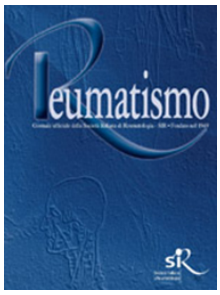

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Development of an algorithm for optimizing the implementation of ultrasound in the diagnostic workflow in clinical practice: preliminary phase of the RADIAL study, a project of the US Study Group of the Italian Society for Rheumatology

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Contributions: GS, AA, interpreted the results, performed the study, drafted the first version of the article and revised the final version for submission; CAS, GF, conceptualized the study, performed the study and interpreted the results; GC, performed the statistical analysis; JMD, AD, AB, MC, EF, FP, MC, AI, performed the study. All authors have revised the draft of the article and approved its final version for submission.

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Ethics approval and consent to participate: the study was approved by the Comitato Etico di area vasta Emilia centrale, approval number 903/2020/Oss/AOUFe.

Informed consent: patients signed a written informed consent upon participation.

Patient consent for publication: not applicable.

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Summary

Objective. To develop and test an algorithm with the aim of optimizing the implementation of ultrasound in the diagnostic workflow in clinical practice.

Methods. Through a consensus among the Musculoskeletal Ultrasound (MSUS) Study Group of the Italian Society for Rheumatology, we identified clinical and laboratory variables to be included in 1000minds surveys to develop an algorithm driving clinical diagnostic suspicion. The algorithm would identify potential differential diagnoses where MSUS protocols targeted for specific diseases (rheumatoid arthritis, psoriatic arthritis, gout, calcium pyrophosphate deposition disease, polymyalgia rheumatica, and osteoarthritis) could be applied. The joint sites and elementary lesions for each disease were selected based on a previously performed systematic literature review (SLR) and consensus. Finally, we conducted a pilot study on patients with new-onset arthritis to assess the performance of the algorithm, comparing the algorithm-based diagnosis with the final clinical diagnosis.

Results. Based on the consensus and the surveys, age, the number of involved joints, anti-citrullinated protein antibody, rheumatoid factor, C-reactive protein, and erythrocyte sedimentation rate were included in the algorithm. The pilot study included 59 patients: median (interquartile range) age 62.2 (54.1-72.6) years, 78% female. The agreement between the diagnosis selected by the algorithm and the final diagnosis by the rheumatologist was 88.1%. The elementary lesions and joint sites included in the different MSUS protocols were selected based on the best diagnostic accuracy, as shown by the SLR and defined by the working group.

Conclusions. The developed algorithm was accurate in identifying the correct diagnosis. Thus, it could reliably drive the decision on the MSUS assessment to perform. The RADIAL study will further investigate the feasibility and added value of MSUS in the diagnostic workflow according to this newly developed clinical suspicion-driven algorithm.

Introduction

The evolution of the strategies for the management of inflammatory arthropathies has driven a shift towards a very early diagnosis, thus allowing the prompt institution of treatment (1). Although such an approach has been strongly supported in rheumatoid arthritis (RA), the consequences of an earlier assessment and diagnosis apply to all diseases presenting with arthritis. The counterpart of the pressure towards an early diagnosis, however, is the high degree of diagnostic uncertainty, and this is particularly true in seronegative diseases, a phenomenon that is also reflected by the limited specificity of the current classification criteria (2, 3).

For this reason, there is an increasing need to find potential markers helping the process of differential diagnosis, including biomarkers and imaging (4, 5).

Among the available techniques, musculoskeletal ultrasound (MSUS) has gained increasing diffusion in the setting of rheumatology, due to its availability in an outpatient setting, low costs and increasingly prevalent training of rheumatologists. However, despite its widespread availability, the optimal placement of this technique in the diagnostic workout is yet to be fully determined. MSUS has shown good diagnostic performance in identifying the elementary lesions characterizing each disease (6), but studies assessing its value in the diagnosis of a disease are scarcer, and they tend to analyze a single condition, often adopting study designs prone to an overestimation of the effect (4). Studies assessing the placement of MSUS assessment in the process of differential diagnosis of patients presenting with new-onset arthritis are lacking, and, in general, ultrasonographic variables are tested without a relationship with clinical variables and outside the context of clinical reasoning.

