

SYSTEMATIC REVIEW & META-ANALYSIS

Diagnostic Accuracy of Ultrasonography and Conventional Radiography for Calcium Pyrophosphate Deposition Disease Against Crystal-Proven Reference Standards: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Calcium pyrophosphate deposition (CPPD) disease, including acute calcium pyrophosphate (CPP) crystal arthritis (pseudogout), is common in older adults, but synovial fluid crystal analysis is often unavailable, so imaging carries much of the diagnosis.

Objective: To compare the accuracy of ultrasonography and conventional radiography for CPP deposition against a crystal-proven reference standard.

Methods: PubMed, Europe PMC, OpenAlex and Scopus were searched without date or language limits, with citation searching. Studies reporting 2×2 data for ultrasonography or radiography against CPP crystals in synovial fluid or tissue were included. Bivariate random-effects models pooled sensitivity and specificity; bivariate meta-regression compared the tests; QUADAS-2 and GRADE assessed risk of bias and certainty.

Results: Eighteen studies (21 reports) were included. Ultrasonography (15 studies; 1,352 units [participants, knees or menisci], 514 CPP-positive) had a sensitivity of 87.8% (95% CI 79.0–93.2) and specificity of 89.4% (82.2–94.0); radiography (11 studies; 1,053 units) had 52.6% (42.3–62.6) and 96.2% (92.2–98.2). In eight studies applying both tests to the same participants, ultrasonography was 30.4 percentage points more sensitive and 8.2 points less specific ($p < 0.001$ for both). In consecutive patients with effusion or acute arthritis, ultrasonography had 80.8% sensitivity and 89.2% specificity. Certainty was low to moderate.

Conclusion: Against crystal proof, ultrasonography detected most CPP deposition, whereas radiography missed about half but rarely gave false-positive results. Ultrasonography appears to be the more useful first imaging test when crystals cannot be sought; a negative radiograph does not exclude CPPD, and neither test establishes acute CPP crystal arthritis on its own.

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1. Introduction

Calcium pyrophosphate deposition (CPPD) disease ranks third among inflammatory arthritides, after gout and rheumatoid arthritis, and it is a frequent cause of acute monoarthritis in older adults, in whom it was historically called pseudogout. How common is the underlying calcium pyrophosphate (CPP) deposition? Imaging and synovial fluid surveys give a sobering answer. Ultrasonography found fibrocartilage deposits in almost half of people older than 80 years who attended with knee pain,¹ and radiographic chondrocalcinosis was present in 4.1% of hospital patients aged 50 years or older in Türkiye.² At a large tertiary center, about one in five synovial fluid samples contained CPP crystals.³

CPPD is no longer seen as a benign radiographic curiosity. Recognizing it has consequences beyond the joint. It has been linked to cardiovascular events,^{4,5} to a higher estimated cardiovascular risk⁶ and to greater resource use during acute coronary syndromes.⁷ Fractures are more frequent,^{8,9} as is nephrolithiasis,¹⁰ and acute CPP crystal arthritis is followed by more hip and knee arthroplasty,¹¹ while chondrocalcinosis predicts incident knee osteoarthritis.¹² A correct diagnosis therefore calls for assessment of bone health, cardiovascular risk and associated metabolic disorders.

Patients describe pain comparable to that of gout, with large unmet treatment needs.¹³ Acute and chronic inflammatory phenotypes differ in their clinical and imaging features,¹⁴ and

genetic work has named ENPP1, a regulator of extracellular pyrophosphate, as a candidate therapeutic target.¹⁵ In hospital, flares are triggered by older age, female sex and in-hospital antibiotic use.¹⁶ Recognition is often late. In one acute-care series, fewer than half of inpatients received effective treatment within a day.¹⁷

The reference diagnosis rests on identifying rhomboid, weakly positively birefringent CPP crystals by compensated polarized light microscopy. The test is not available everywhere. Where it is available, it remains imperfect: observers agree less often on CPP crystals than on monosodium urate crystals,¹⁸ and external quality assessment has shown persistent difficulty in telling the two apart.¹⁹ Synovial fluid analysis misses some deposits that are found in tissue,²⁰ extracellular crystals are less specific for disease than intracellular ones,²¹ and Raman spectroscopy changes a proportion of microscopic identifications.^{22,23} At a Latin American tertiary center, crystal analysis changed the referring diagnosis in one in seven patients.²⁴ Small, deep or dry joints often cannot be aspirated at all. CPPD also mimics rheumatoid arthritis and gout, and it can coexist with septic arthritis.^{25–27}

A correct label matters for management. Acute flares respond to colchicine, glucocorticoids or interleukin-1 blockade,^{28–30} whereas chronic disease needs different long-term strategies.³¹ The diagnosis should also prompt a search for associated metabolic disorders and for precipitating drugs such as diuretics and proton-pump inhibitors.^{32–36} Imaging

therefore carries much of the diagnosis. The American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria accept CPP crystals in synovial fluid as sufficient and otherwise give heavy weight to imaging findings.³⁷ The Outcome Measures in Rheumatology (OMERACT) group has standardized ultrasound definitions and a scoring system,³⁸ and EULAR recommends imaging when crystal analysis is not possible.³⁹

The two imaging tests examine deposition in different ways. On conventional radiography, chondrocalcinosis appears as fine linear or punctate opacities in fibrocartilage (the menisci and the triangular fibrocartilage of the wrist) and in hyaline cartilage. Calcification of the capsule, tendons and synovium may accompany it. Ultrasonography shows hyperechoic deposits in the same structures. It can examine several joints at the bedside without radiation, and dynamic assessment helps separate deposits from artifacts. Radiography is inexpensive and available in almost every hospital. Ultrasonography depends on the equipment and, above all, on the training of the examiner. For an internist facing an older patient with acute monoarthritis, two practical questions arise: how often does each test miss deposition, and how often does it suggest deposition that is not there?

The only earlier meta-analysis that pooled ultrasonography and conventional radiography combined crystal-proven and clinical-criteria reference standards, and it found the reference standard to be the main source of heterogeneity.⁴⁰ The systematic review behind the EULAR recommendations described the accuracy data narratively.⁴¹ There is a built-in problem. Clinical criteria that themselves contain radiographic chondrocalcinosis cannot fairly judge radiography. Since then, studies have compared imaging with histology of surgical specimens, introduced consensus radiographic definitions, evaluated the hip and targeted scanning protocols in acute arthritis, and tested newer techniques such as dual-energy computed tomography and deep learning, with mixed results.^{42–44} Evidence from Asia remains scarce and has relied on clinical criteria.⁴⁵ The gap matters in settings such as Indonesia, where polarized microscopy is rarely available outside referral centers but internists and rheumatologists increasingly perform ultrasonography.

The contribution of this study is threefold. It restricts the reference standard to crystal identification in synovial fluid or tissue, it estimates the accuracy of ultrasonography and radiography with bivariate models that respect the correlation between sensitivity and specificity, and it compares the two tests directly within studies that applied both to the same participants. The aim was to estimate and compare the diagnostic accuracy of ultrasonography and conventional radiography for CPP deposition against a crystal-proven reference standard and to explore sources of heterogeneity. A further aim was practical: to translate the pooled estimates into post-test probabilities that are useful in internal medicine.

2. Methods

2.1 Study design

This systematic review and diagnostic test accuracy meta-analysis was reported according to the Preferred Reporting

Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement⁴⁶ and conducted following the Cochrane guidance for reviews of diagnostic test accuracy.⁴⁷ The review question, eligibility criteria, data items and analysis plan were defined before the searches were run and are summarized in the Supplementary Material. The review used published aggregate data only. The target condition was CPP deposition, that is, the presence of CPP crystals in the examined joint or tissue, rather than any specific clinical phenotype of CPPD disease.

2.2 Search strategy

PubMed/MEDLINE, Europe PMC, OpenAlex and Scopus were searched from inception without language or date restrictions. The strategy combined three concept blocks: CPPD (calcium pyrophosphate, chondrocalcinosis, pseudogout and related free-text terms), imaging (ultrasonography, radiography and other imaging terms) and diagnostic accuracy or a crystal-proven reference (sensitivity, specificity, synovial fluid, histology, polarized light microscopy). The PubMed string was:

("Chondrocalcinosis"[Mesh] OR "Calcium Pyrophosphate"[Mesh] OR "calcium pyrophosphate"[tiab] OR chondrocalcinosis[tiab] OR pseudogout[tiab] OR "pseudo-gout"[tiab] OR CPPD[tiab] OR "CPP crystal"[tiab] OR "CPP deposit"[tiab] OR "pyrophosphate arthropath"[tiab] OR "pyrophosphate crystal"[tiab] OR "cartilage calcification"[tiab] OR "meniscal calcification"[tiab] OR "crowned dens"[tiab]) AND ("Ultrasonography"[Mesh] OR "Radiography"[Mesh] OR "Tomography, X-Ray Computed"[Mesh] OR "diagnostic imaging"[sh] OR ultrasound[tiab] OR ultrasonograph[tiab] OR sonograph[tiab] OR ultrasonic[tiab] OR radiograph[tiab] OR "x-ray"[tiab] OR "plain film"[tiab] OR "computed tomography"[tiab] OR "computerized tomography"[tiab] OR "computerized tomography"[tiab] OR CT[tiab] OR DECT[tiab] OR "dual-energy"[tiab] OR "dual energy"[tiab] OR "cone-beam"[tiab] OR "photon-counting"[tiab] OR imaging[tiab]) AND ("Sensitivity and Specificity"[Mesh] OR "ROC Curve"[Mesh] OR "Synovial Fluid"[Mesh] OR sensitivity[tiab] OR specificity[tiab] OR accuracy[tiab] OR "predictive value"[tiab] OR "receiver operating"[tiab] OR "area under"[tiab] OR "likelihood ratio"[tiab] OR "gold standard"[tiab] OR "reference standard"[tiab] OR validity[tiab] OR "synovial fluid"[tiab] OR histolog[tiab] OR "polarized light"[tiab] OR "polarized light"[tiab] OR microscop*[tiab]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])

Equivalent strings were adapted to the syntax of the other databases (Supplementary Table S1). Backward and forward citation searching was performed for the previous meta-analyses and the systematic review informing the EULAR imaging recommendations.

