA, 54 HS	cross-sectional	PMR (expert opinion)	Shoulder US	Glenohumeral joint Long head of the biceps tendon Subacromial bursa	7.5 MHz linear probe	RA, extrarticular diseases or healthy subjects	–
Falsetti 2002	50 PMR, 100 controls	case-control cross-sectional	PMR (Healey's criteria). Median age (cases) 71, M/F 13/37.	Shoulder and hip US	Glenohumeral joint Long head of the biceps tendon Subacromial bursa Coxofemoral joint Hip enthesis	Toshiba Tosbee SAL 240, linear 7.5 MHz probe	50 AR and SpA patients, 50 healthy subjects	Healey's criteria
Jiménez-Palop 2010	59	prospective cohort	PMR (expert opinion). Mean age74.3.	Shoulder and hip US	Glenohumeral joint Long head of the biceps tendon Subacromial bursa Coxofemoral joint	GE Logiq 5 Pro; linear array transducers (7–12 MHz)	–	–
Koski 1992	19	Cross-sectional	PMR	Shoulder and hip US	Glenohumeral joint Long head of the biceps tendon Subacromial bursa Coxofemoral joint	–	–	–
Lange 1998	13 PMR, 19 controls	Cross-sectional	PMR (expert opinion). Mean age 69, M/F 8/24.	Shoulder US	Glenohumeral joint Long head of the biceps tendon Subacromial bursa	Siemens Sonoline 450 SL, 5–7,5 MHz linear probe	EORA patients	–
Lange 2000	22 PMR, 29 controls	Cross-sectional	PMR (expert opinion). M/F 15/38.	Shoulder US	Glenohumeral joint Long head of the biceps tendon Subacromial bursa	HP image point 5-10 MHz linear probe	EORA patients	–
Macchioni 2009	57	Prospective cohort	PMR (Healey's criteria). Mean age 74, M/F 11/46.	Shoulder US	Glenohumeral joint Long head of the biceps tendon Subacromial bursa PD evaluation	Siemens Acuson Antares 5–13MHz linear array transducer.	–	–
Ruta 2012	30 PMR, 30 RA, 60 HS	Cross-sectional	PMR (Healey's criteria) Mean age 74, M/F 4/26 (cases)	Shoulder US	Glenohumeral joint Long head of the biceps tendon Subacromial bursa	My Lab 70 XVision 6–18 MHz linear transducer	RA or healthy subjects with monolateral symptoms	Healey's criteria

PMR: polymyalgia rheumatica; US: ultrasonography; M: male; F: female; ESR: erythrocyte sedimentation rate; ED: extrarticular disorders; RA: rheumatoid arthritis; SpA: spondyloarthropathies; HS: healthy subjects; EORA: elderly-onset rheumatoid arthritis.

Table III. Prevalence of shoulder US abnormalities. All numbers refer to the percentage of patients presenting a definite abnormality over the total number of cases or controls.

	Glenohumeral joint effusion						Subacromial bursitis						Biceps tendon tenosynovitis					
	Total		Monolateral		Bilateral		Total		Monolateral		Bilateral		Total		Monolateral		Bilateral	
	case	control	case	control	case	control	case	control	case	control	case	control	case	control	case	control	case	control
Balser 2012	34.6	-	-	-	-	-	46.2	-	-	-	-	-	92.3	-	-	-	80.8	-
Cantini 2001 (26)	66.6	-	33.3	-	33.3	-	94.4	-	0	-	94.4	-	72.2	-	22.2	-	50	-
Cantini 2001 (25)	77	58	42	20.1	35	32.4	96	22	3	21	93	0.87	80.6	53	22.8	49	57.8	3.5
Catanoso 2007	33.3	-	0	-	33.3	-	100	-	16.7	-	83.3	-	100	-	50	-	50	-
Coari 1999*	65.6	23	-	-	-	-	9.4	10	-	-	-	-	15	52	-	-	-	-
Falsetti 2002	66	35	12	13	54	22	70	39	16	17	54	22	68	41	30	7	38	34
Jiménez-Palop 2010	18	-	-	-	18	-	65	-	-	-	65	-	45	-	-	-	45	-
Koski 1992	52	-	26	-	26	-	15	-	5.1	-	9.9	-	42	-	26.5	-	15.5	-
Macchioni 2009	-	-	19.3	-	15.8	-	-	-	29.8	-	61.4	-	-	-	26.3	-	71.9	-
Ruta 2012**	-	-	-	-	3	10	-	-	-	-	37	3	-	-	-	-	30	0

* In this study joints and not patients are taken as a statistical unit. ** controls are RA patients.