In the classification criteria of rheumatic diseases that are designed to increase the specificity of diagnosis to enroll "true" patients in clinical studies, the role of MSUS is still limited. In fact, in the setting of RA, the only role of MSUS is that of confirming the presence of synovitis in doubtful cases (2), while only the criteria for polymyalgia rheumatica (PMR), gout, and the recently published criteria for calcium pyrophosphate deposition disease (CPPD) have included MSUS findings among their components (7-9). Along with the limited inclusion of MSUS in classification criteria, also the diffusion of MSUS in the rheumatology setting, including the application for diagnostic purposes (10-12), is not comparable in all geographic regions and could be further implemented.

In 2018, the MSUS Study Group of the Italian Society of Rheumatology (SIR), in collaboration with the MSUS Study Group of the Portuguese Society for Rheumatology, prioritized its activities in this area and started a project, the "Algorithm for including MSUS in the diagnostic process of inflammatory arthropathies in clinical practice" (RADIAL) study, to establish the impact of MSUS for differential diagnosis in early-onset arthritis. To achieve this objective, a multistep process was adopted, starting from a systematic literature review (SLR) (4) and going on with the present study, aimed to develop an algorithm driving the decision on the MSUS assessment to perform. The performance of such an algorithm was tested on a sample of patients with early-onset arthritis. Finally, we developed MSUS protocols, differentiated according to clinical suspicion.

Materials and Methods

All members of the MSUS Study Group of SIR and the MSUS Study Group of the Portuguese Society for Rheumatology were invited to participate. The group was composed of rheumatologists with expertise in MSUS, with particular regard to inflammatory arthropathies, who had previously performed observational studies in this field (13, 14). The study was approved by the Comitato Etico di area vasta Emilia centrale, approval number 903/2020/Oss/AOUFe. The overview of the different phases of the project is shown in Figure 1. The present report presents the results of all the phases of the process that preceded the patient-driven phase.

Definition of subsets of application

In an in-person meeting, held in February 2018, the collaborators of the MSUS study group discussed the areas of application and a list of clinical variables to be assessed, through a process of open discussion. The discussion on the clinical variables was made including comprehensively all the

selected diagnoses. There was no limit on the number of eligible variables and consensus was reached through discussion.
Afterward, six different surveys presenting short clinical scenarios, divided according to disease, were prepared, uploaded on the web-based platform 1000minds, and submitted to all participants. The results of the surveys were used to rank the variables, depending on their weight in driving clinical suspicion. The most significant variables were included in an algorithm, with an order based on their significance, assessed through discussion during a second meeting. The final algorithm was afterward approved through a consensus process by participants during an in-person meeting taking place in 2019.

Algorithm validation
The capability of the algorithm to correctly predict the final diagnosis was tested in a pilot study involving 10 investigators, located in Italy and Portugal, collaborators of the MSUS Study Group of SIR or members of the MSUS Study Group of the Portuguese Society for Rheumatology and willing to contribute to the first part of the RADIAL study. The diagnosis identified through the algorithm was compared to a reference standard, defined as the diagnosis established by the treating rheumatologist at the second follow-up visit.
Patients aged more than 18 years, referred to the local outpatient clinic for a first rheumatologic assessment for a suspected inflammatory arthropathy, with available results of immunoglobulin M rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide antibodies (ACPA), C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR) were eligible for inclusion. Patients with a previous diagnosis of RA, psoriatic arthritis (PsA), PMR, gout, CPPD were excluded, as well as patients not willing to undergo a second evaluation. Upon inclusion, patients signed informed consent.

Clinical assessment
Demographic data were recorded. Among disease-related characteristics, symptom duration and a joint count on 66/68 joints for swelling and pain were collected. Results of RF, ACPA, CRP, and ESR determinations were recorded. Besides information collected to apply the algorithm, further laboratory testing and imaging could be required based on what was deemed necessary for differential diagnosis.

Statistical analysis
Descriptive statistics, including mean with standard deviation, median with interquartile range (IQR) and percentages, were performed as appropriate. The performance of the algorithm was assessed as percentage of agreement. Analyses were performed with R statistical software, version 3.6 (Foundation for Statistical Computing, Vienna, Austria).

