The 2023 ACR/EULAR classification criteria for calcium pyrophosphate deposition disease

Abhishek Abhishek ,[1] Sara K Tedeschi ,[2] Tristan Pascart ,[3] Augustin Latourte ,[4] Nicola Dalbeth ,[5] Tuhina Neogi ,[6] Amy Fuller ,[1] Ann Rosenthal,[7] Fabio Becce ,[8] Thomas Bardin ,[4] Hang-Korng Ea ,[4] Georgios Filippou ,[9] John Fitzgerald ,[10,11] AnnaMaria Iagnocco ,[12] Frédéric Lioté ,[4,13] Geraldine M McCarthy ,[14,15] Roberta Ramonda ,[16] Pascal Richette ,[4] Francisca Sivera,[17,18] Mariano Andrés ,[19] Edoardo Cipolletta ,[20] Michael Doherty,[1] Eliseo Pascual ,[21] Fernando Perez-Ruiz,[22] Alexander So,[23] Tim L Jansen,[24,25] Minna J Kohler,[26] Lisa K Stamp ,[27] Janeth Yinh,[26] Antonella Adinolfi,[28] Uri Arad ,[29] Thanda Aung,[30] Eva Benillouche,[31] Alessandra Bortoluzzi ,[32,33] Jonathan Dau,[34] Ernest Maningding,[35] Meika A Fang,[10,11] Fabiana A Figus,[36] Emilio Filippucci,[20] Janine Haslett,[27] Matthijs Janssen,[24] Marian Kaldas,[10] Maryann Kimoto,[10] Kelly Leamy,[15] Geraldine M Navarro,[30] Piercarlo Sarzi-Puttini,[37] Carlo Scirè ,[38] Ettore Silvagni,[32,33] Silvia Sirotti ,[39] John R Stack,[14,15] Linh Truong,[30] Chen Xie,[30] Chio Yokose ,[40] Alison M Hendry,[41] Robert Terkeltaub,[42] William J Taylor,[27] Hyon K Choi [26]

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For numbered affiliations see end of article.

Correspondence to
Dr Abhishek Abhishek, Academic Rheumatology, University of Nottingham, Nottingham, UK; abhishek.abhishek@nottingham.ac.uk

AA and SKT contributed equally.

AA and SKT are joint first authors.

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ABSTRACT

Objective Calcium pyrophosphate deposition (CPPD) disease is prevalent and has diverse presentations, but there are no validated classification criteria for this symptomatic arthritis. The American College of Rheumatology (ACR) and EULAR have developed the first-ever validated classification criteria for symptomatic CPPD disease.

Methods Supported by the ACR and EULAR, a multinational group of investigators followed established methodology to develop these disease classification criteria. The group generated lists of candidate items and refined their definitions, collected de-identified patient profiles, evaluated strengths of associations between candidate items and CPPD disease, developed a classification criteria framework, and used multi-criterion decision analysis to define criteria weights and a classification threshold score. The criteria were validated in an independent cohort.

Results Among patients with joint pain, swelling, or tenderness (entry criterion) whose symptoms are not fully explained by an alternative disease (exclusion criterion), the presence of crowned dens syndrome or calcium pyrophosphate crystals in synovial fluid are sufficient to classify a patient as having CPPD disease. In the absence of these findings, a score>56 points using weighted criteria, comprising clinical features, associated metabolic disorders, and results of laboratory and imaging investigations, can be used to classify as CPPD disease. These criteria had a sensitivity of 92.2% and specificity of 87.9% in the derivation cohort (190 CPPD cases, 148 mimickers), whereas sensitivity was 99.2% and specificity was 92.5% in the validation cohort (251 CPPD cases, 162 mimickers).

Conclusion The 2023 ACR/EULAR CPPD disease classification criteria have excellent performance characteristics and will facilitate research in this field.

INTRODUCTION

Calcium pyrophosphate deposition (CPPD) disease is a common symptomatic arthritis characterised by the deposition of calcium pyrophosphate (CPP) crystals.[1] The prevalence of radiographic chondrocalcinosis, often used as a proxy for CPPD disease, ranges from 4% to≥10% among older adults, though the prevalence of symptomatic CPPD disease remains incompletely defined.[2–5] Research in CPPD disease has lagged behind other types of arthritis due, in part, to absence of validated classification criteria. Variable reliance on synovial fluid (SF) polarised light microscopy for diagnosis, and a diversity of presentations that include acute CPP crystal arthritis, chronic CPP crystal inflammatory arthritis, osteoarthritis with CPPD, and crowned dens syndrome (CDS) makes it hard to compare between studies.[1] The only published diagnostic criteria for CPPD disease were developed in the 1960s by Ryan and McCarty.[6] For definite diagnosis, they required evidence of crystals based on the presence of both typical calcification on radiography and findings consistent with CPP crystals on SF polarised light microscopy, or alternatively by research laboratory techniques that are not widely available.[7] These diagnostic criteria have since been recognised to be problematic, because conventional radiography (CR)

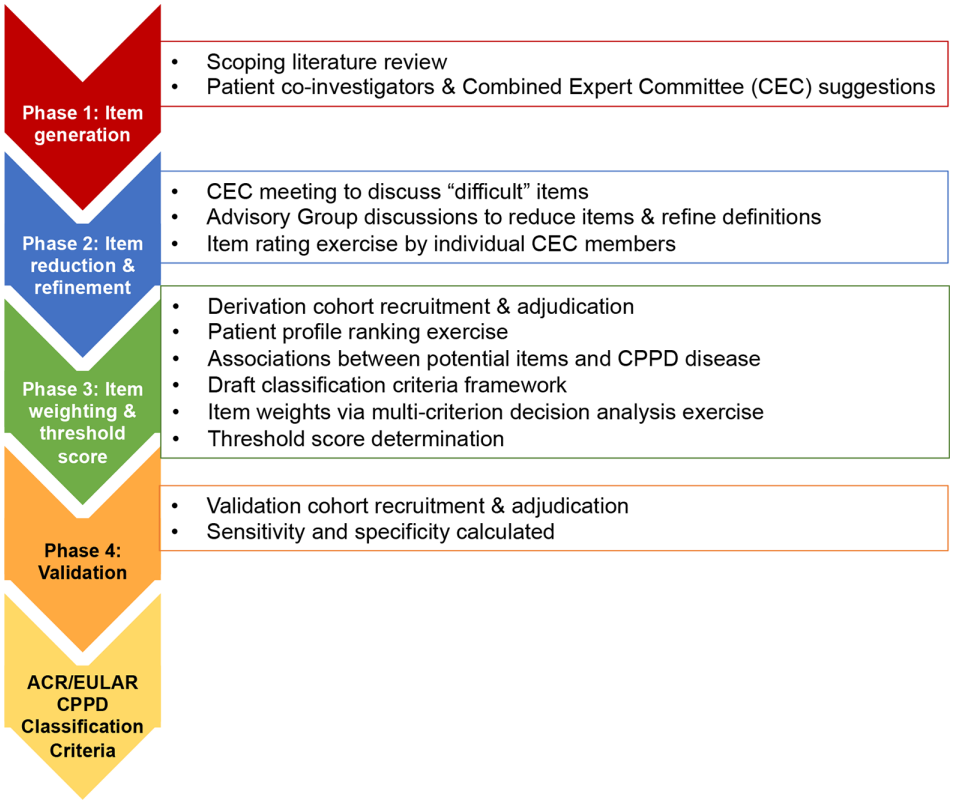

Figure 1 Overview of the ACR/EULAR classification criteria for CPPD disease across the 4 Phases.