2.3 Eligibility criteria

Studies were eligible if they evaluated musculoskeletal ultrasonography or conventional radiography for CPP deposition in adults imaged in vivo, used crystal identification in synovial fluid or tissue as the reference standard in participants with and without the target condition, and reported, or allowed reconstruction of, the numbers of true-positive, false-positive, false-negative and true-negative results. Studies whose reference was a clinical classification (McCarty, Ryan-McCarty or ACR/EULAR criteria) were excluded, because these criteria include radiographic findings and would bias the comparison in favor of radiography. Computed tomography was considered at the outset but, because only one in vivo study with a crystal-proven reference was found, it was not retained as an index test. The full criteria are detailed in Table 1.

Table 1. Eligibility criteria.

Element	Inclusion	Exclusion
Population	Adults with suspected or established CPPD disease, joint effusion, acute mono/oligoarthritis or joint surgery, imaged in vivo	Cadaveric specimens; imaging of excised tissue only (ex vivo); pediatric populations
Index tests	Musculoskeletal ultrasonography or conventional radiography interpreted for CPP deposition (any published definition, including OMERACT ultrasound and consensus radiographic definitions)	Computed tomography, dual-energy CT, magnetic resonance imaging or other modalities as the only index test
Reference standard	CPP crystals identified by polarized light microscopy of synovial fluid, histology or crystallographic analysis of joint tissue, applied to participants with and without the target condition	Clinical classification criteria (McCarty, Ryan–McCarty, ACR/EULAR) or imaging as the reference; non-diseased participants not examined for crystals; reference not specific for CPP crystals
Target condition	CPP crystal deposition (CPPD) at patient, joint or meniscus level	Gout or basic calcium phosphate deposition as the only target condition
Design and data	Diagnostic accuracy studies (consecutive, case-control or index-test-based sampling) reporting or allowing reconstruction of true-positive, false-positive, false-negative and true-negative counts	No participants without CPPD; 2×2 table not reconstructable; overlapping reports of the same cohort and test (largest report retained)
Publication	Peer-reviewed articles in journals indexed in PubMed/MEDLINE, Scopus or Web of Science; any language and date	Conference abstracts, theses, preprints, case reports, reviews and editorials

Notes: ACR, American College of Rheumatology; CPP, calcium pyrophosphate; CPPD, calcium pyrophosphate deposition; CT, computed tomography; EULAR, European Alliance of Associations for Rheumatology; OMERACT, Outcome Measures in Rheumatology.

2.4 Study selection and data extraction

Records were merged and de-duplicated on PubMed identifier, digital object identifier and normalized title. A rule-based triage then excluded records whose publication type or title identified a case report, review, editorial, comment, guideline or conference abstract; records about animal, laboratory or materials-science work without human participants; and records that did not mention CPP deposition, an imaging index test, or any accuracy or crystal-reference term. The rules were applied only to exclude records; records without an abstract were passed to manual screening when the title mentioned imaging, and the rules are listed in Supplementary Table S2. All remaining records were screened on title and abstract against the eligibility criteria, and potentially eligible reports were assessed in full.

One reviewer screened the records and extracted the data with a piloted form. As a safeguard, every 2×2 table was checked by recomputing the sensitivity, specificity and predictive values reported by the authors, and every full-text exclusion was recorded with its reason. The following items were extracted: country, design, sampling (consecutive, case-control or index-test-based), clinical setting, number of participants and of CPP-positive participants, anatomical site, definition of a positive index test, reference standard, unit of analysis and the 2×2 counts.

Before the analysis, each study was assigned to one of three setting groups: consecutive patients with joint effusion or acute mono/oligoarthritis in whom crystals were sought as part of care; osteoarthritis cohorts, mostly patients awaiting arthroplasty whose tissue or synovial fluid was examined at surgery; and case-control or index-test-based studies, in which patients with known CPPD were compared with separately recruited controls or participants were selected according to the result of the index test. The first group corresponds most closely to the internal medicine setting.

When counts were not printed, they were reconstructed from the reported group sizes and percentages and accepted when a unique integer solution reproduced the published estimates. Patient-level data were preferred over joint- or meniscus-level data. When several scanning protocols were reported, the single-joint protocol corresponding to the sampled joint (or the knee, when crystals were sought in any joint) was used, and multi-joint protocols were analyzed in a sensitivity analysis. When several readers were reported, the first reader or the consensus reading was used. When a cohort was described in more than one report, the largest analyzed set for each test was used, and the subset with both tests was used for the paired comparison.

2.5 Risk of bias

Risk of bias and applicability were assessed with the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool in four domains (patient selection, index test, reference

standard, and flow and timing),⁴⁷ and the comparative signaling questions of QUADAS-C were applied to studies that reported both tests.⁴⁸ A study was rated at high overall risk if any domain was at high risk and as having some concerns if any domain was unclear. The reason for each judgment is given in Supplementary Table S3.

2.6 Statistical analysis

For each study and test, sensitivity (Se) and specificity (Sp) were calculated from the numbers of true positives (TP), false negatives (FN), true negatives (TN) and false positives (FP), with exact binomial confidence intervals (Equation 1).

$$Se = \frac{TP}{TP+FN}, Sp = \frac{TN}{TN+FP} \quad (1)$$

Sensitivity and specificity were pooled with a bivariate binomial-normal generalized linear mixed model.⁴⁷ Within study i , the number of true positives y_{Ai} among the n_{Ai} participants with CPP deposition and the number of true negatives y_{Bi} among the n_{Bi} participants without it follow binomial distributions with probabilities p_{Ai} (sensitivity) and p_{Bi} (specificity) (Equation 2). Between studies, logit p_{Ai} and logit p_{Bi} follow a bivariate normal distribution with means μ_A and μ_B , variances σ_A^2 and σ_B^2 , and covariance σ_{AB} (Equation 3). Models were fitted by maximum likelihood with the Laplace approximation. When the model with correlated random effects was singular or failed to converge, uncorrelated random effects ($\sigma_{AB} = 0$) were used, which is equivalent to two univariate random-effects logistic models.

$$y_{Ai} \sim \text{Bin}(n_{Ai}, p_{Ai}), y_{Bi} \sim \text{Bin}(n_{Bi}, p_{Bi}) \quad (2)$$

$$\begin{pmatrix} \text{logit}(p_{Ai}) \\ \text{logit}(p_{Bi}) \end{pmatrix} \sim N \left(\begin{pmatrix} \mu_A \\ \mu_B \end{pmatrix}, \Sigma \right), \Sigma = \begin{pmatrix} \sigma_A^2 & \sigma_{AB} \\ \sigma_{AB} & \sigma_B^2 \end{pmatrix} \quad (3)$$

Positive (LR+) and negative (LR−) likelihood ratios and the diagnostic odds ratio (DOR) were derived from the pooled estimates (Equation 4), with confidence intervals from 20,000 draws of the multivariate normal distribution of the fixed effects. Summary receiver operating characteristic (SROC) curves were drawn from the shape (β) and accuracy (Λ) parameters of the hierarchical model derived from the bivariate estimates (Equations 5 and 6), with 95% confidence and prediction regions for the summary points; the prediction region shows where the results of a new study are expected to lie.

$$LR^+ = \frac{Se}{1-Sp}, LR^- = \frac{1-Se}{Sp}, DOR = \frac{LR^+}{LR^-} \quad (4)$$

$$\beta = \ln \left(\frac{\sigma_B}{\sigma_A} \right), \Lambda = \left(\frac{\sigma_B}{\sigma_A} \right)^{1/2} \mu_A + \left(\frac{\sigma_A}{\sigma_B} \right)^{1/2} \mu_B \quad (5)$$

$$\text{logit}(Se) = \Lambda e^{-\beta/2} + e^{-\beta} \text{logit}(1-Sp) \quad (6)$$

Heterogeneity was quantified with the I^2 statistic, computed from Cochran's Q and its degrees of freedom (df) in univariate

random-effects logit models for sensitivity and specificity (Equation 7).

$$I^2 = \max\left\{0, \frac{Q-df}{Q}\right\} \times 100\% \quad (7)$$

Ultrasonography and radiography were compared by bivariate meta-regression with test type as a covariate. In these models the random effects were defined at study level and shared by the two tests, so that studies reporting both tests contributed within-study information, whereas studies reporting one test contributed between-study information. The comparison was made first across all studies and then restricted to the studies that applied both tests to the same participants. Covariates were tested with likelihood-ratio tests comparing the log-likelihoods ℓ_0 and ℓ_1 of the models without and with the covariate (Equation 8), separately for sensitivity and specificity in the comparative models. The same approach was used for the prespecified subgroups: setting and sampling, reference standard, anatomical site, unit of analysis, publication before or after the OMERACT definitions, and overall risk of bias. No adjustment was made for multiple testing, and subgroup findings were interpreted as exploratory.

$$G^2 = -2(\ell_0 - \ell_1) \sim \chi^2_2 \quad (8)$$

Sensitivity analyses excluded studies at high risk of bias, case-control or index-test-based designs, non-patient units, histology-referenced studies, counts reconstructed only approximately, and possibly overlapping series; replaced the single-joint data with multi-joint or alternative-site protocols; and omitted each study in turn. Small-study effects were examined with Deeks' funnel-plot asymmetry test, regressing the log diagnostic odds ratio on the inverse square root of the effective sample size (ESS) weighted by ESS, when at least ten studies were available (Equation 9); 0.5 was added to all cells of tables containing a zero for this regression only; the binomial mixed models used the observed counts.

$$\ln DOR_i = \alpha + \beta_1 \frac{1}{\sqrt{ESS_i}}, \quad ESS_i = \frac{4n_{1i}n_{0i}}{n_{1i} + n_{0i}} \quad (9)$$

To support clinical interpretation, the post-test probability (p_{post}) was calculated from the pre-test probability (p_{pre}) and the pooled likelihood ratio (Equation 10) at pre-test probabilities of 10%, 20%, 30% and 50%, and with the likelihood ratios of the consecutive cohorts at the median prevalence observed in those cohorts. Analyses were performed in R 4.5.3 (lme4 2.0.1, meta 8.2.1, MASS 7.3.65) and Python 3.14 (matplotlib 3.10).

$$p_{\text{post}} = \frac{\frac{p_{\text{pre}}}{1-p_{\text{pre}}} \times LR}{1 + \frac{p_{\text{pre}}}{1-p_{\text{pre}}} \times LR} \quad (10)$$

2.7 Certainty of evidence

Certainty of evidence for sensitivity, specificity and the comparison between tests was rated with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for test accuracy, starting at high certainty for cross-sectional accuracy studies and considering risk of bias, indirectness, inconsistency, imprecision and publication bias.⁴⁹

3. Results

3.1 Study selection

The searches identified 2,932 records. After removal of 1,493 duplicates and 709 records excluded by the rule-based triage, 730 records were screened and 32 reports were sought in full. Six could not be retrieved with sufficient data, 26 were assessed and five were excluded, leaving 21 reports of 18 studies, as illustrated in Figure 1. Citation searching identified 287 additional records, none was eligible on title and abstract. The excluded reports and their reasons are listed in Supplementary Table S2.