Definition of elementary lesions and sites
To identify the most suitable MSUS protocols for each disease to be implemented in the algorithm, the results of the preliminary SLR (4) were presented to the members of the MSUS Study Group, in the in-person meeting in 2018. At first, elementary lesions of interest were selected based on their diagnostic accuracy to identify a specific disease; participants' opinions were expressed through an open discussion. The joint areas to scan in each protocol were also defined based on the available evidence in the SLR and the opinion of the participants through discussion. In the same meeting, participants drafted disease-specific statements to guide MSUS assessment. In the subsequent in-person meeting, taking place in 2019, the participants voted their agreement on each statement on a 1-5 Likert scale: agreement was defined as values of 4 or higher. Consensus was reached with a concordance of at least 70%; statements not reaching this cut-off were modified through discussion and voted again until agreement was achieved.

Results

Definition of subsets of application

Based on the discussion occurring at the one-day in-person meeting, involving 53 participants from all Italian regions, the members of the MSUS Study Group identified the diseases of interest, including RA, PsA, PMR, gout, CPPD, and osteoarthritis (OA). Afterward, the group listed the variables to test in the subsequent steps of the creation of the algorithm. Age (≥50 years), sex, extent of joint involvement (monoarticular, oligoarticular, or polyarticular), RF or ACPA positivity, ESR or CRP elevation (defined according to the local range of normality), symptom duration (with a cut-off of 3 months) and the type of manifestation (arthralgia *vs.* arthritis) were included in the 1000minds surveys.

The ranking of the variables was defined through six different surveys, whose results drove the final inclusion of age, extent of joint involvement, RF or ACPA positivity, ESR or CRP elevation in the algorithm. The ranking of each variable in the disease-specific survey is shown in *Supplementary Table 1*. The way in which each variable would determine the likelihood of clinical diagnosis is summarized in Figure 2.

The two principal investigators of the study (GF, CAS), based on the results of the 1000minds survey, drafted the algorithm for the attribution of the MSUS assessment, depending on the clinical suspicion. The algorithm defines the most likely diagnosis or group of diagnoses; however, the probability of each single disease is not specified. This was presented to the participants of the in-person meeting in 2019, who proposed modifications through open discussion and then approved the algorithm in its final form (Figure 3). As symptom duration and arthralgia *vs.* arthritis did not seem to provide any advantage, they were not included in the algorithm.

Algorithm validation

The pilot study to validate the algorithm enrolled 59 patients, assessed by 10 members of the MSUS Study Group. Patients had a median (IQR) age of 62.2 (54.1-72.6) years, 46/59 (78%) were females, RF and/or ACPA were positive in 19 (32.2%) patients, ESR and/or CRP were increased in 40 (67.8%) patients. The diagnoses based on the algorithm and the rheumatologist's opinion, described as absolute numbers and percentages, are shown in Table 1. A single patient with an initial diagnosis of gout was classified as having PMR by clinical diagnosis at the final assessment.

The algorithm-based diagnosis was consistent with the final diagnosis in 52/59 cases, corresponding to an agreement of 88.1%. Diagnoses based on the algorithm and clinical diagnoses are shown in *Supplementary Table 2*, and the areas of discrepancy are described in Figure 4.

The major area of misclassification was that of OA, where 4/12 patients received and incorrect diagnosis. The features of the 7 patients in which diagnoses were discrepant are summarized in *Supplementary Table 3*.

Statement definition

After presenting the results of the SLR to the MSUS Study Group members, the task force defined through discussion the elementary lesions, the type of scoring, and sites of interest for each disease initially identified. The results of this process are reported in Table 2.

Subsequently, a set of statements was defined for each disease. These statements underwent a Delphi process and were modified until an agreement was reached (*Supplementary Table 4*). The US study protocol was based on the joints, lesions and scoring previously identified and on the statements subsequently developed.

Discussion and Conclusions

While MSUS has gained increasing popularity in rheumatology, its standardized placement in disease management is still lacking. In line with the existing gaps, an in-depth knowledge of the potential role of this technique in supporting the diagnostic process is unclear. In fact, so far, research has focused on single diseases, assessing the diagnostic accuracy of elementary lesions. However, this

scenario does not reproduce the usual clinical setting, especially for patients at their first evaluation in a rheumatology clinic, who generally present with new-onset symptoms that might be attributable to a variety of causes. In addition to this limitation, the few studies that have tried to define diagnostic performance in more complex settings had sub-optimal study designs, leading to an overestimation of the diagnostic accuracy and a high risk of bias (4). Moreover, MSUS has been tested for diagnostic purposes without proper integration with clinical findings, and this does not reproduce clinical reasoning. The frailty of diagnostic studies in rheumatology covers several different conditions and has finally determined the poor relevance given to this technique in international classification criteria and recommendations (2, 4, 15, 16).