has low sensitivity for CPPD,[8–10] advanced imaging modalities such as ultrasonography and dual-energy computed tomography were not available in the 1960s, and SF analysis for CPP crystals has a high false-negative rate and high interobserver variability.[11–14]

To develop validated classification criteria in order to facilitate research in CPPD disease, an international collaborative working group was convened with the support of the American College of Rheumatology (ACR) and EULAR. The goal was to develop a framework enabling investigators to identify people with CPPD disease for entry into research studies, including clinical trials and observational studies. Such criteria are not intended to capture all possible cases, but rather to capture the majority of people with symptomatic CPPD disease.

METHODS

Criteria development phases 1 and 2

These classification criteria were developed in sequential phases (figure 1) following previously established methodology.[15–19] A 9-member Steering Committee oversaw the process and a 22-member Combined Expert Committee (CEC) contributed throughout. Phases 1 and 2 were described previously.[20] Briefly, in Phase 1 we developed a comprehensive list of potential classification criteria items based on a scoping literature review and input from the CEC and two patient research partners. In Phase two we reduced and refined the list of potential items to those considered most specific for CPPD disease. These potential items were included in the case report form (CRF) that was used to collect patient profiles in the derivation and validation cohorts.

Criteria development phase 3

Phase 3 involved six steps as described below (and as outlined in figure 1).

Derivation cohort recruitment and adjudication

De-identified information on people with differing likelihood of developing CPPD disease was collected using a standardised CRF, aided by item definitions for imaging features adopted from the literature or specifically developed for this project.[21–24] Data were collected retrospectively using medical record review with approval of the Health Research Authority (Research Ethics Committee reference no. 20/SC/0243) and the local Ethics Committee at each participating site. In addition to reporting clinical manifestations, risk factors for CPPD disease, and results of imaging and laboratory tests, the submitting clinicians rated their clinical impression of the likelihood that the individual had CPPD disease on a 7-point Likert scale, ranging from+3 = highly likely to −3=highly unlikely.

Each patient profile was categorized as definite CPPD disease (case), definite mimicker (control), or uncertain using the submitted information. Profiles rated as +3 or +2 by the submitting clinician with CPP crystals confirmed by SF analysis were considered definite CPPD disease. Profiles rated as −3 or −2 by the submitting clinician were considered definite mimickers. All other profiles underwent adjudication in a blinded manner by 2 independent experts from institutions that did not submit that specific patient profile. After adjudication, profiles rated+2or higher by both adjudicators and by the submitting clinician were considered to be definite CPPD disease, and those profiles rated −one or lower by both adjudicators were considered to be definite mimickers (see online supplemental table S1). Patient profiles in which both adjudicators did not provide a rating of either+2or higher or −one or lower and those profiles in

which SF CPP crystals were absent and for which the submitting clinician's rating was −1, 0, or+1 were considered uncertain. The adjudicators did not discuss the patient profiles among themselves.

Patient profile ranking by CEC

Among the derivation cohort, 30 patient profiles representing the full spectrum of likelihood of CPPD disease were selected. This included seven profiles with a clinician rating of −two or −3, 15 profiles with a clinician rating of −1, 0, or+1, and eight profiles with a clinician rating of+2or +3. These patient profiles were purposefully selected so that all candidate items were present in at least one of the profiles. CEC members then ranked the profiles individually from 1 to 30 according to their perceived likelihood of CPPD disease.

Association between potential classification criteria items and CPPD disease

Data from definite cases and definite mimickers (controls) in the whole derivation cohort were used to calculate the odds of CPPD disease given the presence of each of the potential classification criteria in univariate analyses. Unadjusted logistic regression models provided estimated ORs and 95% confidence intervals (95% CIs) for CPPD disease. Uncertain cases were excluded since their true case/control status was unclear.

Classification criteria framework

The CEC convened four videoconferences to review results of the ranking exercise and the estimated ORs that were calculated for candidate items. Based on these discussions, the CEC decided to include entry criteria (required to be considered for CPPD disease classification) as well as exclusion criteria (if present classification as CPPD disease should not proceed), and developed the initial draft of the classification criteria framework. The framework consisted of domains comprising similar items. The goal was to order items within each domain into mutually exclusive levels, ranging from least influential to most influential, when considering the likelihood of classifying a person as having CPPD disease. Decisions regarding domains, their levels, and the relative ordering of the levels within domains were guided by expert opinion and supported by the ORs from derivation cohort data. The Steering Committee iteratively refined the classification criteria framework between and after the CEC videoconferences.

Assigning relative weights

Using a multi-criterion decision analysis (MCDA) approach, members of the CEC undertook a discrete-choice conjoint analysis exercise using 1000Minds Potentially All Pairwise RanKings of all possible Alternatives (PAPRIKA) software (http://www.1000minds.com), guided by an experienced facilitator (AH) over four 2 hour virtual meetings (for details, see online supplemental methods).[25] During the virtual meetings, the CEC was presented with paired CPPD disease clinical scenarios that included items from two different domains; all other patient features were assumed to be equivalent. CEC members were asked to decide which clinical scenario was more likely to have CPPD disease: for instance, a patient with acute inflammatory arthritis in a peripheral joint other than the knee, wrist, or first metatarsophalangeal (MTP) joint and evidence of calcification on imaging of 1 peripheral joint (regardless of symptoms) vs a patient with acute inflammatory arthritis in the first MTP joint and evidence of calcification in four peripheral joints (regardless of symptoms). The facilitator encouraged discussion until consensus was reached on each pairwise decision. With the 1000Minds software, the CEC used these decisions to determine weights that were automatically scaled so that the sum across all domains ranged from 0 to 100 (see online supplemental methods).