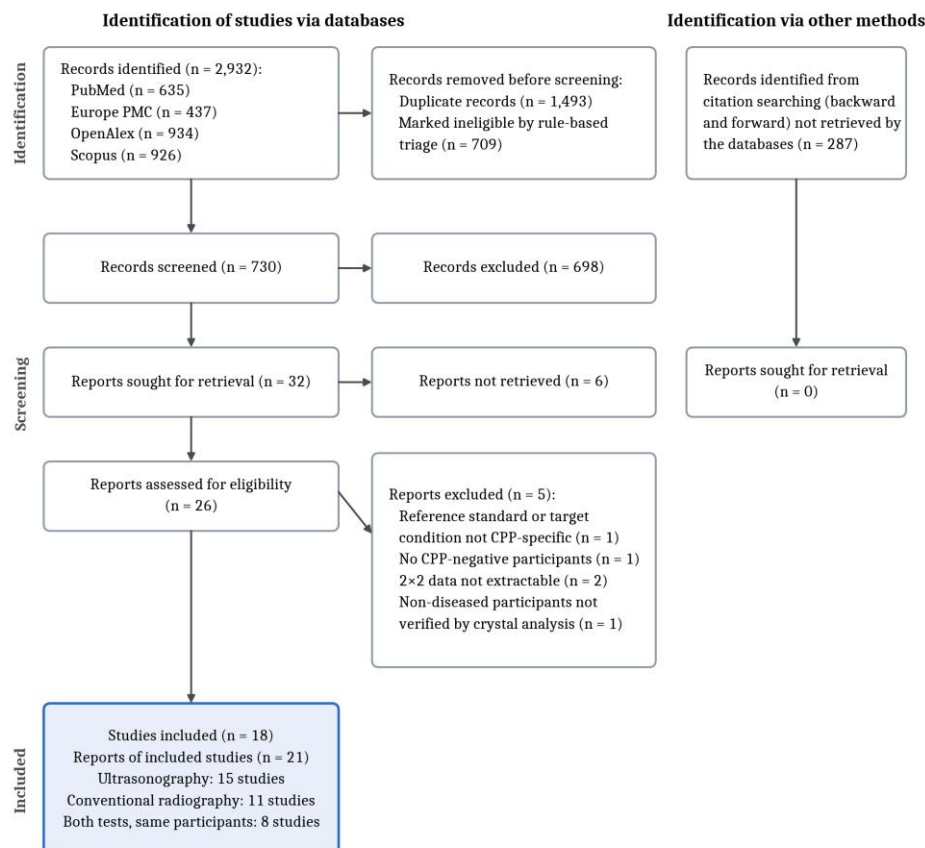


Figure 1. PRISMA 2020 flow diagram of the identification, screening and inclusion of diagnostic accuracy studies of ultrasonography and conventional radiography for calcium pyrophosphate deposition.

3.2 Study characteristics

The 18 studies were conducted in 13 countries, mostly in Europe, and 12 were prospective. As detailed in Table 2, 12 sampled participants consecutively and six used case-control or index-test-based sampling. Seven studies enrolled patients with joint effusion or acute mono/oligoarthritis, five examined osteoarthritis cohorts (four before arthroplasty, three of them with histology), and six compared patients with known CPPD with controls. The reference standard was synovial fluid analysis in 15 studies and histology of surgical specimens in three. The prevalence of CPP crystals ranged from 17.6–49.0% in the consecutive effusion and acute arthritis cohorts (median 24.7%). In the osteoarthritis cohorts, prevalence was higher when tissue was examined, reaching 61% in the hip cohort and 50% in the OMERACT knee cohort,^{50,51} than when only synovial fluid was analyzed

at surgery or in clinic.^{52,53} The case-control studies were designed with balanced groups, so their prevalence reflects the sampling rather than any clinical population.

Fifteen studies (1,352 units, 514 CPP-positive) evaluated ultrasonography and 11 (1,053 units, 377 CPP-positive) evaluated radiography; eight reported both tests. Units were patients in most studies; data were analyzed per knee or meniscus in three studies.^{53–56} The knee was the examined joint in 12 studies; the others examined the hip,⁵⁰ the wrist⁵⁷ or the symptomatic joint with or without additional sites.^{58–61} The OMERACT cohort contributed 68 patients to the ultrasonography analysis⁵¹ and 51 patients, with both tests, to the radiography and paired analyses.^{62,63} Two pairs of single-center series may have shared participants and were examined in a sensitivity analysis.

Table 2. Characteristics of the included studies.

Study	Country	Design; sampling	Setting	n (CPP+)	Tests	Site	Reference standard	QUADAS-2
Consecutive effusion or acute arthritis cohorts								
Ogun 2026 ⁶⁴	Türkiye	Prospective cross-sectional; consecutive	Unilateral knee effusion	85 (15; 18%)	US + CR	Knee	Polarized light microscopy of knee synovial fluid	Some concerns
Cipolletta 2023 ⁵⁸	Italy	Prospective single-center; consecutive	Acute mono/oligoarthritis requiring aspiration	161 (30; 19%)	US	Target (aspirated) joint; knee in 59.6%	Compensated polarized light microscopy (blinded biologist)	Some concerns
Kravchenko 2022 ⁵⁹	Germany	Retrospective; consecutive	Suspected acute gout or acute CPP crystal arthritis	36 (11; 31%)	US + CR	Affected joint (knee, wrist, others)	Compensated polarized light microscopy	High
Lee 2019 ⁶⁵	South Korea	Prospective cross-sectional; consecutive	Knee effusion	174 (43; 25%)	US + CR	Knee	Synovial fluid analysis	Some concerns
Ruta 2016 ⁶⁶	Argentina	Prospective cross-sectional; consecutive	Knee effusion, age ≥ 50 years	75 (15; 20%)	US + CR	Knee	Plain and polarized light microscopy	Low
Ottaviani 2015 ⁶⁷	France	Prospective cross-sectional; consecutive	Knee effusion	51 (25; 49%)	US + CR	Knee	Polarized light microscopy (blinded senior rheumatologist)	Low
Zufferey 2015 ⁶⁰	Switzerland	Prospective single-center; consecutive	Acute arthritis of suspected microcrystalline origin	109 (37; 34%)	US	Symptomatic joint	Crystal identification by microscopy	Some concerns
Osteoarthritis cohorts								
Soto-Fajardo 2025 ⁵⁰	Mexico	Prospective diagnostic accuracy; consecutive	Hip osteoarthritis before arthroplasty	100 (61; 61%)	US	Hip	Polarized light microscopy of acetabular fibrocartilage and femoral hyaline cartilage (plus synovial fluid)	Low
Filippou 2021; Sirotti 2023; Filippou 2025 ^{51,62,63}	Multinational (Italy, Spain, Switzerland, Mexico, Romania, USA, France)	Prospective multicenter (OMERACT); consecutive	Knee osteoarthritis before arthroplasty	68 (34; 50%)	US + CR	Knee	Optical and compensated polarized light microscopy of menisci and femoral hyaline cartilage	High
Filippou 2012; 2013 ^{54,55}	Italy	Prospective pilot; consecutive	Knee osteoarthritis before arthroplasty	11 (9; 82%)	US	Knee (menisci)	Light and polarized microscopy of meniscal samples	Some concerns
Tanikawa 2018 ⁵²	Japan	Prospective; consecutive	Knee osteoarthritis before arthroplasty	25 (9; 36%)	CR	Knee	Polarized light microscopy of synovial fluid aspirated at surgery	Some concerns
Patrick 1993 ⁵³	United Kingdom	Cross-sectional; consecutive knees with radiographic OA and aspiration	Knee osteoarthritis (symptomatic and asymptomatic knees)	300 (97; 32%)	CR	Knee	Polarized light microscopy of synovial fluid	Some concerns
Case-control or index-test-based sampling								
Cipolletta 2024 ⁶⁸	Italy	Prospective cross-sectional (two centers); case-control	Crystal-proven CPPD disease vs age/sex-matched disease controls with negative synovial fluid analysis	204 (102; 50%)	US	Knee (20-joint protocol)	Compensated polarized light microscopy	High
Forien 2018 ⁵⁷	France	Prospective cross-sectional; case-control	CPP crystals in synovial fluid of any joint vs crystal-negative controls	58 (32; 55%)	US + CR	Wrist	Synovial fluid analysis	High
Gutierrez 2014 ⁶⁹	Italy	Cross-sectional; case-control	Crystal-proven CPPD vs other chronic arthritides (RA, SpA, OA, gout)	153 (74; 48%)	US + CR	Knee (both knees)	Compensated polarized light microscopy; repeat aspiration in US-positive controls	High
Filippou 2007 ⁷⁰	Italy	Cross-sectional; index-test-based	Knee pain with effusion	43 (15; 35%)	US	Knee	Polarized light microscopy of synovial fluid	High
Frediani 2005 ⁶¹	Italy	Cross-sectional; index-test-based	Joint pain with effusion	24 (11; 46%)	US	Multiple (knee, wrist, others)	Wet-preparation microscopy of synovial fluid	High
Falkowski 2020 ⁵⁶	United States	Retrospective; case-control	Knee crystal arthritis	49 (30; 61%)	CR	Knee	Knee aspiration (crystal analysis)	High

Notes: n, participants (or knees/menisci where indicated) in the largest analyzed set; CPP+, participants with CPP crystals by the reference standard, with the prevalence in the study. QUADAS-2, overall judgment (High if any domain was at high risk; Some concerns if any domain was unclear). The OMERACT cohort contributed ultrasonography (68 patients) and radiography and paired data (51 patients) from three reports, and the two Filippou pilot reports describe the same series. CR, conventional radiography; OA, osteoarthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis; US, ultrasonography. Radiography n for Kravchenko 2022 is 32 (11 CPP-positive), as shown in Figure 4; n in this table is the largest analyzed set.