The ideal study design to define the correct position of MSUS in the differential diagnosis of inflammatory arthritis would imply the enrollment of consecutive patients with new-onset inflammatory arthralgia or arthritis, in which MSUS would be applied according to the leading clinical suspicion, to increase the likelihood of a correct diagnosis. To achieve this, a multi-step process was planned. The present study represents the second step of this process, the first one being the summary of the existing evidence through an SLR (4). The present part of the work involved many rheumatologists with expertise in MSUS from two European countries, working in different settings, ranging from first-level to academic third-level centers. The study participants identified the candidate diseases, the sites of involvement, and lesions based on their expertise, encompassing clinical management of inflammatory arthropathies and applications of MSUS, after being informed by the results of the SLR. The first aim was to define the most likely diagnoses depending on clinical variables, and we adopted a methodology based on 1000minds, which led to the design of the algorithm. While this type of design aimed to incorporate the expertise of participants, the weight of some variables might have been influenced by concurrent variables in the clinical vignettes. This could be the case of the male gender for PMR (although this variable was not included in the algorithm) or monoarticular presentation for RA, also related to the description of palindromic onset in the vignettes. To verify the accuracy of this process, we tested the performance of the algorithm against the reference standard of the final diagnosis made by the rheumatologist in consecutive patients presenting with suspected arthritis. By doing so, we demonstrated the high accuracy of this tool and moved on to the subsequent steps of the process. Although the complex process of differential diagnosis cannot be entirely summarized by an algorithm, also considering the overlapping of some diseases, this approximation was necessary to design the subsequent phases of the study.

Among the possible barriers to a more extensive application of MSUS in the diagnostic process in suspected arthritis, the limited amount of available time represents a significant issue. In general, the prescription of imaging implies the assessment of entire joint areas, but for an efficient differential diagnosis, this might not be particularly effective. Some very specific lesions (*e.g.*, double contour in gout, calcium pyrophosphate depositions, and bone erosions in RA) tend to occur at specific sites in different joints. Therefore, a rational approach to MSUS examination might be that of scanning specific structures in different areas, avoiding a full scan of a joint, thus allowing a shorter examination time for each structure. There is no evidence supporting such an approach but there have been several attempts to develop MSUS protocols based on a limited number of joints without, however, defining a universally accepted set of sites to be assessed for differential diagnosis (17-20). Moreover, the focus of these studies was only RA, and the main aims were to identify and monitor inflammation. In line with these purposes, most of the available MSUS protocols were validated against inflammatory markers, and their diagnostic value was not tested, being of limited help in differential diagnosis. In this study, we adopted a wider approach, in which the presence of inflammation was already highly suspected based on clinical assessment, and the main interest was establishing the final diagnosis. We considered several possible diagnoses and defined the sites to be scanned based on evidence from an SLR and expert opinion. Our aim was to include in our scanning protocols the lesions and sites with the maximal diagnostic accuracy in identifying diseases, resulting

in a diagnosis-focused assessment. The final purpose of this process is to provide less time-consuming tools to be tested in a subsequent observational study.

To our knowledge, this is the first attempt to incorporate MSUS and clinical assessment into a single process for making a diagnosis. So far, we have defined the areas of interest, integrated clinical variables into a standardized pathway, and defined the MSUS protocols to be tested in subsequent research.

Our study might have some drawbacks. The diagnostic process is by far more complex than what has been summarized in the algorithm, although we felt that its application provided an adequate surrogate, allowing a standardized approach for clinical research. Although we selected the most relevant differential diagnoses of peripheral inflammatory arthritis, other possible diagnoses were not included in our study.

Despite these limitations, we believe that our results represent the first attempt to clarify the optimal placement of MSUS in the diagnostic process of inflammatory arthritis, assessing its additional value over clinical assessment and the ideal setting of utilization. The results of this study will serve as a basis for the conduction of the RADIAL observational study, promoted by SIR, that will approach all these aspects. We are confident that the US protocols developed in this study could provide a significant added value for the differential diagnosis and that clinicians could apply them for the diagnostic process even independently of the algorithm.

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Online supplementary material
Supplementary Table 1. Ranking of the variables in the surveys.
Supplementary Table 2. Diagnosis based on the algorithm and final diagnosis defined by the clinician.
Supplementary Table 3. Characteristics of the misclassified patients.
Supplementary Table 4. Final statements.