Early in this process it became apparent that 2 of the items dominated decision-making, and therefore it was decided to make them sufficient criteria, meaning that if either was present then proceeding to score the other criteria was not necessary. The CEC then re-voted on a series of pairwise decisions with those two items removed, to update the weights for the remaining criteria.

On completing the MCDA exercise, some domains were re-centred to maintain the face validity of item weights. Levels in a domain with a weight difference<1% were merged, as a difference of<1% was considered unlikely to improve discrimination on a 100-point scale. Item weights were rounded to integers for consistency with published classification criteria.[15–19] These steps were undertaken by the Steering Committee and approved by the CEC.

Threshold score determination

Steering Committee members were asked to individually decide whether they would feel comfortable classifying each of the 30 patient profiles used in the ranking exercise as CPPD disease when considering enrolling a patient into a research study. The percentage of the Steering Committee classifying each case as CPPD disease was plotted against the total additive criteria score to visualise where the threshold may fall.

Classification criteria additive scores were then calculated for the whole derivation cohort, receiver operator characteristic (ROC) curves were plotted, and tables of sensitivity and specificity were inspected to select a preliminary threshold score that maximised specificity while retaining high sensitivity. This was done first for definite cases and definite mimickers that were eligible for scoring (ie, those who had no exclusion criteria nor sufficient criteria). Next, the sensitivity and specificity of the entire classification criteria system – including sufficient criteria and scored criteria – were calculated at the proposed threshold score among all definite cases and definite mimickers. After this, the percentage classified as CPPD disease according to the submitting clinician's rating of likelihood of CPPD disease was examined using the entire derivation cohort.

Criteria development phase 4

In Phase 4, validation of the CPPD disease classification criteria was conducted. An independent validation cohort was concurrently recruited from centres that were not contributing cases to the derivation cohort. Investigators contributing to the validation cohort were unaware of the classification criteria framework, relative item weights, and the threshold score. Recruitment, definition of cases and mimickers (controls), and blinded case adjudication were performed as for the derivation cohort. ROC curves were developed and sensitivity and specificity of the threshold score were calculated among validation cohort definite cases eligible for scoring and definite mimickers. Then, the sensitivity and specificity of the entire classification criteria system at the proposed threshold score were calculated among all definite cases and definite mimickers. Finally, using the entire validation cohort, we examined the distribution of the percentage classified as CPPD disease per the submitting clinician's rating of likelihood of CPPD disease.

Table 1 Characteristics of the subjects in the derivation and validation cohorts by patient profile

	Derivation cohort			Validation cohort		
	Definite case (n=190)	Uncertain (n=80)	Mimicker (n=148)	Definite case (n=251)	Uncertain (n=204)	Mimicker (n=162)
Symptom onset at age ≥60 years, no. (%)	144 (75.8)	63 (78.8)	76 (51.4)	201 (80.1)	147 (72.1)	81 (50.0)
Female, no. (%)	113 (59.5)	48 (60.0)	88 (59.5)	141 (56.2)	104 (51.0)	63 (38.9)
Inflammatory arthritis, no. (%)*						
Acute	175 (92.1)	56 (70.0)	116 (78.4)	244 (97.2)	161 (78.9)	138 (85.2)
Persistent	44 (23.2)	29 (36.3)	66 (44.6)	51 (20.3)	53 (26.0)	50 (30.9)
None	9 (4.7)	14 (17.5)	19 (12.8)	5 (2.0)	31 (15.2)	9 (5.6)
Race/ethnicity, no. (%)†						
Caucasian	164 (86.8)	72 (90.0)	136 (91.9)	175 (82.5)	139 (74.7)	124 (80.0)
Other‡	25 (13.2)	8 (10.0)	12 (8.1)	37 (17.5)	47 (25.3)	31 (20.0)
Regions, no. (%)						
US	50 (26.3)	19 (23.8)	43 (29.1)	120 (47.8)	113 (55.4)	54 (33.3)
Europe	131 (68.9)	54 (67.5)	91 (61.5)	117 (46.6)	76 (37.3)	92 (56.8)
New Zealand	9 (4.7)	7 (8.8)	14 (9.5)	14 (5.6)	15 (7.4)	16 (9.9)

*Patients could have more than one presentation of inflammatory arthritis.
†In the derivation cohort, ethnicity was recorded for 189 definite cases due to missing data for 1 subject. In the validation cohort, ethnicity was recorded for 212 definite cases, 186 uncertain cases, and 155 mimickers due to restrictions on sharing ethnicity data for the patient profiles of 39 definite cases, 18 uncertain cases, and 7 mimickers.
‡Due to a number of racial/ethnic groups being identified in only a few patient profiles each, the race/ethnicity data are presented in aggregate for non-Caucasian categories (designated "Other"), to maintain confidentiality.

RESULTS

Patient profiles and cohorts

Rheumatologists from 13 sites in 6 countries submitted 418 patient profiles, forming the derivation cohort: 190 definite cases, 148 definite mimickers, and 80 uncertain (62 rated −1, 0, or+1 likelihood of CPPD disease by the submitting clinician, and 18 judged uncertain by two adjudicators). Primary diagnoses among the 148 definite mimickers included gout (n=43), rheumatoid arthritis (RA; n=38), osteoarthritis (n=27), psoriatic arthritis (PsA; n=12), other inflammatory arthritis (n=11), polymyalgia rheumatica (n=6), others (n=5), and not specified (n=6). Rheumatologists from 12 sites in 6 countries submitted 617 patient profiles, forming the validation cohort: 251 definite cases, 162 definite mimickers, and 204 uncertain. Among the 162 definite mimickers, primary diagnoses were gout (n=45), RA (n=40), osteoarthritis (n=21), PsA (n=19), other inflammatory arthritis (n=19), septic arthritis (n=5), polymyalgia rheumatica (n=1), and others (n=12) (table 1) summarises the demographic and clinical characteristics of the derivation and validation cohorts.