Definitions of a positive index test evolved over time. The earlier studies described hyperechoic bands within hyaline cartilage, punctate deposits in fibrocartilage and mobile

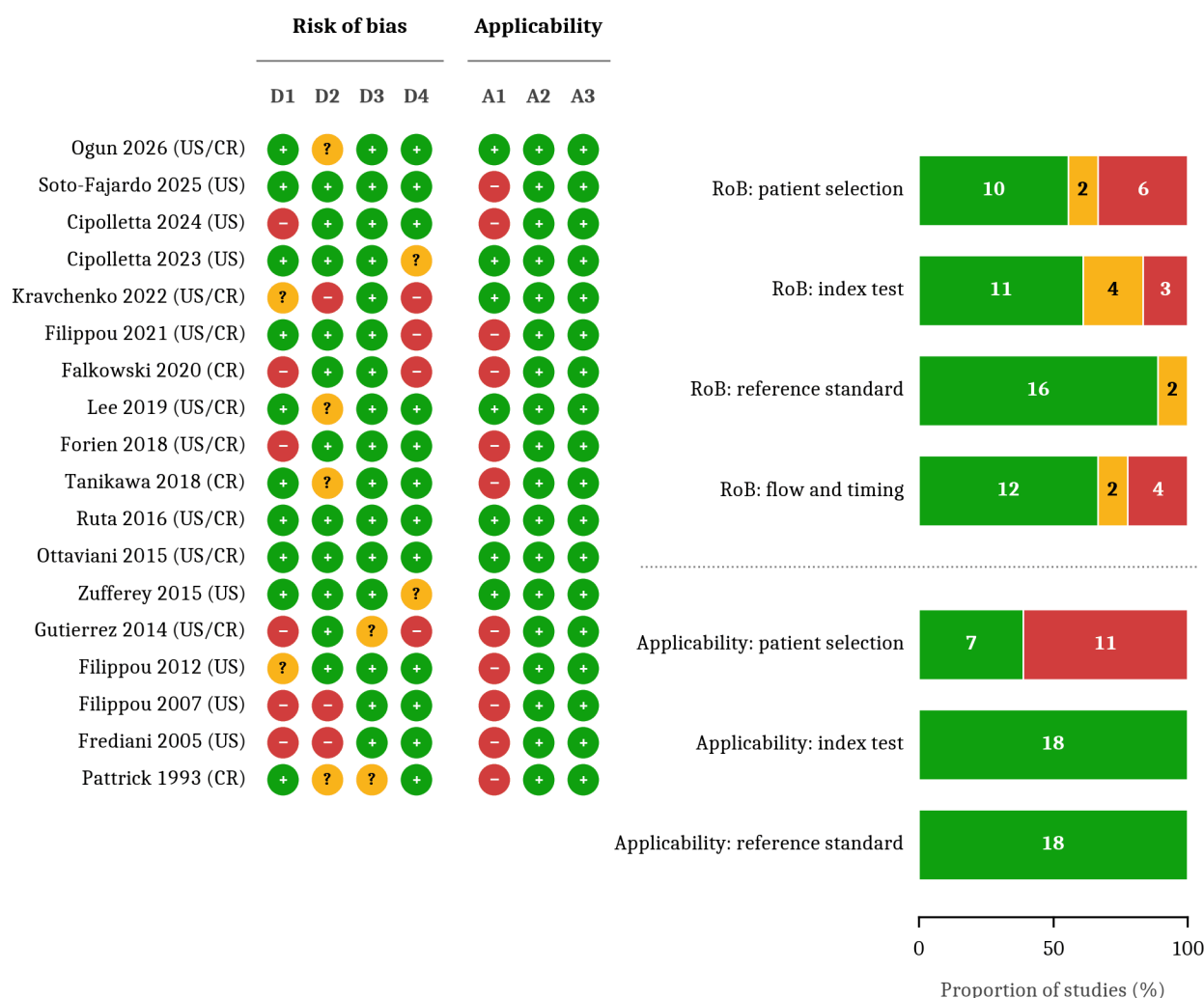
hyperechoic foci in synovial fluid, whereas the more recent studies applied the OMERACT definitions, which describe CPP deposits as hyperechoic foci of variable shape within

fibrocartilage or hyaline cartilage that move with the cartilage on dynamic assessment.^{51,58,65,68} Radiography was read for chondrocalcinosis of the menisci, hyaline cartilage or triangular fibrocartilage in most studies, and with the consensus radiographic definitions of capsular, tendinous and synovial calcification in the OMERACT cohort.⁶² Index tests were interpreted by rheumatologists or radiologists with specific experience in crystal arthritis, usually without knowledge of the crystal results, although blinding was not reported in all studies.

3.3 Risk of bias

Overall risk of bias was low in three studies, with some concerns in seven and high in eight, as illustrated in Figure 2.

Patient selection was the domain most often at high risk, because of case-control or index-test-based sampling. Flow and timing was at high risk in studies with many unanalyzed participants,⁵¹ differential verification⁶⁹ or long intervals between radiography and aspiration.⁵⁶ The index-test domain was at high risk when participants were selected by the result of ultrasonography or when the readers knew the suspected diagnosis.^{59,61,70} Applicability concerns related to patient selection were frequent, because pre-arthroplasty cohorts and selected cases do not represent patients presenting with undiagnosed arthritis. The studies reporting both tests applied them to the same participants within the same episode of care.



D1, patient selection; D2, index test; D3, reference standard; D4, flow and timing; A1–A3, applicability concerns for patient selection, index test and reference standard. US, ultrasonography; CR, conventional radiography. Numbers in the bars are counts of studies.

Figure 2. Risk of bias and applicability concerns of the included studies (QUADAS-2). Left, judgment for each study and domain (+, low; ?, unclear; -, high); right, proportion of studies at each level per domain (numbers are counts of studies). D1, patient selection; D2, index test; D3, reference standard; D4, flow and timing; A1–A3, applicability concerns for patient selection, index test and reference standard. US, ultrasonography; CR, conventional radiography.

3.4 Accuracy of ultrasonography

Across 15 studies, the sensitivity of ultrasonography ranged from 44.4% in a meniscus-level pilot series⁵⁴ to 100% in two studies,^{61,67} and specificity ranged from 50.0% to 100%, as illustrated in Figure 3. Among consecutive patients, sensitivity was highest in the knee effusion cohorts from France and Türkiye^{64,67} and lowest in the Argentinian effusion cohort and the Swiss acute arthritis cohort, in which

a single symptomatic joint was examined.^{60,66} The pooled sensitivity was 87.8% (95% CI 79.0–93.2) and the pooled specificity 89.4% (95% CI 82.2–94.0). The positive likelihood ratio was 8.31 (95% CI 4.90–14.46), the negative likelihood ratio 0.14 (95% CI 0.08–0.24) and the diagnostic odds ratio 60.8 (95% CI 25.2–148.5), as detailed in Table 3. Heterogeneity was substantial for sensitivity (I^2 71.7%, 95% CI 52.4–83.2) and specificity (I^2 65.0%, 95% CI 39.3–79.8).

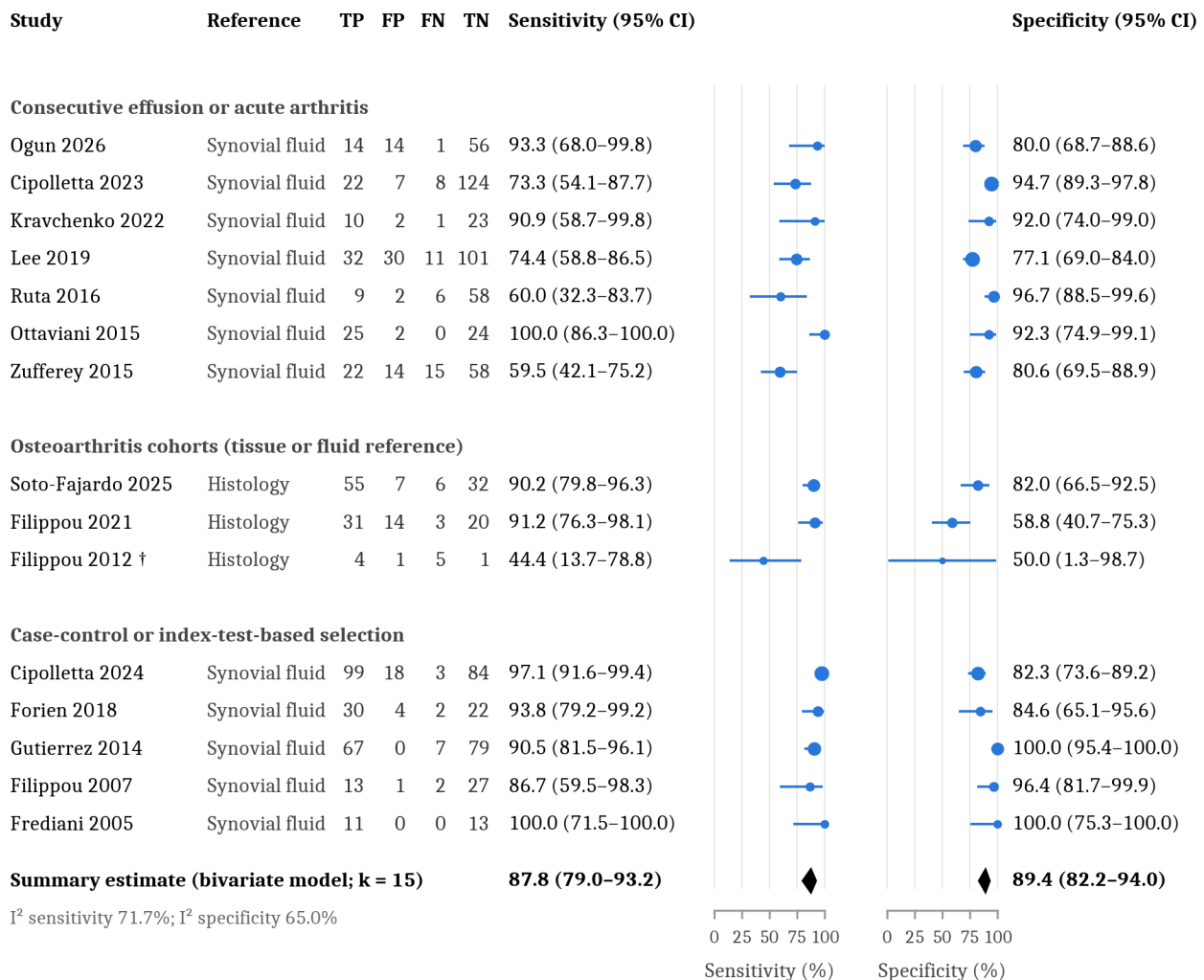


Figure 3. Forest plot of the sensitivity and specificity of ultrasonography for calcium pyrophosphate deposition, grouped by setting and sampling. Markers are study estimates (size proportional to the number of CPP-positive or CPP-negative units) with exact 95% confidence intervals; diamonds are the bivariate summary estimates. † Meniscus-level data. Philippou 2021 is the OMERACT cohort (68-patient set; refs. 51, 62, 63). FN, false negatives; FP, false positives; TN, true negatives; TP, true positives.