Table 1. Diagnoses based on the algorithm and clinical diagnosis. The table displays the descriptive results of the diagnoses as absolute numbers and percentages.

Algorithm diagnosis		Clinical diagnosis	
Diagnosis	**n (%)**	**Diagnosis**	**n (%)**
Gout/CPPD/PsA	4 (6.8)	RA	22 (37.3)
Gout/CPPD/RA/PsA	2 (3.4)	PsA	10 (17)
OA/CPPD/PsA	12 (20.3)	PMR	8 (13.6)
PMR/RA/PsA	31 (52.5)	Gout	3 (5.1)
RA/PsA	2 (3.4)	CPPD	4 (6.8)
PsA	3 (5.1)	OA	12 (12.3)

RA, rheumatoid arthritis; PsA, psoriatic arthritis; PMR, polymyalgia rheumatica; CPPD, calcium pyrophosphate deposition disease; OA, osteoarthritis.

Table 2. Sites of interest, elementary lesions and scoring identified for the inclusion in the US protocol for each disease.

Disease	Sites to scan	US elementary lesions	Score
RA	II- V MCPs	SH	Semi-quantitative score (0-3)
		PD	Semi-quantitative score (0-3)
		Bone erosions	Dichotomous score (presence/absence)
	Wrists	SH	Semi-quantitative score (0-3)
		PD	Semi quantitative score (0-3)
	V MTP	Bone erosions	Dichotomous score (presence/absence)
PsA	II-III MCPs	Peritendonitis	Dichotomous score (presence/absence)
	PIPs	Enthesitis	Dichotomous score (presence/absence)
		Soft tissue edema	
	Flexor tendons of the hands	Tenosynovitis	Dichotomous score (presence/absence)
		Soft tissue edema	
	Achille's tendon enthesis	PD	Dichotomous score (presence/absence)
	Proximal patellar tendon enthesis	Erosions	
CPPD	Knees (menisci and hyaline cartilage)	CPP deposits	Dichotomous score (presence/absence)
	Wrists (triangular fibrocartilage complex)	CPP deposits	
	Any involved sites	CPP deposits SH, PD	
Gout	Knees	Double contor, Tophi	Dichotomous score (presence/absence)
	I MTP	Double contor, Tophi	
	Any involved sites	Double contor, Tophi SH, PD	
OA	Involved sites	Osteophytes Cartilage changes	Dichotomous score (presence/absence)
PMR	Shoulders	Bursitis, arthritis, rotator cuff integrity	Dichotomous score (presence/absence)

RA, rheumatoid arthritis; PsA, psoriatic arthritis; PMR, polymyalgia rheumatica; CPPD, calcium pyrophosphate deposition disease; OA, osteoarthritis; MCP, metacarpophalangeal; PIP, proximal interphalangeal; MTP, metatarsophalangeal; GS, grey scale; PD, power Doppler; SH, synovial hypertrophy; CPP, calcium pyrophosphate.

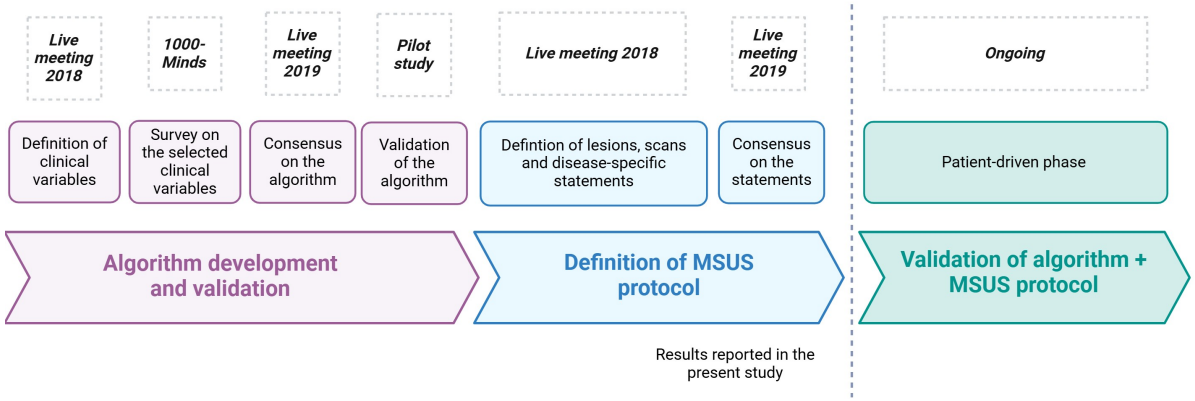

Figure 1. Study design of the RADIAL study. MSUS, musculoskeletal ultrasound.