The CEC comprised 22 experts (20 rheumatologists, 1 radiologist, and one methodologist). Thirteen members were from Europe, 6 from the US, and three from New Zealand; 41% were women. Results of the rank-ordering exercise by individual CEC members are presented in online supplemental figure S1. The CEC identified key factors important for distinguishing CPPD disease from mimickers by reviewing ranking results and ORs (see online supplemental tables S2–S9). These key factors were as follows: presence of CPP crystals in SF (or in biopsy tissue), presence of CDS, symptom onset after age 60 years, persistent inflammatory arthritis, typical episode(s) of acute inflammatory arthritis defined by acute onset or acute worsening of joint pain with joint swelling and/or warmth that resolves irrespective of treatment, location of typical episode(s) (knee, wrist, first MTP joint, other peripheral joints), metabolic conditions that predispose to CPPD (hereditary hemochromatosis, primary hyperparathyroidism, hypomagnesemia, Gitelman syndrome, hypophosphatasia, or familial history of CPPD disease), radiographic osteoarthritis of specific hand joints (scaphotrapeziotrapezoidal joint without first carpometacarpal joint involvement, radiocarpal joint, second metacarpophalangeal (MCP) joint, third MCP joint), and imaging evidence of CPPD (linear or punctate calcification in the hyaline cartilage or fibrocartilage) in peripheral joints. Imaging item definitions and example images were developed in parallel to this endeavour and have been previously published.[21] Onset of symptoms after 60 years of age was included as a domain even though it was not associated with CPPD disease in the case-mimicker analysis. This decision was based on expert opinion and demographic characteristics of patients with CPPD disease in the published literature. Additionally, the lack of association with age was thought to be due to recruitment of potential mimickers who were older adults, that is, the age group in which CPPD disease is a possibility.

Entry, exclusion, and sufficient criteria

The CPPD disease classification framework must be applied in the following sequence (figure 2): (1) entry criteria must be fulfilled; (2) exclusion criteria must be absent; (3) sufficient criteria are evaluated (present vs absent); and (4) if sufficient criteria are absent, then proceed with scoring of domains.

CEC members agreed that to be classified as CPPD disease, an individual must have had at least one episode of joint pain, swelling, or tenderness at a peripheral joint or axial joint (entry criteria). Symptomatic CPPD disease is required for classification since the intention of classification criteria is to enable enrollment into clinical trials that would focus on symptomatic individuals.

Exclusion criteria were intended to identify individuals in whom all musculoskeletal symptoms potentially attributable to CPPD disease were more likely explained by an alternate condition such as RA, gout, PsA, or osteoarthritis, to whom the classification criteria should not be further applied. The CEC noted that symptom attribution can be difficult, and if at least some symptoms are attributable to CPPD disease, then the classification criteria can be applied. It was also agreed that the classification criteria would apply to CPPD disease as a whole, and

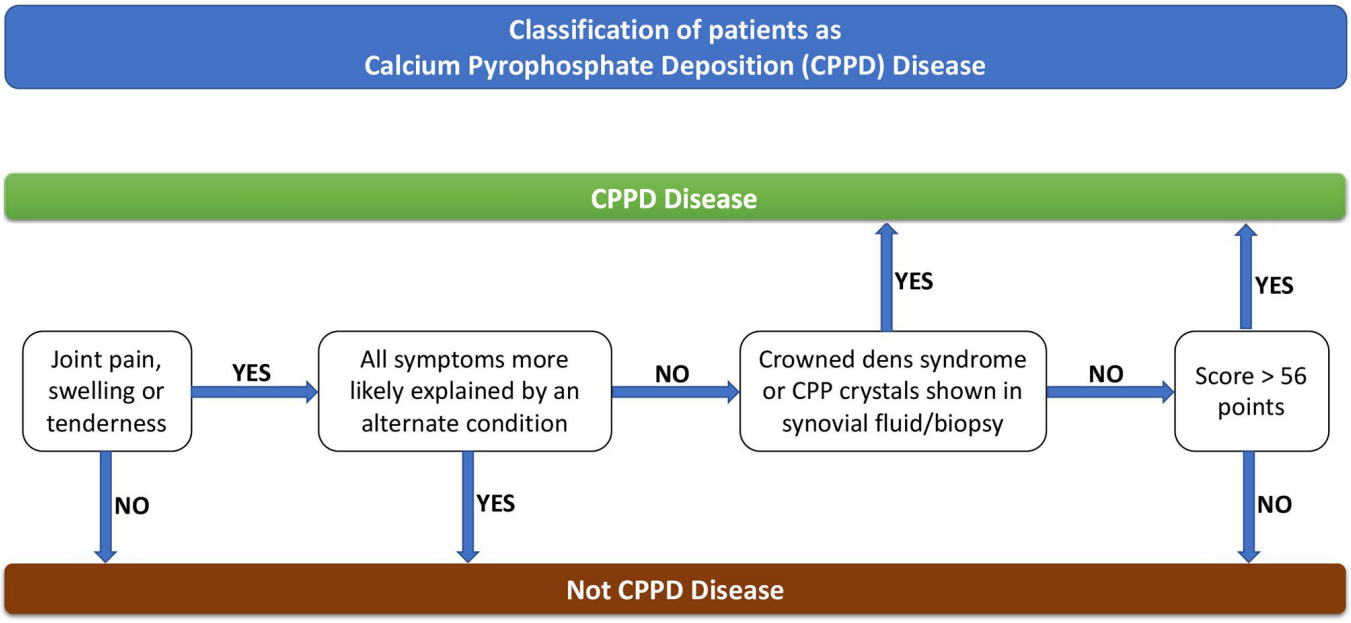

Figure 2 Conceptual schematic for applying the CPPD disease classification criteria.

development of separate classification criteria for each clinical presentation would not be attempted within this endeavour.

Two sufficient criteria were agreed on: CDS and SF analysis demonstrating CPP crystals in a joint with swelling, tenderness, or pain (any quantity of intra- and/or extracellular crystals). In the initial MCDA exercise, presence of SF CPP crystals and CDS accounted for>40% of the weighting, and cases with SF CPP crystals or CDS had consistently been ranked most likely to have CPPD disease in the ranking exercise.

Sufficient criteria are also met if CPP crystals are demonstrated on histopathologic assessment of joint tissue, provided the patient does not meet exclusion criteria. For instance, articular cartilage CPPD disease in patients with end-stage osteoarthritis cannot be used to classify the patient as having CPPD disease when all symptoms are better explained by osteoarthritis.[26]

Domains and categories

The final framework included four clinical, 1 laboratory, and three imaging domains (table 2). The levels within each domain are scored based on a patient's disease experience to date, such that if a higher and a lower weighted level were fulfilled at different points in time, the higher one is scored.

Assigning relative weights to domains and categories

All weights were initially zero or positive. Domain C (sites of typical episodes of inflammatory arthritis), domain E (SF CPP crystal analysis), and domain G (imaging evidence of CPPD in a symptomatic joint) were re-zeroed such that the level least likely to be present in a person with CPPD disease was assigned negative weight to maintain face validity (for details see online supplemental results and online supplemental table S10).

In domain G (imaging of a symptomatic joint), advanced imaging modalities were initially considered separately from CR; however, item weights differed by<1% so advanced imaging and CR were combined. Item weights, re-zeroing, merging of levels, and rounding-off are reported in online supplemental table S10.