Table IV. Prevalence of hip US abnormalities. All numbers refer to the percentage of patients presenting a definite abnormality over the total number of cases and controls.

	Coxofemoral joint effusion/synovitis						Trochanteric bursitis					
	Total		Monolateral		Bilateral		Total		Monolateral		Bilateral	
	case	control	case	control	case	control	case	control	case	control	case	control
Balser 2012	25.7	-	20	-	-	-	-	-	-	-	-	-
Cantini 2005	45	45	-	-	-	-	100	30	-	-	90	-
Falsetti 2002	40	-	8	-	32	-	-	-	-	-	-	-
Jiménez-Palop 2010	-	-	-	-	30	-	-	-	-	-	-	-
Koski 1992	53	-	-	-	-	-	-	-	-	-	-	-

A limited number of studies dealt with hip US, and in only one case, hip was the main focus of the paper (23). Table IV summarises the prevalence of US abnormalities at hip level in patients and controls, with a high proportion of PMR patients presenting with inflammatory signs at the hip. One of these studies provided data on follow-up (19) and, similarly to what happened to shoulder US, detectable abnormalities decreased along with main clinical and laboratory parameters.

Discussion

Since US has been introduced in the field of rheumatology, its application to rheumatological diseases, including PMR, has been wide. In particular, in patients with PMR, presenting with characteristic symptoms, attention has been focused on the examination of girdles and shoulders in particular (31). The utility of US has been tested in particular for its potential to differentiate PMR from EORA or non-specific shoulder conditions, but also the main differences between healthy subjects and PMR patients have been taken into account.

We adopted a comprehensive search strategy in order not to miss any relevant study. The search terms were meant to include studies dealing with both PMR and EORA patients. Filters for specific study designs were not used, since we did not aim to include a single type of study. Due to the use of a sensitive rather than specific search strategy, all relevant studies have probably been included.

When we examined the characteristics of the studies that were included, a high degree of variability was evident. These studies were conducted over a long period, from the beginning of the nineties to 2012. The US equipment that was adopted was not uniform, and in some cases not described in detail. The criteria used to include patients were variable, and control groups were even more variable. In fact, control groups were made up of healthy subjects, patients with non-specific shoulder conditions, patients with EORA or other rheumatic diseases, in different proportions. Even if heterogeneity has not been statistically tested, in its likely occurrence we decided not to summarise data in a meta-analysis. Moreover, the number of studies included was limited and there was not sufficient data in all of them to make a 2x2 table, and these are further reasons that limited the synthesis of data.

When we evaluated the sensitivity and specificity of single US findings for the diagnosis of PMR in the limited number of studies that presented sufficient data, the differences across studies became even more evident. Taking single US abnormalities into account, the one that seemed to provide the best diagnostic accuracy is the presence of SAD bursitis (monolateral or bilateral); the detection of a bilateral bursitis seemed to be the most specific finding in all studies. In general, when the alterations were bilateral, higher values of specificity were reached, but with lower sensitivity. The amount of evidence that has accumulated on this topic is greater for US examination of the shoulders, while only a minority of studies examined the hips. Only one study performed PD examination, however, the limited use of PD might be due to the low sensitivity of PD in these specific joints (37) and future technological improvements might help to overcome this limitation.

Another field that might be further investigated is the potential use of US to monitor patients with PMR after the prescription of treatment. The studies that used US to examine patients with PMR after the beginning of treatment suggest a potential utility of US follow-up.

When PMR classification criteria were developed and tested, the possible in-

clusion of US parameters was taken into consideration as a possible tool to improve their performance. However, probably due to the knowledge of some heterogeneity in the literature on this subject, the incorporation of US parameters in the final set of criteria was driven by a study specifically designed to test their accuracy (8). In this case, US alterations at shoulders or hips were tested in variable combinations. The diagnostic value of US has not been taken into account separately, but only in addition to the clinical features included in the final set. In the context of the new criteria, US is an optional instrument, however, in the validation of the criteria it has shown to improve their sensitivity.