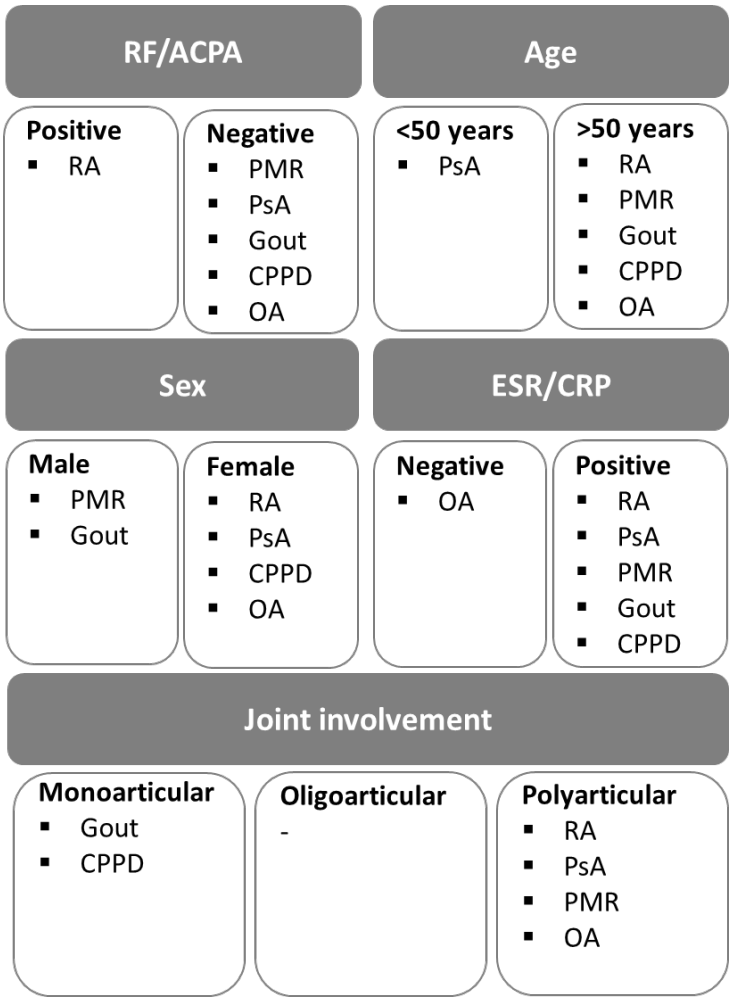

Figure 2. Results of the 1000minds survey: the value of each variable in defining the most likely diagnosis. RA, rheumatoid arthritis; PsA, psoriatic arthritis; PMR, polymyalgia rheumatica; CPPD, calcium pyrophosphate deposition disease; OA, osteoarthritis; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide antibodies; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