The final ACR/EULAR CPPD disease classification criteria and weights are presented in table 2. The CEC agreed that imaging of at least one symptomatic peripheral joint is required for scoring when sufficient criteria are not fulfilled, given the important role of imaging when considering the likelihood of CPPD disease. A web-based calculator is accessible at https://bblinks.live/acr-classification-criteria-for-cppd-disease.

A plot of the percent agreement among Steering Committee members voting 'yes' for classifying patients as having CPPD disease for enrollment in a research study vs the final additive classification criteria score suggested the feasibility of a score threshold between 53 and 57 (figure 3).

Classification criteria performance in the derivation and validation cohorts

Among the 190 definite cases in the derivation cohort, 130 fulfilled sufficient criteria and were ineligible for scoring. The classification criteria score separated the remaining 60 definite cases from 148 mimickers with an area under the curve (AUC) of 0.95 (95% CI 0.93 to 0.98) (figure 4). A threshold score of>56 was chosen, as this threshold maximised specificity at 87.9% while retaining a high sensitivity of 92.2% (see online supplemental table S11). When the entire classification criteria system (ie, entry, exclusion, sufficient, and scored criteria) was applied to all definite cases and definite mimickers in the derivation cohort, the threshold score of>56 had a specificity of 87.9% and sensitivity of 97.8%.

The face validity of a threshold score of>56 was assessed. Examples of patient profiles with scores just below the threshold included the following: (1) a single typical episode of acute inflammatory arthritis involving the wrist, with symptom onset after age 60 years and chondrocalcinosis only at that wrist (score 56); (2) a single typical episode of acute inflammatory arthritis involving the knee, with symptom onset at age<60 years and chondrocalcinosis in that knee only (score 53); and (3) joint pain without inflammatory arthritis with symptom onset at age>60 years, presence of osteoarthritis in the radiocarpal joints bilaterally and second MCP joints, and chondrocalcinosis in the wrists bilaterally (score 50). The CEC reviewed these cases and agreed that they should not be classified as CPPD disease, because sufficient clinical uncertainty existed.

Table 2 ACR/EULAR classification criteria for CPPD disease

Definition of criteria

The CPPD disease classification criteria should be applied in the following order:

1. Entry criterion: Ever had at least one episode of joint pain, swelling, or tenderness.*
2. Absolute exclusion criteria: All symptoms are more likely explained by an alternative condition (such as rheumatoid arthritis, gout, psoriatic arthritis, OA, etc.).
3. Sufficient criteria: Presence of either crowned dens syndrome or synovial fluid analysis demonstrating CPP crystals in a joint with swelling, tenderness, or pain.†

An individual is classified as having CPPD disease if the entry criterion is met, exclusion criteria are not met, and at least one sufficient criterion is fulfilled.

If none of the sufficient criteria are present, an individual is classified as having CPPD disease if the sum of the criteria is>56 points.

Scoring of criteria

Items can be scored if they were ever present during a patient's lifetime. If a patient fulfils>1 item in a given domain, only the highest weighted item will be scored. Imaging of at least one symptomatic joint by CR, US, CT, or DECT is required.

Domains and levels	Points
A Age at onset of joint symptoms (pain, swelling, and/or tenderness)	
≤60 years	0
>60 years	4
B Time course and symptoms of inflammatory arthritis‡	
No persistent or typical inflammatory arthritis	0
Persistent inflammatory arthritis	9
One typical acute arthritis episode	12
More than one typical acute arthritis episode	16
C Sites of typical episode(s) of inflammatory arthritis in peripheral joints	
First MTP joint	−6
No typical episode(s)	0
Joint(s) other than wrist, knee, or first MTP joint	5
Wrist	8
Knee	9
D Related metabolic diseases§	
None	0
Present	6
E Synovial fluid crystal analysis from a symptomatic joint¶	
CPP crystals absent on 2 occasions	−7
CPP crystals absent on 1 occasion	−1
Not performed	0
F OA of hand/wrist on imaging (defined as present if the K/L score is≥2)	
None of the below findings or no wrist/hand imaging performed	0
OA of radiocarpal joints bilaterally	2
≥2 of the following findings: STT joint OA without first CMC joint OA; second MCP joint OA; third MCP joint OA	7
G Imaging evidence of CPPD in symptomatic peripheral joint(s)**	
None on US, CT, or DECT (and absent on CR or CR not performed)	−4
None on CR (and US, CT, DECT not performed)	0
Present on either CR, US, CT, or DECT	16
H Number of peripheral joints with evidence of CPPD on any imaging modality regardless of symptoms**	
None	0
1	16
2–3	23
≥4	25

*Episode occurring in a peripheral joint or, in the case of crowned dens syndrome, an axial joint such as C1/C2.

†Crowned dens syndrome is defined as presence of a) clinical features and b) imaging features. Clinical features include acute or subacute onset of severe pain localised to the upper neck with elevated inflammation markers, limited rotation, and often fever. Mimicking conditions such as polymyalgia rheumatica and meningitis should be excluded. Imaging features include conventional CT showing calcific deposits, typically linear and less dense than cortical bone, in the transverse retro-odontoid ligament (transverse ligament of the atlas), often with an appearance of 2 parallel lines in axial views. Calcifications at the atlanto-axial joint, alar ligament, and/or in pannus adjacent to the tip of the dens are also characteristic. Dual-energy computed tomography (DECT) features include a dual-energy index between 0.016 and 0.036. Both the clinical features and the imaging features must be present. Sufficient criteria are also met if calcium pyrophosphate (CPP) crystals are demonstrated on histopathologic analysis of the joint tissue, provided that the patient is eligible for classification, that is, does not already meet the exclusion criteria. For instance, articular cartilage CPP crystal deposition in patients with end-stage osteoarthritis (OA) cannot be used to classify the patient as having calcium pyrophosphate deposition (CPPD) disease when *all* symptoms are better explained by the presence of OA (exclusion criteria).

‡Persistent inflammatory arthritis was defined as ongoing joint swelling with pain and/or warmth in≥1 joint(s). Typical episode was defined as an episode with acute onset or acute worsening of joint pain with swelling and/or warmth that resolves irrespective of treatment.

§Including hereditary hemochromatosis, primary hyperparathyroidism, hypomagnesemia, Gitelman syndrome, hypophosphatasia, or familial history of CPPD disease.

¶Synovial fluid analysis should be performed by an individual trained in the use of compensated polarised light microscopy for crystal identification.