Table 3. Pooled diagnostic accuracy of ultrasonography and conventional radiography.

Analysis	k	Units (CPP+)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)	I^2 Se / Sp
Ultrasonography, all studies	15	1352 (514)	87.8 (79.0–93.2)	89.4 (82.2–94.0)	8.31 (4.90–14.46)	0.14 (0.08–0.24)	60.8 (25.2–148.5)	71.7% / 65.0%
Conventional radiography, all studies	11	1053 (377)	52.6 (42.3–62.6)	96.2 (92.2–98.2)	13.73 (6.56–29.08)	0.49 (0.39–0.60)	27.8 (11.9–66.3)	74.4% / 40.5%
Ultrasonography, paired studies	8	683 (241)	89.7 (79.8–95.1)	90.2 (78.5–95.8)	9.13 (4.14–21.13)	0.11 (0.06–0.23)	79.9 (24.5–258.2)	—
Conventional radiography, paired studies	8	679 (241)	54.6 (41.5–67.1)	96.8 (91.9–98.8)	16.95 (5.77–49.77)	0.47 (0.34–0.62)	36.1 (9.7–138.5)	—
Comparison of ultrasonography with radiography (bivariate meta-regression)								
All studies (US – CR)	18	—	Δ 32.6 (23.1 to 42.0); $p < 0.001$	Δ –8.7 (–13.4 to –5.0); $p < 0.001$	—	—	—	—
Paired studies (US – CR)	8	—	Δ 30.4 (21.1 to 40.0); $p < 0.001$	Δ –8.2 (–14.5 to –3.9); $p < 0.001$	—	—	—	—

Notes: Estimates are percentages with 95% confidence intervals from bivariate random-effects models (uncorrelated random effects for the all-study models, in which the correlated model was singular). Units are participants or knees/menisci (CPP-positive units in parentheses). Δ , difference in percentage points between ultrasonography and radiography (positive values favor ultrasonography), with likelihood-ratio test p values. DOR, diagnostic odds ratio; k, number of studies; Se, sensitivity; Sp, specificity; I^2 , from univariate random-effects logit models (sensitivity / specificity); LR+, positive likelihood ratio; LR-, negative likelihood ratio.

3.5 Accuracy of conventional radiography

Radiography was evaluated in 11 studies, as illustrated in Figure 4. Sensitivity ranged from 36.1% in a knee-level osteoarthritis series⁶⁹ to 83.8% for meniscal calcification in a case-control series.⁶⁹ The pooled sensitivity was 52.6% (95% CI 42.3–62.6) and the pooled specificity 96.2% (95% CI 92.2–

98.2), with a positive likelihood ratio of 13.73 (95% CI 6.56–29.08), a negative likelihood ratio of 0.49 (95% CI 0.39–0.60) and a diagnostic odds ratio of 27.8 (95% CI 11.9–66.3). Heterogeneity was substantial for sensitivity (I^2 74.4%, 95% CI 53.5–85.9) but moderate for specificity (I^2 40.5%, 95% CI 0.0–70.6); specificity exceeded 90% in all but one study.⁶⁶

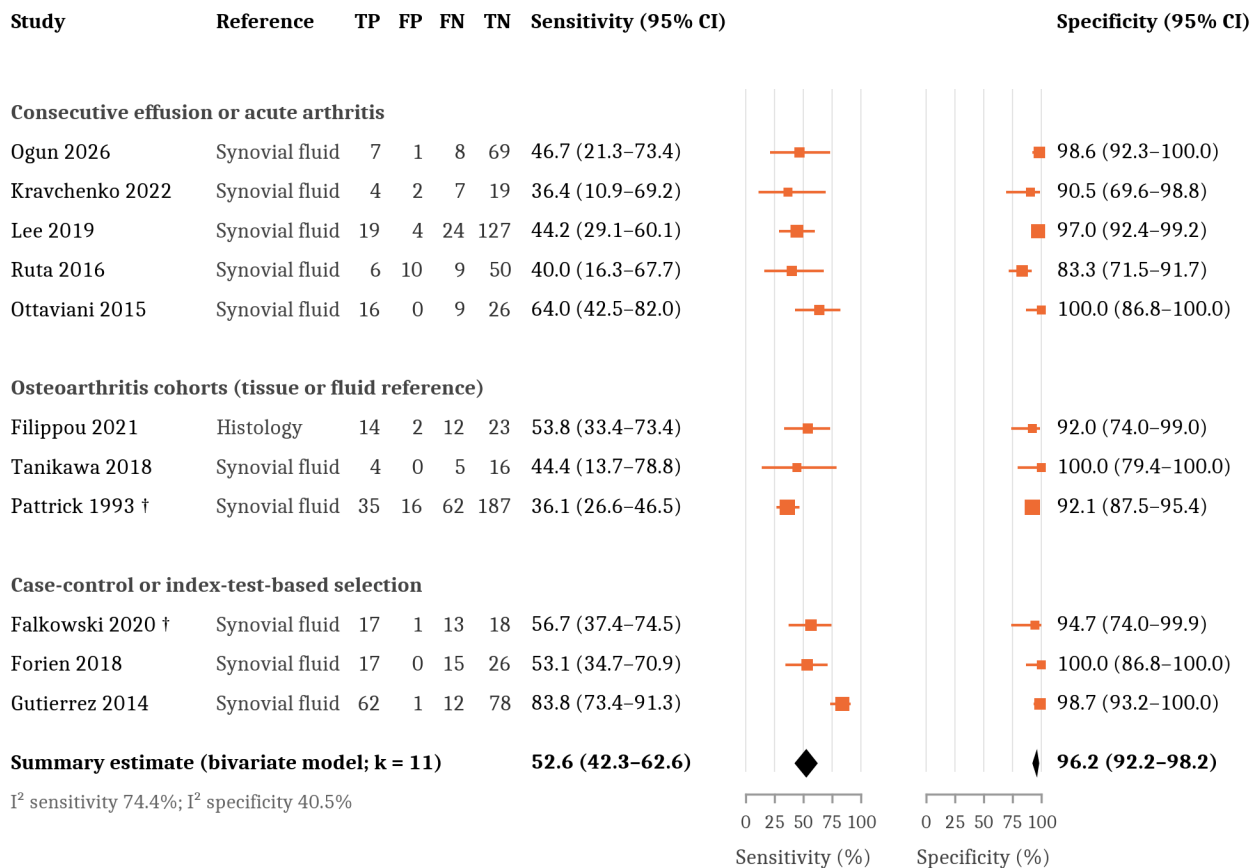


Figure 4. Forest plot of the sensitivity and specificity of conventional radiography for calcium pyrophosphate deposition, grouped by setting and sampling. Layout as in Figure 3; † knee-level data. Philippou 2021 is the OMERACT cohort (51-patient radiography set; refs. 51, 62, 63).

3.6 Comparison of ultrasonography and radiography

The summary points and confidence regions of the two tests did not overlap, as shown in Figure 5. Ultrasonography lay in the upper part of the plot, with higher sensitivity and slightly lower specificity, and radiography in the lower left, with lower sensitivity and higher specificity. The prediction region of ultrasonography was wide, extending to false-positive rates above 50%, which indicates that a new study in a

different setting could find a considerably lower specificity. Across all studies, ultrasonography was 32.6 percentage points (95% CI 23.1 to 42.0) more sensitive ($p < 0.001$) and 8.7 percentage points (95% CI –13.4 to –5.0) less specific ($p < 0.001$). These differences are not the same as the differences between the separately pooled estimates (35.2 and –6.8 points) because the meta-regression shares a study-level random effect across the two tests (Section 2.6).

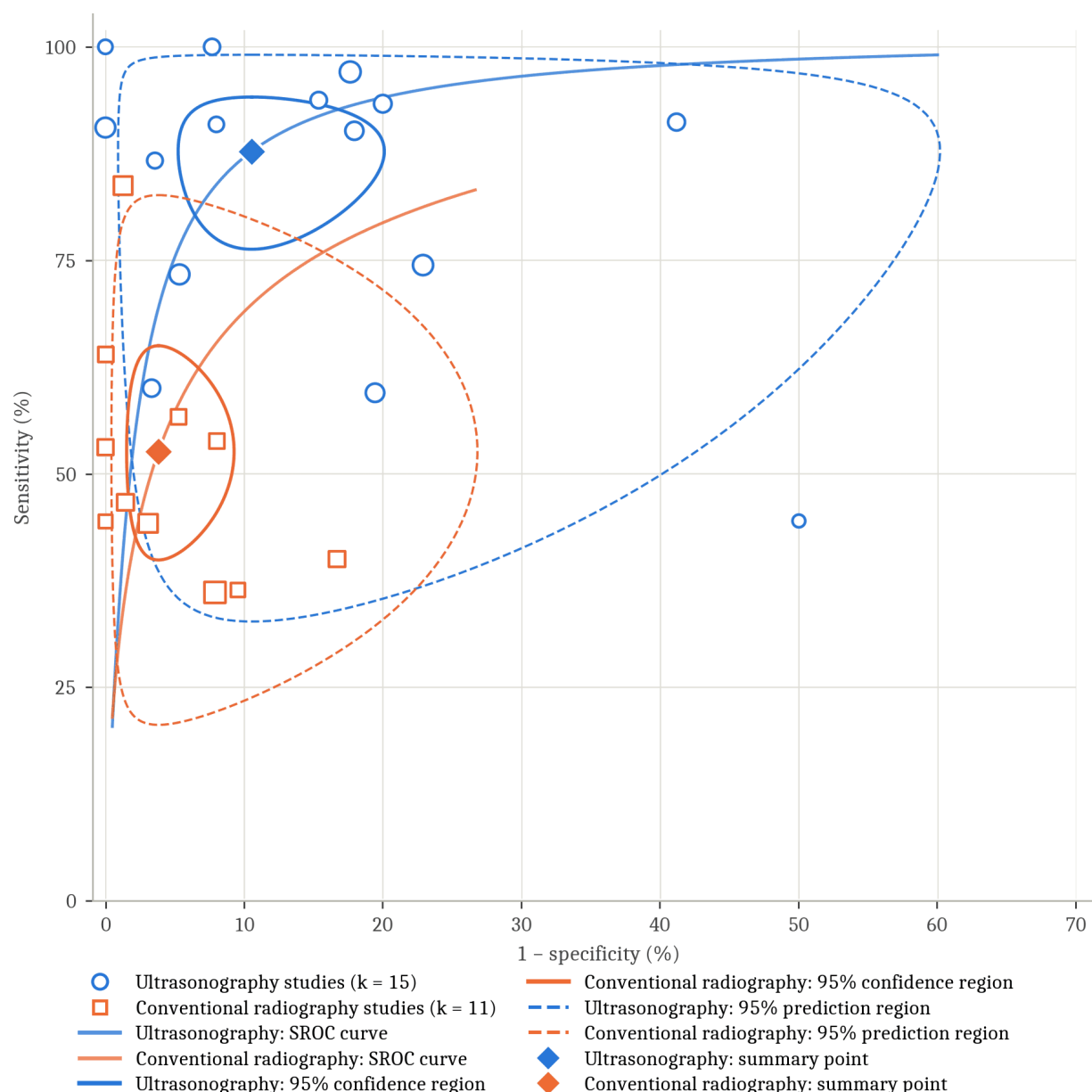


Figure 5. Summary receiver operating characteristic plot of ultrasonography (blue circles) and conventional radiography (orange squares). Open markers are individual studies (size proportional to sample size); diamonds are the bivariate summary points with their 95% confidence regions (solid ellipses) and 95% prediction regions (dashed); curves are the summary ROC curves derived from the bivariate parameters.