The results of the present review seem to point to the very same conclusion. US abnormalities, especially at the level of the shoulders (bursitis and LHBT tenosynovitis in particular) and especially when bilateral, occur more frequently in patients with PMR compared to controls. However, the finding of isolated US abnormalities, in the absence of suggestive clinical features, should not lead to a diagnosis of PMR. Based on this consideration, the main effort might now be that of testing the performance of the new classification criteria, examining the additive value of US, in an observational setting. Interestingly, two studies presented at the 2012 ACR congress had already tested the new classification criteria, applying also US, proving the validity of the new criteria. However, in one study the addition of US proved to increase the performance of the criteria (38), while in the second one sensitivity was not increased (39).

The performance of the new criteria and US could be tested particularly in the settings in which differential diagnosis is more difficult, such as in EORA. A group of patients with rheumatoid arthritis has also been included in the validation cohort, but especially in this subgroup US seemed to be less helpful to distinguish cases and controls. The two studies included in this review that evaluated EORA control patients (21, 26) failed to prove differences in shoulder US between cases and controls.

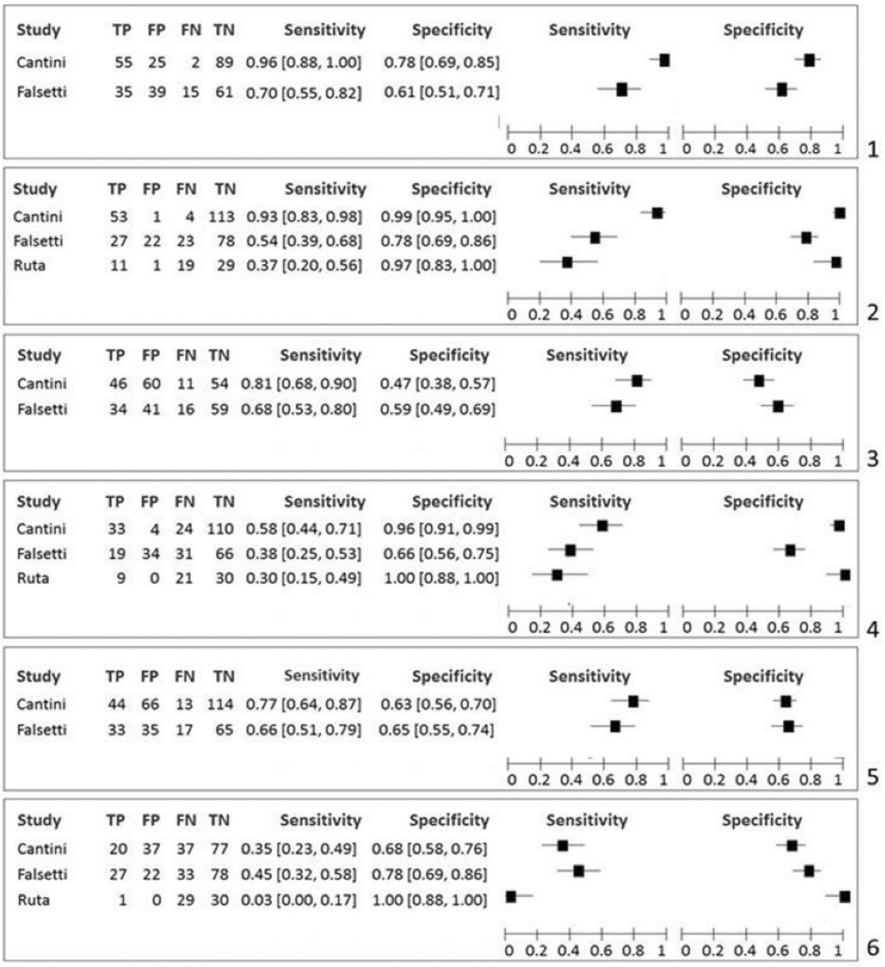

Fig. 2. Sensitivity and specificity of US shoulder abnormalities for the diagnosis of PMR. 1) SAD bursitis (monolateral or bilateral); 2) bilateral SAD bursitis; 3) LHBT tenosynovitis (monolateral or bilateral); 4) bilateral LHBT tenosynovitis; 5) GH synovitis (monolateral or bilateral); 6) bilateral GH synovitis.

Despite these limitations, US has emerged as a useful tool to improve the management of patients with PMR. Moreover, its application might be extended in specific settings with more defined objectives.

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