**Imaging of at least one symptomatic peripheral joint by CR, US, CT, or DECT is required to be considered for classification if sufficient criteria are not met. Imaging evidence of CPPD refers to calcification of the fibrocartilage or hyaline cartilage. Do not score calcification of the synovial membrane, joint capsule, or tendon. Imaging definitions are published elsewhere.[21] Only consider involvement of peripheral joints.

CMC, carpometacarpal; CR, conventional radiography; CT, computed tomography; K/L, Kellgren/Lawrence; MCP, metacarpophalangeal; MTP, metatarsophalangeal; STT, scaphotrapeziotrapezoid; US, ultrasound.

Among the 251 definite cases in the validation cohort, 186 fulfilled sufficient criteria and were ineligible for scoring. The threshold score of>56 separated the remaining 65 definite cases from 162 mimickers with an AUC of 0.98 (95% CI 0.96 to 0.99) (figure 4) and had a sensitivity and specificity of 96.5% and 92.5%, respectively, in this

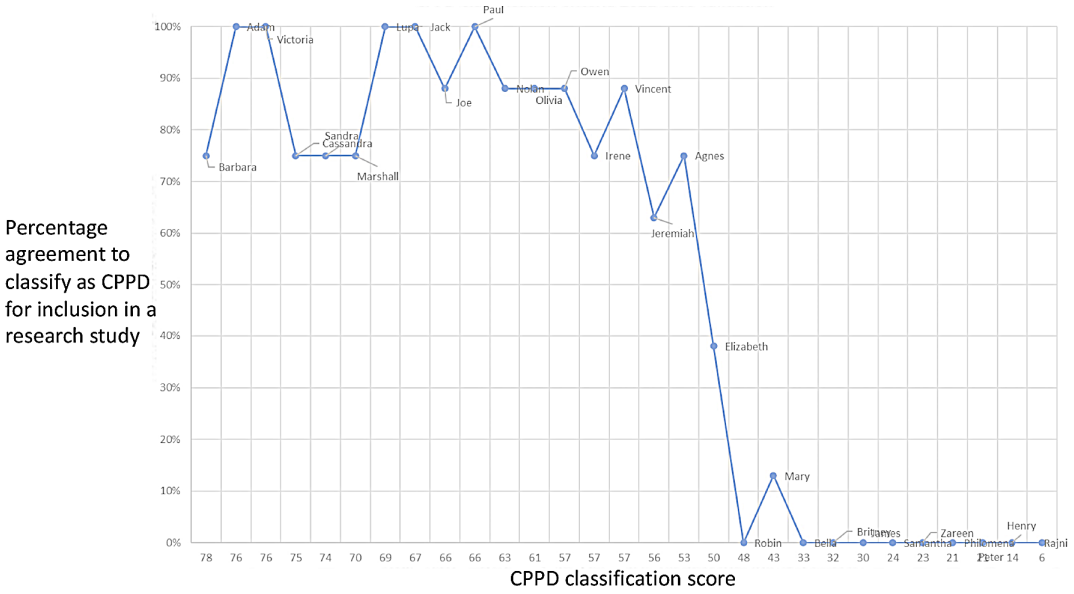

Figure 3 Plot of percent agreement of Steering Committee members for classifying patient profiles as CPPD disease for inclusion in a research study (n=8 participating Steering Committee members). The patient profiles were given pseudonyms.

subgroup of the validation cohort. Assessment of the entire classification criteria framework (entry, exclusion, and sufficient criteria and the threshold score of>56) among the 413 definite cases and definite mimickers in the validation cohort demonstrated a sensitivity of 99.2% and specificity of 92.5%. The percentage of patient profiles classified as CPPD disease increased with the submitting clinician's rating of CPPD disease in both the derivation and validation cohorts (see online supplemental table S12).

DISCUSSION

These are the first-ever validated classification criteria for CPPD disease and we believe they will facilitate future observational studies and clinical trials in CPPD disease. These classification criteria were derived and validated using established methodology relying on data from 751 patient profiles and expert consensus. The classification criteria demonstrated high sensitivity and specificity in an independent validation cohort. Presence of CDS (imaging plus clinical features) or the identification of CPP crystals in SF from a symptomatic joint were sufficient for classification as CPPD disease as long as exclusion criteria were not met (eg, another condition did not explain the entire presentation). Patients without those features can be classified by scoring the remaining imaging and clinical criteria.

Among the scored criteria, imaging features and recurrent typical episodes of acute inflammatory arthritis carried the greatest weight. This reflects consensus among the multidisciplinary CEC that imaging evidence of CPP crystal deposition and acute inflammatory arthritis are central constructs in CPPD disease when laboratory evidence of SF CPP crystals is lacking. An imaging study of at least one symptomatic joint is required in patients not meeting sufficient criteria. No additional imaging is absolutely required; however, the more peripheral joints that are imaged, the greater the potential score, as may be the case for centres in which patients' joints are routinely imaged bilaterally. The Steering Committee considered requiring imaging of a standardised set of joints (eg, bilateral knees and wrists) when considering patients for classification, but decided against this due to concerns about practical feasibility of this approach. Requiring imaging of at least one symptomatic peripheral joint was considered a reasonable compromise that would permit widespread, more

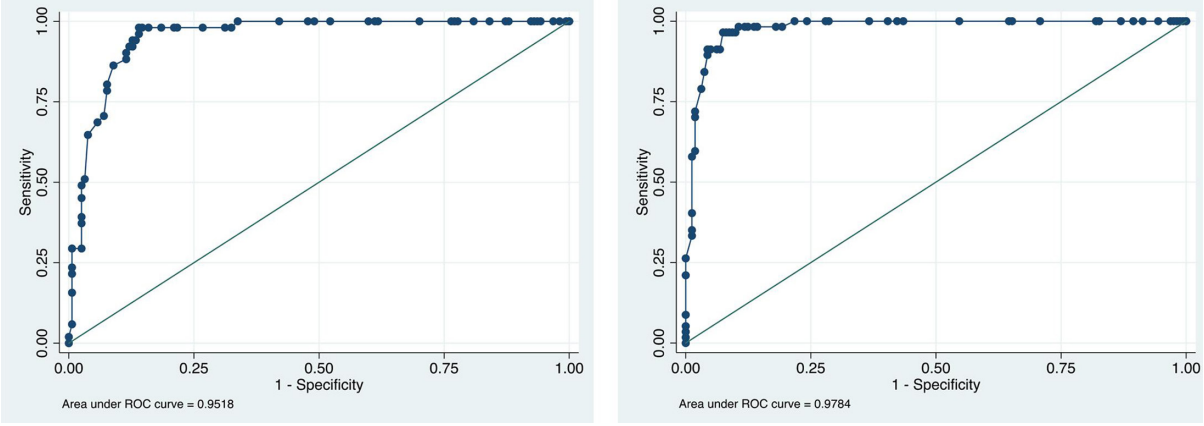

Figure 4 Receiver operating characteristic (ROC) curves in the derivation cohort (left) and validation cohort (right) for the patients who were eligible to be scored for classification of CPPD disease. In the derivation cohort, data for 60 definite cases and 148 definite mimickers were included. In the validation cohort, data for 65 definite cases and 162 definite mimickers were included.

equitable application of these classification criteria in all potential CPPD disease patients internationally.