In the eight studies that applied both tests to the same participants, the pooled sensitivity was 89.7% (95% CI 79.8–95.1) for ultrasonography and 54.6% (95% CI 41.5–67.1) for radiography, and the pooled specificity 90.2% (95% CI 78.5–95.8) and 96.8% (95% CI 91.9–98.8), respectively; in these subsets the correlated bivariate models could be fitted (correlation of the random effects –0.11 for ultrasonography

and 0.90 for radiography). Ultrasonography was 30.4 percentage points (95% CI 21.1 to 40.0) more sensitive ($p < 0.001$) and 8.2 percentage points (95% CI –14.5 to –3.9) less specific ($p < 0.001$). Ultrasonography was more sensitive in every paired study, whereas radiography was more specific in five of the eight, as illustrated in Figure 6.

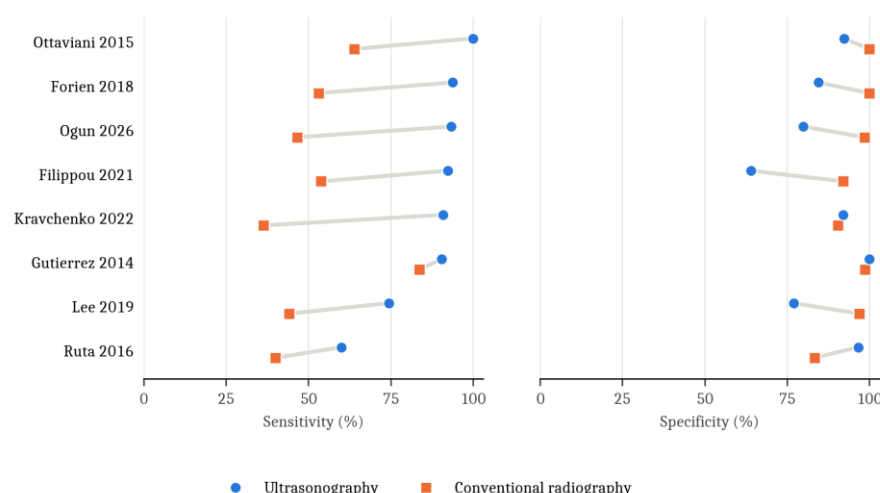


Figure 6. Within-study comparison of ultrasonography (blue circles) and conventional radiography (orange squares) in the studies that applied both tests to the same participants, ordered by the sensitivity of ultrasonography. For the OMERACT cohort (Filippou 2021), the 51-patient paired set is shown.

3.7 Heterogeneity and subgroup analyses

Setting and sampling explained part of the heterogeneity in ultrasonography ($p=0.03$), as detailed in Table 4. Case-control or index-test-based studies gave a sensitivity of 94.5% (95% CI 87.0–97.8) and a specificity of 94.3% (95% CI 85.9–97.9), compared with 80.8% (95% CI 66.7–89.8) and 89.2% (95% CI 80.5–94.3) in consecutive effusion or acute arthritis cohorts. In osteoarthritis cohorts, most of them referenced to histology, specificity was lower (69.8%, 95% CI 42.0–88.0). Studies at high risk of bias reported higher sensitivity than the others (93.9% (95% CI 87.6–97.1) versus 78.6% (95% CI 66.5–87.1); $p=0.03$).

The reference standard ($p=0.08$), the period relative to the OMERACT definitions ($p=0.10$) and the anatomical site ($p=0.96$) were not significantly associated with the accuracy of ultrasonography. For radiography, none of the covariates reached significance (setting $p=0.11$; risk of bias $p=0.25$; unit of analysis $p=0.48$), although sensitivity was again higher in case-control studies (67.9%, 95% CI 54.6–78.8) than in consecutive cohorts (47.3%, 95% CI 35.0–60.0). Of ten covariate tests, two had $p<0.05$ without correction for multiple testing, and several levels contained only two studies.

Table 4. Subgroup analyses (bivariate meta-regression).

Covariate: level	k	Sensitivity, % (95% CI)	Specificity, % (95% CI)	p (LRT)
Ultrasonography				
Setting: case-control/index-test-based	5	94.5 (87.0–97.8)	94.3 (85.9–97.9)	p=0.03
Setting: consecutive effusion/acute arthritis	7	80.8 (66.7–89.8)	89.2 (80.5–94.3)	
Setting: osteoarthritis cohorts	3	83.4 (63.0–93.7)	69.8 (42.0–88.0)	p=0.08
Reference: histology	3	82.8 (55.4–94.9)	69.7 (41.3–88.3)	
Reference: synovial fluid	12	88.9 (79.3–94.4)	91.4 (85.4–95.1)	
Site: knee	9	88.1 (76.8–94.3)	88.8 (78.6–94.5)	p=0.96
Site: other or multiple joints	6	87.2 (71.4–94.9)	90.3 (78.6–95.9)	
Period: after OMERACT definitions	7	89.8 (78.4–95.5)	83.3 (71.9–90.6)	p=0.10
Period: before OMERACT definitions	8	85.4 (71.1–93.3)	94.0 (87.3–97.2)	
Risk of bias: high	7	93.9 (87.6–97.1)	91.7 (81.1–96.6)	p=0.03
Risk of bias: low or some concerns	8	78.6 (66.5–87.1)	87.3 (75.7–93.8)	
Conventional radiography				
Setting: case-control/index-test-based	3	67.9 (54.6–78.8)	98.5 (92.9–99.7)	p=0.11
Setting: consecutive effusion/acute arthritis	5	47.3 (35.0–60.0)	95.2 (89.5–97.9)	
Setting: osteoarthritis cohorts	3	42.9 (29.2–57.7)	94.1 (84.3–97.9)	p=0.86
Site: knee	9	53.8 (42.7–64.5)	96.1 (91.7–98.2)	
Site: other or multiple joints *	2	46.4 (24.0–70.5)	96.6 (80.8–99.5)	
Unit: knee or meniscus *	2	44.9 (26.3–65.0)	93.4 (78.6–98.2)	p=0.48
Unit: patient	9	54.9 (43.7–65.7)	96.7 (92.6–98.5)	
Period: after OMERACT definitions	6	47.8 (34.1–61.8)	96.6 (91.6–98.7)	p=0.61
Period: before OMERACT definitions	5	57.3 (43.3–70.2)	95.5 (88.4–98.4)	
Risk of bias: high	5	61.3 (48.3–72.8)	96.7 (90.5–98.9)	p=0.25
Risk of bias: low or some concerns	6	45.1 (33.6–57.3)	95.7 (90.0–98.3)	

Notes: Sensitivity and specificity (%) with 95% confidence intervals from bivariate meta-regression (uncorrelated random effects); k, number of studies; LRT, likelihood-ratio test; p values from likelihood-ratio tests of the covariate (2 degrees of freedom for two levels, 4 for three). Covariates with fewer than two studies in a level were not tested; * levels with only two studies (unstable estimates). Setting: consecutive patients with effusion or acute arthritis, osteoarthritis cohorts (pre-arthroplasty or osteoarthritis clinics) and case-control or index-test-based sampling. Period: publication before or after the Outcome Measures in Rheumatology (OMERACT) ultrasound definitions. No adjustment was made for multiple testing.

3.8 Sensitivity analyses

The main findings were robust, as detailed in Table 5. Excluding studies at high risk of bias lowered the sensitivity of ultrasonography to 79.4% (95% CI 63.4–89.6) with a specificity of 87.0% (95% CI 79.4–92.1), and restricting the analysis to studies without case-control or index-test-based sampling gave 82.1% (95% CI 69.3–90.3) and 85.7% (95% CI 77.3–91.3). The corresponding estimates for radiography were 43.9% (95% CI 35.1–53.0) and 96.1% (95% CI 89.1–

98.7), and 44.6% (95% CI 36.9–52.6) and 95.0% (95% CI 89.9–97.6). Multi-joint protocols (sensitivity 87.6%, 95% CI 79.0–93.0; specificity 88.7%, 95% CI 80.5–93.7), patient-level data, synovial fluid references and exclusion of possibly overlapping series changed the estimates by at most 3.1 percentage points. Omitting one study at a time, the pooled sensitivity of ultrasonography ranged from 86.0–89.1% and its specificity from 87.1–90.5%; for radiography the ranges were 47.0–54.7% and 95.5–96.8%.

Table 5. Sensitivity analyses.