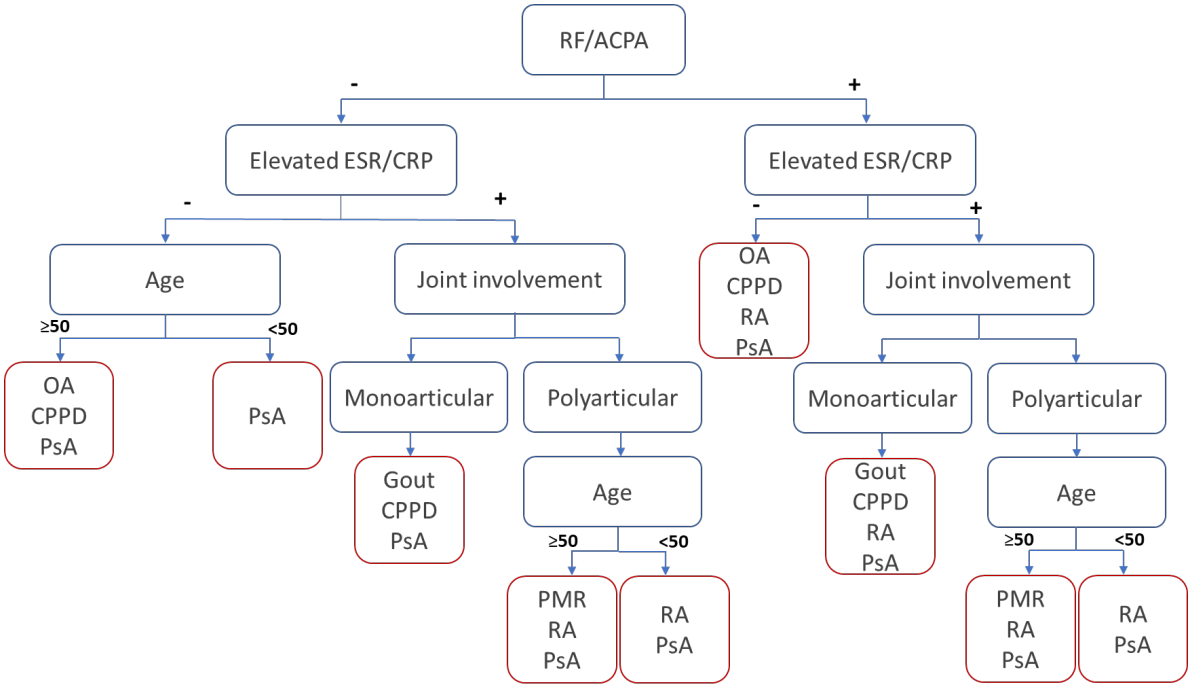

Figure 3. Algorithm. RA, rheumatoid arthritis; PsA, psoriatic arthritis; PMR, polymyalgia rheumatica; CPPD, calcium pyrophosphate deposition disease; OA, osteoarthritis; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide antibodies; ESR, erythrosedimentation rate; CRP, C-reactive protein.

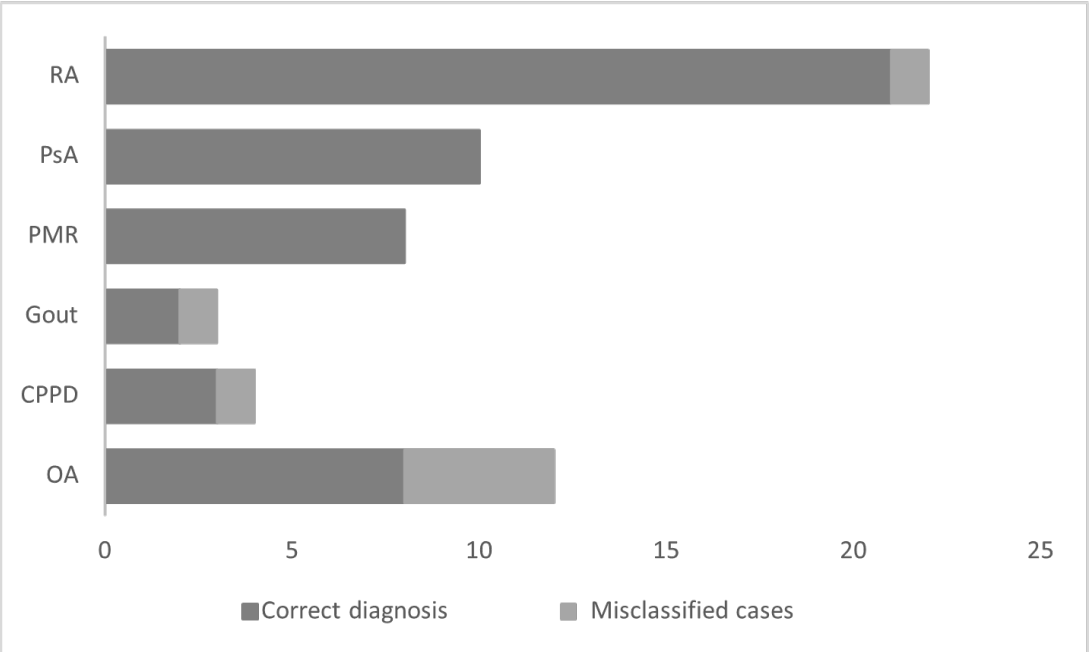

Figure 4. Final diagnosis in accordance with international classification/diagnostic criteria and physician expertise and proportion of correct diagnosis based on the algorithm. RA, rheumatoid arthritis; PsA, psoriatic arthritis; PMR, polymyalgia rheumatica; CPPD, calcium pyrophosphate deposition disease; OA, osteoarthritis.