The criteria highlight the importance of imaging evidence of CPP crystal deposition, as its absence prevents classification if an individual does not meet sufficient criteria. The highest levels of 2 imaging domains account for nearly half of the weighting, comprising evidence of CPP crystals in a symptomatic joint, and evidence of CPP crystals in≥4 peripheral joints. While imaging features alone in a patient with joint pain would not be sufficient for classification, they were weighted heavily in the MCDA exercise such that they became a necessary component in the scored criteria. The CEC discussed at length the high sensitivity of ultrasound and CT, particularly in early CPPD disease, compared with CR.[10 27] This higher sensitivity is reflected in negative points assigned if no evidence of CPPD disease is found on advanced imaging. Because advanced techniques demonstrate high, yet imperfect specificity for CPPD disease, the group did not reach agreement with regard to evidence of CPPD on advanced imaging as being sufficient to confer a classification of CPPD disease. Imaging evidence of CPPD on advanced imaging modalities and evidence on CR received nearly equal weight (<1% difference), given the high specificity associated with both modalities, resulting in their being grouped together and reflecting expert consensus that imaging evidence of CPPD on any modality is equally convincing.

A practical gold standard for CPPD disease does not exist in clinical settings, as SF CPP crystal positivity on polarised light microscopy is specific but has a high false-negative rate and significant interobserver variability.[11–14] Challenges of CPP crystal identification include small crystal size and absent or weak positive birefringence.[11] Furthermore, feasibility of CPP crystal identification may be limited by the difficulty of joint aspiration, particularly from small joints. Thus, although the CEC determined that presence of any quantity of CPP crystals in a symptomatic joint can lead to classifying an individual as having CPPD disease, requiring presence of SF CPP crystals in all cases is not practical for classification. To that end, the proposed criteria are intended to enable accurate classification of CPPD disease, regardless of whether joint aspiration was performed. Nevertheless, joint aspiration remains important to clinically diagnose CPPD disease in practice and to exclude mimicking conditions including gout and septic arthritis.

Attribution of symptoms to CPPD disease can be challenging, particularly in patients with osteoarthritis or in those with RA, as these diseases can coexist with CPPD disease and/or be misdiagnosed initially.[28–30] These CPPD disease classification criteria acknowledge the frequent coexistence of CPPD disease with other rheumatic and musculoskeletal diseases (RMDs), by excluding from classification only those patients for whom all symptoms are better explained by another condition, and allowing investigators to attempt classification if they suspect that at least some symptoms are due to CPPD disease. Distinguishing between CPP crystal deposition and basic calcium phosphate deposition on imaging can be challenging, although imaging definitions for CPPD disease developed as part of this project may mitigate this issue.[21]

The current endeavour has strengths. First, the criteria establish the clinical picture of CPPD disease as an inflammatory arthritis among older adults, typically manifesting with acute inflammatory features (and occasionally with chronic inflammation) and a predilection for knee and wrist joints. Discussions about the threshold made clear that requiring joint inflammation provided superior specificity for CPPD disease classification while maintaining>90% sensitivity in patients who lack evidence of CDS or SF CPP crystals. Inflammatory arthritis is not absolutely required; individuals with osteoarthritis and SF CPP crystals could be classified by sufficient criteria if not all symptoms are explained by osteoarthritis. Critically, the classification criteria must be applied in the order presented in figure 2 and table 2 so that individuals whose symptoms are attributable to osteoarthritis and who have SF CPP crystals would not be classified as having CPPD disease. Second, patient profiles in the derivation and validation cohorts were collected from a large international pool, supporting generalizability of the findings. Nevertheless, further testing of the criteria in other populations would be valuable. Third, we followed well-established methodology for classification criteria development, supporting the validity of the process and final product. Fourth, the criteria allow people with CPPD disease and another RMD to be classified as having CPPD disease.

Several limitations warrant a mention. Given the absence of a pathologic gold standard for CPPD disease diagnosis, expert opinion was used to label cases and mimickers. We excluded a significant number of uncertain patient profiles from ROC analyses and sensitivity/specificity calculations, as their true case/control status could not be reliably determined. The heterogeneous nature of CPPD disease can lead to differences in clinical opinion about whether particular features are attributable to CPPD disease, reflected in the clinician's rating of −1 to +1 for likelihood of CPPD disease and/or lack of agreement among adjudicators. Together with its heterogeneous nature, different rheumatologists' perceptions of the clinical phenotype that may be attributed to CPPD disease vary substantially. To minimise the possibility that differences in opinion would affect threshold determination, we adopted stringent case and mimicker definitions – often requiring unequivocal evidence of CPPD disease or agreement between the submitting clinician and two experts. The inclusion of only definite cases and definite mimickers may have contributed to the classification criteria's high sensitivity and specificity in our validation cohort. Nevertheless, the proportion of individuals classified as having CPPD disease increased progressively across the submitting clinician's rating, including among cases deemed uncertain (rated −1, 0, or+1 by the submitting clinician), further supporting the internal validity of this approach. Even so, we recommend that the performance of these criteria be evaluated in other cohorts. Despite challenges with attribution, the CPPD disease classification criteria enable identification of a relatively homogeneous group of patients with a preponderance of evidence for CPP crystal deposition and characteristic clinical symptoms, in whom all features are not better explained by another disease. We did not address asymptomatic CPPD, since the purpose of classification criteria is to identify individuals with symptomatic disease to be included in clinical studies. The current criteria represent an endeavour to identify patients with symptomatic CPPD disease with maximal sensitivity and specificity for inclusion in prospective studies, including clinical trials and observational studies.

In conclusion, the 2023 ACR/EULAR classification criteria for CPPD disease represent the first validated criteria set for the condition, with robustly validated performance characteristics. Future studies of CPPD disease may employ these as inclusion criteria for participant screening and enrollment.