Analysis	k	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Ultrasonography			
Main analysis (all studies)	15	87.8 (79.0–93.2)	89.4 (82.2–94.0)
Excluding studies at high risk of bias	8	79.4 (63.4–89.6)	87.0 (79.4–92.1)
Excluding case-control or index-test-based selection	10	82.1 (69.3–90.3)	85.7 (77.3–91.3)
Patient-level data only	14	89.0 (81.3–93.8)	89.9 (82.7–94.4)
Synovial fluid reference standard only	12	89.0 (79.2–94.5)	91.7 (85.2–95.5)
Studies published after the OMERACT definitions	7	89.2 (80.3–94.3)	82.9 (73.7–89.4)
Excluding counts reconstructed only approximately	14	89.1 (81.2–93.9)	90.2 (82.6–94.7)
Alternative (multi-joint or alternative-site) protocols	15	87.6 (79.0–93.0)	88.7 (80.5–93.7)
Excluding possibly overlapping series (Cipolletta 2024, Frediani 2005)	13	84.7 (75.5–90.9)	89.2 (81.1–94.1)
Leave-one-out (range of pooled estimates)	14	86.0–89.1%	87.1–90.5%
Conventional radiography			
Main analysis (all studies)	11	52.6 (42.3–62.6)	96.2 (92.2–98.2)
Excluding studies at high risk of bias	6	43.9 (35.1–53.0)	96.1 (89.1–98.7)
Excluding case-control or index-test-based selection	8	44.6 (36.9–52.6)	95.0 (89.9–97.6)
Patient-level data only	9	54.2 (42.0–66.0)	97.0 (92.5–98.8)
Synovial fluid reference standard only	10	52.4 (41.2–63.3)	96.5 (92.2–98.5)
Studies published after the OMERACT definitions	6	48.5 (40.2–56.9)	96.5 (93.5–98.1)
Leave-one-out (range of pooled estimates)	10	47.0–54.7%	95.5–96.8%

Notes: Sensitivity and specificity (%) with 95% confidence intervals from bivariate random-effects models. Case-control or index-test-based selection: studies sampling participants with known CPPD and separate controls, or selecting participants by the index-test result. Alternative protocols: multi-joint scanning (Cipolletta 2023, Cipolletta 2024, Zufferey 2015) and hyaline cartilage instead of fibrocartilage (Gutierrez 2014).

3.9 Small-study effects

Deeks' funnel-plot asymmetry tests did not suggest small-study effects for ultrasonography ($p=0.61$) or radiography

($p=0.92$), as illustrated in Figure 7, although the tests have limited power with 15 and 11 studies.

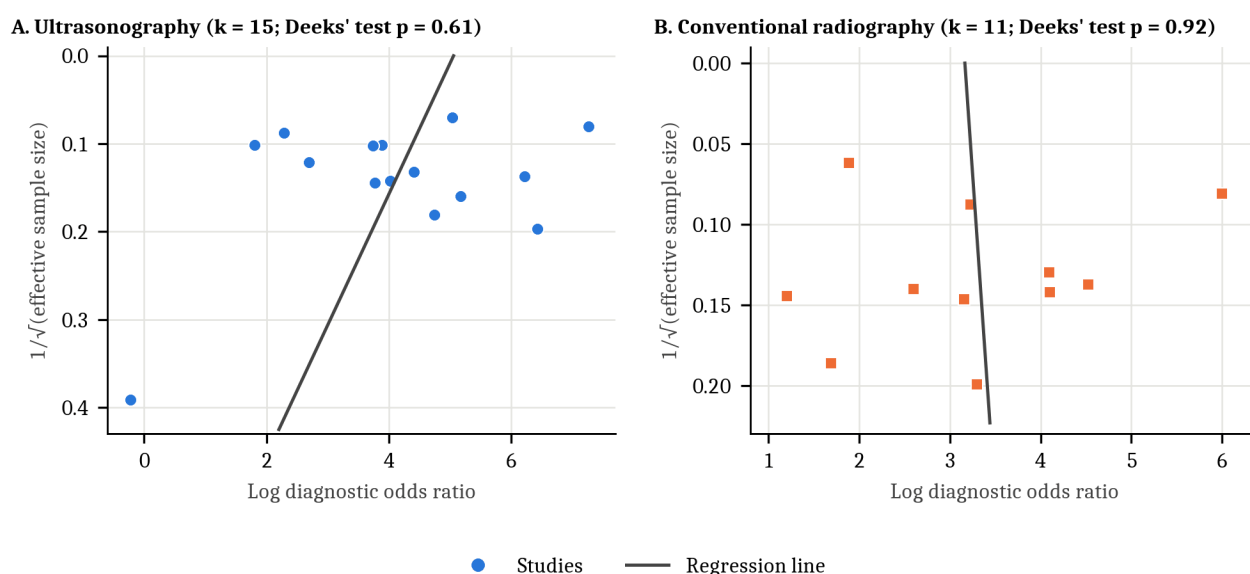


Figure 7. Deeks' funnel plots of the log diagnostic odds ratio against the inverse square root of the effective sample size for ultrasonography (A) and conventional radiography (B), with the fitted regression lines.

3.10 Clinical interpretation and certainty of evidence

At a pre-test probability of 20%, a positive ultrasonographic examination raised the probability of CPP deposition to 67.5% and a negative examination lowered it to 3.3%; for radiography, the corresponding values were 77.4% and 11.0%. With the likelihood ratios of the consecutive cohorts,

which are less affected by spectrum bias (LR+ 7.5 and LR– 0.22 for ultrasonography; 9.9 and 0.55 for radiography), the post-test probabilities at the median prevalence of those cohorts (24.7%) were 71.0% after a positive and 6.6% after a negative ultrasonographic examination, and 76.5% and 15.4% for radiography. At a pre-test probability of 50%, a

negative radiograph still left a 33.0% probability, compared with 12.0% after a negative ultrasonographic examination.

In absolute terms, using ultrasonography instead of radiography in 1,000 patients with a 20% prevalence of deposition would identify about 61 more patients with CPP deposition, at the cost of about 66 more false-positive results, based on the paired comparison. Whether this trade-off is acceptable depends on the consequences of each error: a missed diagnosis may lead to unnecessary antibiotics, urate-

lowering therapy or immunosuppression for presumed rheumatoid arthritis, whereas a false-positive result may lead to a missed alternative diagnosis if the clinical picture is not reassessed.

Certainty of evidence was low for the sensitivity and specificity of ultrasonography and for the sensitivity of radiography, and moderate for the specificity of radiography and for the comparison between the tests, mainly because of risk of bias and inconsistency, as detailed in Table 6.

Table 6. Summary of findings and certainty of evidence (GRADE).

Outcome	Studies (units)	Pooled estimate, % (95% CI)	Consequences per 1,000 tested	Certainty	Reasons
Ultrasonography: sensitivity	15 (514)	87.8 (79.0–93.2)	True positives / false negatives: 176 (158–186) / 24 (14–42)	Low	Risk of bias (serious): case-control or index-test-based sampling in five of fifteen studies and high risk in at least one QUADAS-2 domain in seven; inconsistency (serious): I^2 71.7% and wide prediction region
Ultrasonography: specificity	15 (838)	89.4 (82.2–94.0)	True negatives / false positives: 716 (658–752) / 84 (48–142)	Low	Risk of bias (serious), as for sensitivity; inconsistency (serious): I^2 65.0%, with the lowest specificity in osteoarthritis cohorts referenced to histology
Conventional radiography: sensitivity	11 (377)	52.6 (42.3–62.6)	True positives / false negatives: 105 (85–125) / 95 (75–115)	Low	Risk of bias (serious): high risk in at least one domain in five of eleven studies and knee-level units in two; inconsistency (serious): I^2 74.4%
Conventional radiography: specificity	11 (676)	96.2 (92.2–98.2)	True negatives / false positives: 769 (737–785) / 31 (15–63)	Moderate	Risk of bias (serious); specificity consistently high across settings (I^2 40.5%); not downgraded for inconsistency or imprecision
Ultrasonography versus radiography (paired studies)	8 (683)	Δ sensitivity 30.4 (21.1 to 40.0); Δ specificity –8.2 (–14.5 to –3.9)	Per 1,000 tested (prevalence 20%): about 61 more true positives and 66 more false positives with ultrasonography	Moderate	Risk of bias (serious); direction of the sensitivity difference consistent in all paired studies

Notes: Consequences per 1,000 people tested at an illustrative pre-test probability of 20% (prevalence of CPP crystals in the consecutive effusion and acute arthritis cohorts 17.6–49.0%, median 24.7%), calculated from the pooled sensitivity and specificity (95% confidence interval ranges in parentheses). Certainty of evidence was rated with GRADE for test accuracy, starting at high for cross-sectional accuracy studies. Δ , difference in percentage points (ultrasonography minus radiography).

4. Discussion

This meta-analysis of 18 studies with crystal identification as the reference standard found that ultrasonography identified most CPP deposition, with a sensitivity of 87.8% (95% CI 79.0–93.2) and a specificity of 89.4% (95% CI 82.2–94.0). Conventional radiography detected only about half (52.6%, 95% CI 42.3–62.6). It was, however, highly specific (96.2%, 95% CI 92.2–98.2). The pattern held in the eight studies that applied both tests to the same participants, in which ultrasonography was about 30 percentage points more sensitive and about 8 points less specific. In consecutive patients with effusion or acute arthritis, the population most relevant to internal medicine, the accuracy of ultrasonography fell below the overall estimate but stayed clinically useful (sensitivity 80.8%, 95% CI 66.7–89.8; specificity 89.2%, 95% CI 80.5–94.3). A negative radiograph leaves a clinically relevant probability of CPP deposition at the pre-test probabilities seen in these patients. A negative ultrasonographic examination makes deposition unlikely.

The target condition of this review was CPP deposition, not CPPD disease or a particular phenotype. Imaging shows that crystals are present in the joint. It does not show that they caused the presenting arthritis. In the ACR/EULAR classification criteria, imaging evidence of deposition earns points but must be combined with clinical features when crystals have not been seen in synovial fluid.³⁷ A positive ultrasonographic or radiographic examination in a patient with acute monoarthritis therefore supports a diagnosis of acute CPP crystal arthritis without establishing it. The clinical picture, the inflammatory markers and the exclusion of infection and gout remain essential.

The distinction matters most in older adults. Ultrasonographic deposits were present in almost half of people older than 80 years with knee pain,¹ meniscal CPP deposits were as common in donors without osteoarthritis as in patients with it,⁷¹ and a small but appreciable proportion of people without osteoarthritis showed radiographic chondrocalcinosis.¹² In an older patient, then, a positive scan may reflect incidental deposition next to another cause of

arthritis. The lower specificity of ultrasonography in osteoarthritis cohorts referenced to histology fits this picture, since deposits in advanced osteoarthritis were often unconfirmed by the reference standard or consisted of other calcium crystals. A positive test deserves more weight when the clinical phenotype is typical, for example acute inflammatory arthritis of the knee or wrist. It deserves less when it is incidental in a patient with chronic mechanical pain.

