

Osteoarthritis and Cartilage



Review

The diagnostic value of conventional radiography and musculoskeletal ultrasonography in calcium pyrophosphate deposition disease: a systematic literature review and meta-analysis



E. Cipolletta [†]*, G. Filippou [‡], C.A. Scirè [§], A. Di Matteo [†]||, J. Di Battista [†], F. Salaffi [†], W. Grassi [†], E. Filippucci [†]

[†] Rheumatology Unit, Department of Clinical and Molecular Sciences, Polytechnic University of Marche, Ancona, Italy

[‡] Rheumatology Unit, ASST Fatebenefratelli "Luigi Sacco" University Hospital, Milan, Italy

[§] Section of Rheumatology, Department of Medical Sciences, University of Ferrara and Azienda Ospedaliero-Universitaria Sant'Anna di Cona, Ferrara, Italy

|| Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom

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SUMMARY

Objective: To examine and compare the accuracy of conventional radiography (CR) and musculoskeletal ultrasonography (US) in the diagnosis of calcium pyrophosphate (CPP) crystals deposition disease (CPPD).

DESIGN: A systematic search of electronic databases (PubMed, Embase, and Cochrane), conference abstracts and reference lists was undertaken. Studies which evaluated the accuracy of CR and/or US in the diagnosis of CPPD, using synovial fluid analysis (SFA), histology or classification criteria as reference tests were included. Subgroup analyses by anatomic site and by reference test were performed.

Results: Twenty-six studies were included. Using SFA/histology as reference test, CR and US showed an excellent (CR AUC = 0.889, 95%CI = 0.811–0.967) and an outstanding (US AUC = 0.954, 95%CI = 0.907–1.0) diagnostic accuracy ($p < 0.01$), respectively. Furthermore, US showed a higher sensitivity (0.85, 95%CI = 0.79–0.90 vs 0.47, 95%CI = 0.40–0.55) and only a little lower specificity (0.87, 95%CI = 0.83–0.91 vs 0.95, 95%CI = 0.92–0.97) than CR. A considerable heterogeneity between the studies was found, with adopted reference test being the main source of heterogeneity. In fact, subgroup analysis showed a significant change in the diagnostic accuracy of CR, but not of US, using Ryan and McCarty criteria or SFA/histology as reference test (CR: AUC = 0.956, 95%CI = 0.925–1.0 vs AUC = 0.889, 95%CI = 0.828–0.950, respectively, $p < 0.01$) (US: AUC = 0.922, 95%CI = 0.842–1.0 vs AUC = 0.957, 95%CI = 0.865–1.0, respectively, $p = 0.08$).

Conclusions: Although US is more sensitive and a little less specific than CR for identifying CPP crystals, both these two techniques showed a great diagnostic accuracy and should be regarded as complementary to each other in the diagnostic work-up of patients with CPPD.

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* Address correspondence and reprint requests to: Edoardo Cipolletta, Rheumatology Unit, Department of Clinical and Molecular Sciences, Polytechnic University of Marche "Carlo Urbani" Hospital, Via Aldo Moro 25, 60035, Jesi, Italy. Tel.: 39 / 0731-534125; fax: 39 / 0731-534124.

E-mail addresses: edoardocipolletta@gmail.com (E. Cipolletta), gf.filippou@gmail.com (G. Filippou), c.scire@reumatologia.it (C.A. Scirè), andrea.dimatteo@hotmail.com (A. Di Matteo), jacopeta@gmail.com (J. Di Battista), faustosalaffi@gmail.com (F. Salaffi), walter.grassi@univpm.it (W. Grassi), emilio_filippucci@yahoo.it (E. Filippucci).

Introduction

Calcium pyrophosphate deposition disease (CPPD) is a crystal arthropathy characterised by the deposition of calcium pyrophosphate (CPP) crystals in articular and periarticular structures^{1,2}.

In 1977, Ryan and McCarty provided classification criteria for CPPD³. According to these criteria, a "definite" diagnosis of CPPD requires both the microscopic identification of CPP crystals on the synovial fluid analysis (SFA) and the presence of typical calcifications on conventional radiography (CR) (e.g., linear calcifications, parallel to the underlying cortex at hyaline cartilage; shaggy

SFA and histology were considered together because they are the reference tests currently recommended by the EULAR for the diagnosis of CPPD².

Quality assessment

The quality of each study was evaluated using the modified version of the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool¹⁴. Data extraction and quality assessment were performed independently by the two reviewers (E.C. and J.D.B.). Any disagreement was resolved by a third reviewer (E.F.). Publication bias was estimated using Egger's regression asymmetry test.

Statistical analysis

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic odds ratio (DOR) of CR and US were calculated for each 2 × 2 set of data. Heterogeneity among included studies was examined by the Chi-square test, using n-1 degrees of freedom, and by inconsistency (I^2). An I^2 value close to

0% indicates no heterogeneity between studies, close to 25% indicates low heterogeneity, close to 50% indicates moderate heterogeneity, and close to 75% indicates high heterogeneity. Subgroup analyses by anatomic site and reference test were performed. Moreover, the diagnostic accuracy of CR and US was directly compared using only the studies in which the performance of CR and US were simultaneously tested against SFA or histology. Paired summary points, such as pooled sensitivity/specificity and pooled PPV/NPV, and summary lines, such as summary receiver operating characteristic (SROC) curves, were calculated using bivariate random effect models. These models are the most appropriate in presence of significant between-study heterogeneity^{15–19}. Covariates were not considered in the models.