Author affiliations
[1]Academic Rheumatology, University of Nottingham, Nottingham, UK
[2]Division of Rheumatology, Inflammation and Immunity, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts, USA
[3]Department of Rheumatology, Lille Catholic University, Saint-Philibert Hospital, Lille, France

[4]Université de Paris, INSERM, UMR-S 1132 BIOSCAR, and Service de Rhumatologie, AP-HP, Lariboisière Hospital, Paris, France
[5]Department of Medicine, University of Auckland, Auckland, New Zealand
[6]Department of Medicine, Section of Rheumatology, Boston University School of Medicine, Boston, Massachusetts, USA
[7]Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin, USA
[8]Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[9]Rheumatology Department, IRCCS Istituto Ortopedico Galeazzi, Milan, Italy
[10]David Geffen School of Medicine, University of California, Los Angeles, California, USA
[11]Veterans Administration for Greater Los Angeles, Los Angeles, California, USA
[12]Academic Rheumatology Center, Università degli Studi di Torino, Turin, Italy
[13]Université Paris Cité, Faculté de Santé, Paris, France
[14]School of Medicine and Medical Science, University College Dublin, Dublin, Ireland
[15]Mater Misericordiae University Hospital, Dublin, Ireland
[16]Rheumatology Unit, Department of Medicine, University of Padova, Padova, Italy
[17]Department of Rheumatology, Hospital General Universitario Elda, Elda, Spain
[18]Department of Clinical Medicine, Universidad Miguel Hernandez, Elche, Spain
[19]Department of Medicine, Rheumatology Section, Hospital General Universitario de Alicante, Universidad Miguel Hernández, Alicante, Spain
[20]Rheumatology Unit, Department of Clinical and Molecular Sciences, Polytechnic University of Marche, Ancona, Italy
[21]Rheumatology Division, Cruces University Hospital, Bilbao, Spain
[22]Arthritis Investigation Group, Biocruces-Bizkaia Health Research Institute, Spain, Department of Medicine, Medicine and Nursing School, University of the Basque Country, and Basque Country Rheumatology Society, Bilbao, Spain
[23]Lausanne University Hospital, Lausanne, Switzerland
[24]VieCuri Medical Centre, Venlo, The Netherlands
[25]Medical Cell BioPhysics Group, University of Twente, Enschede, The Netherlands
[26]Department of Medicine, Rheumatology Unit, Massachusetts General Hospital, and Harvard Medical School, Boston, Massachusetts, USA
[27]Department of Medicine, University of Otago, Christchurch, New Zealand
[28]Rheumatology Unit, Grande Ospedale Metropolitano Niguarda, Milan, Italy
[29]Department of Rheumatology, Te Whatu Ora–Health New Zealand Waikato, Hamilton, New Zealand
[30]Division of Rheumatology, University of California, Los Angeles, California, USA
[31]Department of Rheumatology, Lausanne University Hospital, Lausanne, Switzerland
[32]Section of Rheumatology, Department of Medical Sciences, University of Ferrara, Ferrara, Italy
[33]Azienda Ospedaliera-Universitaria di Ferrara (Cona FE), Cona FE, Italy
[34]Department of Medicine, Rheumatology Unit, Massachusetts General Hospital, Boston, Massachusetts, USA
[35]Highland Hospital, Oakland, California, USA
[36]Rheumatology Division, Local Health Unit (ASL), Turin-3, Collegno and Pinerolo, Italy
[37]Department of Rheumatology, IRCCS Galeazzi-Sant'Ambrogio Hospital, Milan, Italy
[38]Epidemiology Unit, Italian Society for Rheumatology, Milan, Italy
[39]Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy
[40]Harvard Medical School, Boston, Massachusetts, USA
[41]Department of Medicine, General Medicine and Rheumatology, Middlemore Hospital, Counties Manukau Health District, Auckland, New Zealand
[42]San Diego Veterans Administration Healthcare Service, and University of California, San Diego, California, USA

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Twitter Augustin Latourte @A_Latourte, Francisca Sivera @FranciscaSivera and Carlo Scirè @rthritis

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Contributors All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. AAb had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design: AAb, SKT, TP, AL, ND, TN, AR, FB, HKE, GF, JFG, AMI, GMM, RR, FP-R, MJK, LKS, FAF, MKa, KL, AMH, RT, WJT, HKC. Acquisition of data: AR, GF, JFG, AMI, GMM, RR, MA, EC, MD, AS, TLJ, MJK, LKS, JY, AAd, UA, TA, EB, AB, JD, EM, MAF, FAF, EF, JH, MJ, MKa, MKi, KL, GMN, PS-P, CS, ES, SS, JRS, LT, CX, CY, RT, HKC. Analysis and interpretation of data: AF, TB, HKE, JFG, AMI, FL, GMM, RR, PR, FS, MA, EP, AS, MJK, JY, MJ, AMH, RT, WJYT, HKC.

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ORCID iDs
Abhishek Abhishek http://orcid.org/0000-0003-0121-4919
Sara K Tedeschi http://orcid.org/0000-0001-9475-1363
Tristan Pascart http://orcid.org/0000-0002-8395-826X
Augustin Latourte http://orcid.org/0000-0002-1087-7768
Nicola Dalbeth http://orcid.org/0000-0003-4632-4476
Tuhina Neogi http://orcid.org/0000-0002-9515-1711
Amy Fuller http://orcid.org/0000-0002-9669-1816
Fabio Becce http://orcid.org/0000-0001-8444-8504
Thomas Bardin http://orcid.org/0000-0002-5080-4790
Hang-Korng Ea http://orcid.org/0000-0002-2393-7475
Georgios Filippou http://orcid.org/0000-0002-1647-2083
John Fitzgerald http://orcid.org/0000-0002-8419-7538
AnnaMaria Iagnocco http://orcid.org/0000-0001-5592-724X
Frédéric Lioté http://orcid.org/0000-0003-4419-0726
Geraldine M McCarthy http://orcid.org/0000-0003-4078-8499
Roberta Ramonda http://orcid.org/0000-0002-9683-8873
Pascal Richette http://orcid.org/0000-0003-2132-4074
Mariano Andrés http://orcid.org/0000-0002-0219-9055
Edoardo Cipolletta http://orcid.org/0000-0002-6881-8197
Eliseo Pascual http://orcid.org/0000-0002-3056-4478
Lisa K Stamp http://orcid.org/0000-0003-0138-2912
Uri Arad http://orcid.org/0000-0002-2881-7739
Alessandra Bortoluzzi http://orcid.org/0000-0003-2416-8134
Carlo Scirè http://orcid.org/0000-0001-7451-0271
Silvia Sirotti http://orcid.org/0000-0001-9795-131X
Chio Yokose http://orcid.org/0000-0001-7557-3303
Hyon K Choi http://orcid.org/0000-0002-2862-0442

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