Our estimates are close to those of the earlier meta-analysis by Cipolletta et al. With synovial fluid or histology as the reference, that review reported a sensitivity of 85% and a specificity of 87% for ultrasonography, and 47% and 95% for radiography.⁴⁰ It also found radiography considerably more accurate when clinical classification criteria were the reference. This is incorporation bias, which we avoided by design. The present analysis adds the OMERACT histology studies, the consensus radiographic definitions, the hip, targeted scanning in acute arthritis and new effusion cohorts.^{50,51,58,62,64,68} It estimates the comparison within studies, which removes confounding by setting and population, and reports the accuracy in consecutive patients separately. The pattern of high specificity and variable sensitivity agrees with the systematic review that informed the EULAR imaging recommendations.⁴¹

The difference between the tests is biologically plausible. Ultrasonography detects small hyperechoic deposits in fibrocartilage and hyaline cartilage that lie below the threshold of radiographic visibility, and it examines structures that project poorly on radiographs. Radiography needs a sufficient mass of mineral. In advanced osteoarthritis, joint-space narrowing and osteophytes obscure it, which may explain the low prevalence of radiographic calcification in the hip cohort.⁵⁰ False-positive results of either test may reflect basic calcium phosphate crystals, which dominate the mineral in osteoarthritic cartilage and menisci and often coexist with CPP,^{71,72} or fibrous tissue that mimics punctate deposits on ultrasonography.⁵⁵ Calcium crystal deposits have been linked to synovial cytokines in some studies and not to pain or inflammation in others.^{73,74} Imaging identifies deposition. It does not measure disease activity.

Gout is the main alternative diagnosis in acute monoarthritis, and the two crystal diseases can coexist. One acute arthritis cohort excluded patients with both monosodium urate and CPP crystals,⁵⁸ another counted them as CPP-positive,⁶⁰ and a third found CPP crystals on repeat aspiration in some controls with other arthritides.⁶⁹ CPP deposits on the cartilage surface can mimic the double contour sign of gout. The pseudo double contour, however, moves with the cartilage on dynamic scanning, and deposits at the metacarpophalangeal joints help to separate CPPD from gout and rheumatoid arthritis.^{75,76} Imaging cannot exclude septic arthritis, which may coexist with crystal arthritis.²⁷ Aspiration therefore remains essential whenever infection is possible.

Heterogeneity was substantial, and study design explained part of it. Case-control and index-test-based studies compare clear-cut cases with healthy or unrelated controls, and they tended to give higher sensitivity and specificity, in keeping with a spectrum effect. The estimates from consecutive patients with effusion or acute arthritis are the most applicable to practice. Scanning protocols, anatomical targets and operator experience differed, and definitions changed from the earlier ones to the OMERACT definitions,³⁸ but the available data could not separate these sources. The imperfect reference standard is another source. Synovial fluid analysis misses some deposits that histology detects,²⁰ so in fluid-referenced studies some apparent false positives of ultrasonography may have been true deposits, and specificity would be underestimated. Specificity was nonetheless higher in fluid-referenced than in histology-referenced studies, which suggests that differences in population outweighed this effect: the histology studies were confined to advanced osteoarthritis with abundant mixed calcification.

The choice of scanning protocol also matters. In one series, meniscal fibrocartilage was the most sensitive target (90.5%, compared with 59.5% for hyaline cartilage spots).⁶⁹ Reduced protocols reached high accuracy without scanning every joint, whether they covered both knees, wrists and hips, or the knees and wrists plus the symptomatic joint.^{58,68} Replacing the single-joint data with these multi-joint protocols changed the pooled estimates very little (sensitivity 87.6%, 95% CI 79.0–93.0; specificity 88.7%, 95% CI 80.5–93.7). A focused examination of the knees, supplemented by the wrists and the symptomatic joint, is therefore probably sufficient in most patients. Such a protocol took about 12 minutes on average in one study.⁶⁸ Internists who already use point-of-care ultrasonography can learn it, but training in the OMERACT definitions and periodic calibration against crystal-proven cases are needed to reproduce the accuracy reported by expert centers.

This review has several strengths. Restricting the reference standard to crystal identification avoided incorporation bias against radiography. Four databases, including Scopus, were searched without language limits, and citation searching supplemented them. Bivariate models accounted for the correlation between sensitivity and specificity, and the tests were compared both across studies and within studies. Prespecified subgroup and sensitivity analyses examined the robustness of the findings, and the certainty of evidence was rated with GRADE.

Several limitations should be considered. First, most studies were small, eight were at high risk of bias, and six used case-control or index-test-based sampling. The conclusions held in consecutive cohorts, but absolute estimates should be read alongside the applicability concerns. Second, the reference standard is itself imperfect. Synovial fluid analysis has limited sensitivity and inter-observer agreement,^{18,19} and misclassification of the reference would underestimate the specificity of a sensitive index test. Third, one reviewer performed screening and data extraction; every table was

checked against the published estimates, but independent duplicate assessment would have reduced the risk of error. Fourth, 18 of the 26 2×2 tables were reconstructed from published percentages. All but one reconstruction was exact, and excluding the approximate one did not change the results. Fifth, Embase and Web of Science were not searched, and six reports could not be retrieved with sufficient data. The rule-based triage may also have removed eligible records despite its conservative design.

Sixth, two Italian centers produced six of the included studies, and the operators were mostly experienced academic sonographers, which may limit generalizability. Seventh, some studies analyzed data per knee or meniscus and ignored clustering, although patient-level analyses gave similar results. Eighth, the subgroup analyses were numerous, were not corrected for multiple testing and had little power, and Deeks' test cannot exclude small-study effects with this number of studies. Finally, the evidence for computed tomography against a crystal-proven reference was too limited to pool. The only in vivo study found a sensitivity of 55% for dual-energy computed tomography in acute arthritis.⁵⁹ Other studies scanned excised tissue, used non-specific calcium-crystal references or found that calcium crystal types could not be distinguished.^{42,43,52} No included study was conducted in Southeast Asia.

For internists, these findings support ultrasonography of the knees and wrists, plus the symptomatic joint, as the more useful first imaging test when CPPD is suspected and crystals cannot be sought. Examples are older inpatients with acute monoarthritis and patients with possible seronegative rheumatoid arthritis.^{25,26} Radiography remains useful when positive, because false positives are uncommon. A negative radiograph should not be used to exclude CPPD. When ultrasonography is unavailable, radiographs of the knees (the joint examined in most included studies) and of the wrists can be obtained first, and patients with a negative radiograph and a typical presentation should then be referred for ultrasonography or synovial fluid analysis rather than labeled as having another disease. In Indonesia, crystal microscopy is concentrated in referral hospitals (authors' observation). A practical pathway could combine aspiration and microscopy wherever possible with a focused ultrasonographic protocol performed by trained internists or rheumatologists, using radiography as a widely available but insensitive adjunct.

Several clinical scenarios show how the estimates can be used. Consider an older inpatient who develops fever and a hot knee after surgery or during antibiotic treatment. Aspiration is needed to exclude infection. If crystal microscopy is unavailable, an ultrasonographic examination showing meniscal and hyaline cartilage deposits makes CPP deposition likely. Together with the clinical picture, it supports a diagnosis of acute CPP crystal arthritis while culture results are awaited.^{16,17} In a patient with recurrent wrist and knee arthritis and negative rheumatoid factor, deposits at the wrist and knee should prompt reconsideration of seronegative rheumatoid arthritis.^{25,26} In a younger patient with chondrocalcinosis, imaging findings should lead to screening for hyperparathyroidism, hemochromatosis and hypomagnesemia, including inherited tubulopathies.^{34–36} In any patient with CPPD, a review of diuretics and proton-pump inhibitors is reasonable.^{32,33} In each scenario the imaging result shifts the probability of deposition, but the decision rests on the whole clinical picture.

The findings are also relevant to research. The ACR/EULAR classification criteria use imaging evidence of deposition to classify patients in whom crystals have not been sought,³⁷ and trials increasingly use ultrasonographic scores to quantify the extent of deposition.³⁸ Our estimates suggest that imaging-based classification relying on radiography alone would miss many patients with deposition. Ultrasonography-based

enrollment would include some patients whose deposits crystal analysis does not confirm, particularly in advanced osteoarthritis. Trials of new treatments, such as those targeting the pathway of extracellular pyrophosphate production,¹⁵ will need clear and validated imaging definitions.

Future studies should enroll consecutive patients with undiagnosed arthritis in general internal medicine and emergency settings. They should report patient-level 2×2 tables for standardized OMERACT protocols and include operators with different levels of experience. They should also be conducted in low- and middle-income countries, including Indonesia, where the balance between access to microscopy and to ultrasonography differs from that of the European centers that produced most of the evidence. Newer techniques, such as dual-energy computed tomography and automated analysis of radiographs or ultrasound images, should be evaluated against crystal proof, not against clinical criteria.⁴⁴

5. Conclusion

Against a crystal-proven reference standard, musculoskeletal ultrasonography identified CPP deposition with a sensitivity of about 88% and a specificity of about 89%, whereas conventional radiography had a sensitivity of about 53% and a specificity of about 96%. Within studies that used both tests, ultrasonography was roughly 30 percentage points more sensitive and 8 points less specific than radiography, and its accuracy remained clinically useful in consecutive patients with effusion or acute arthritis. Ultrasonography is therefore likely to be the more useful first imaging test when CPPD is suspected and synovial fluid crystal analysis is unavailable or not feasible, provided that the examiner is trained in standardized definitions. A positive radiograph can support the diagnosis, but a negative radiograph cannot exclude it. Neither test establishes acute CPP crystal arthritis on its own, because deposition is common in older adults and infection and gout must still be excluded. The certainty of the evidence is low to moderate because many studies were small, used case-control sampling or were conducted in specialist centers, and consecutive studies in general internal medicine settings, including Indonesia, are needed.

Declarations

Ethics approval and consent to participate

Not required; this study analyzed published aggregate data only.

Consent for publication

Not applicable. This study analyzed only previously published aggregate data and contains no individual person's data.

Use of artificial intelligence

None.

Author contributions

Conceptualization: L.N., N. Methodology, data curation and formal analysis: L.N. Validation: N., E.K. Investigation, software, writing – original draft: L.N. Writing – review & editing: L.N., N., E.K. Supervision: N. All authors approved the final manuscript.

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Conflict of interest

The authors declare no conflict of interest.

Data availability

The study-level 2×2 data, the risk-of-bias judgments, the list of excluded reports, the search strings and the R and Python

scripts that reproduce every analysis and figure are provided as Supplementary Material and are available from the corresponding author on reasonable request.

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