The area under the curve (AUC) was calculated to evaluate the discriminative power of each imaging tool. The AUC was interpreted as follows: $AUC = 0.5$ no diagnostic ability (i.e., results by pure chance); $0.5 \leq AUC < 0.7$ poor diagnostic ability; $0.70 \leq AUC < 0.80$ acceptable diagnostic ability; $0.80 \leq AUC < 0.90$ excellent diagnostic ability; $AUC \geq 0.9$ outstanding diagnostic ability²⁰. The AUC and the Q index represent an overall measure of test

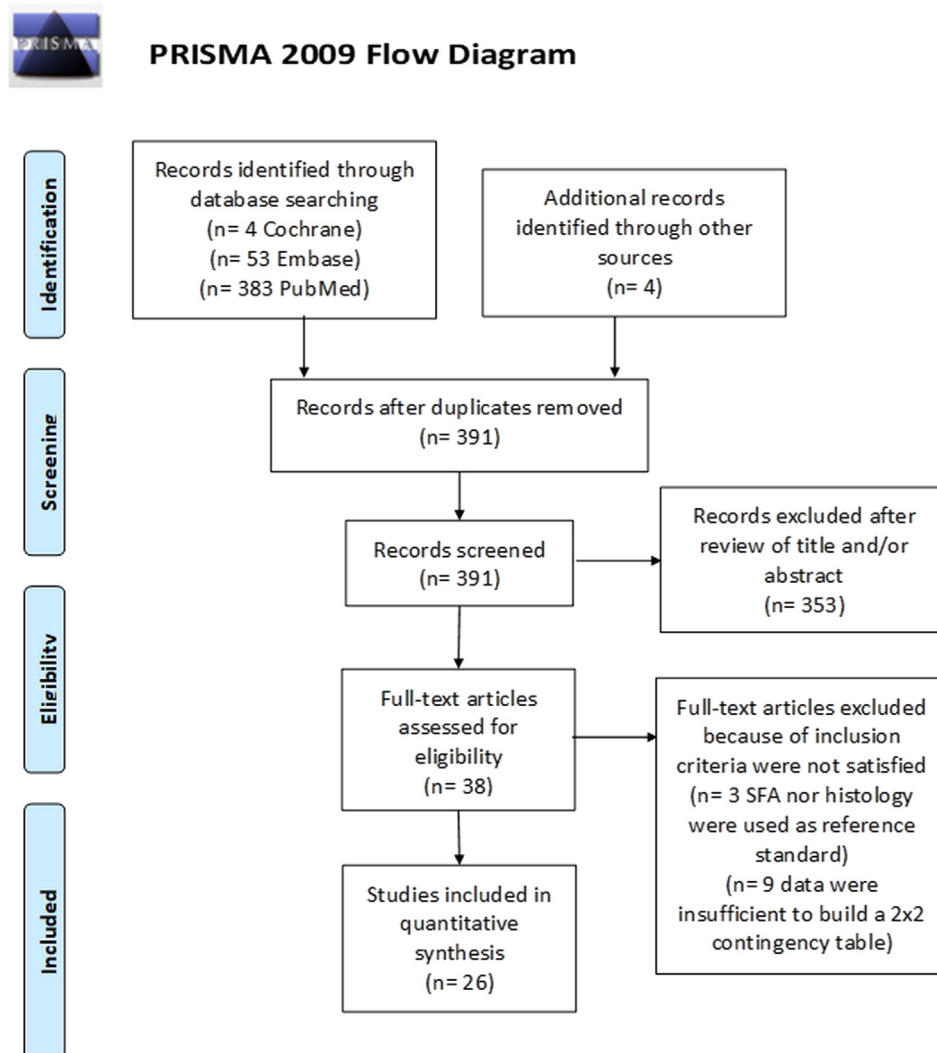


Fig. 1

Flow diagram of the review process.

accuracy. The comparison of AUCs was performed using the DeLong method^{21,22}, MetaDiSc, version 1.4 (Clinical Biostatistics team of the Ramón y Cajal Hospital, Madrid, Spain), MedCalc, version 18.6 (MedCalc Software, Ostend, Belgium) and STATA, version 15.1 (StataCorp, College Station, TX, USA), were used to perform the statistical analysis.

Results

Description of the included studies

The search strategy identified 391 articles. After the examination of titles and abstracts, 38 articles were included for the review

and after the evaluation of the full-text articles, 12 articles were excluded from the subsequent analyses (Fig. 1).

Of the latter studies, three were excluded as neither the SFA nor histology was used as reference method^{23–25} and nine had insufficient data to build the 2×2 contingency tables^{26–34}. Of the remaining 26 articles, 17 were case control studies^{35–51}, five were cross sectional uncontrolled studies^{52–56} and four were prospective cohort studies^{57–60}.

Thirteen (50.0%) articles evaluated only the knee^{35–38,40–42,50,52,53,57–59}, 2 (7.7%) evaluated the knee and other anatomic structures (wrist in two and Achilles tendon in 1^{39,54}), one (3.8%) the shoulder and the acromioclavicular joint⁴⁵ and 10 (42.3%) other anatomic sites (wrist in 5^{46,47,49,55,56}, Achilles tendon

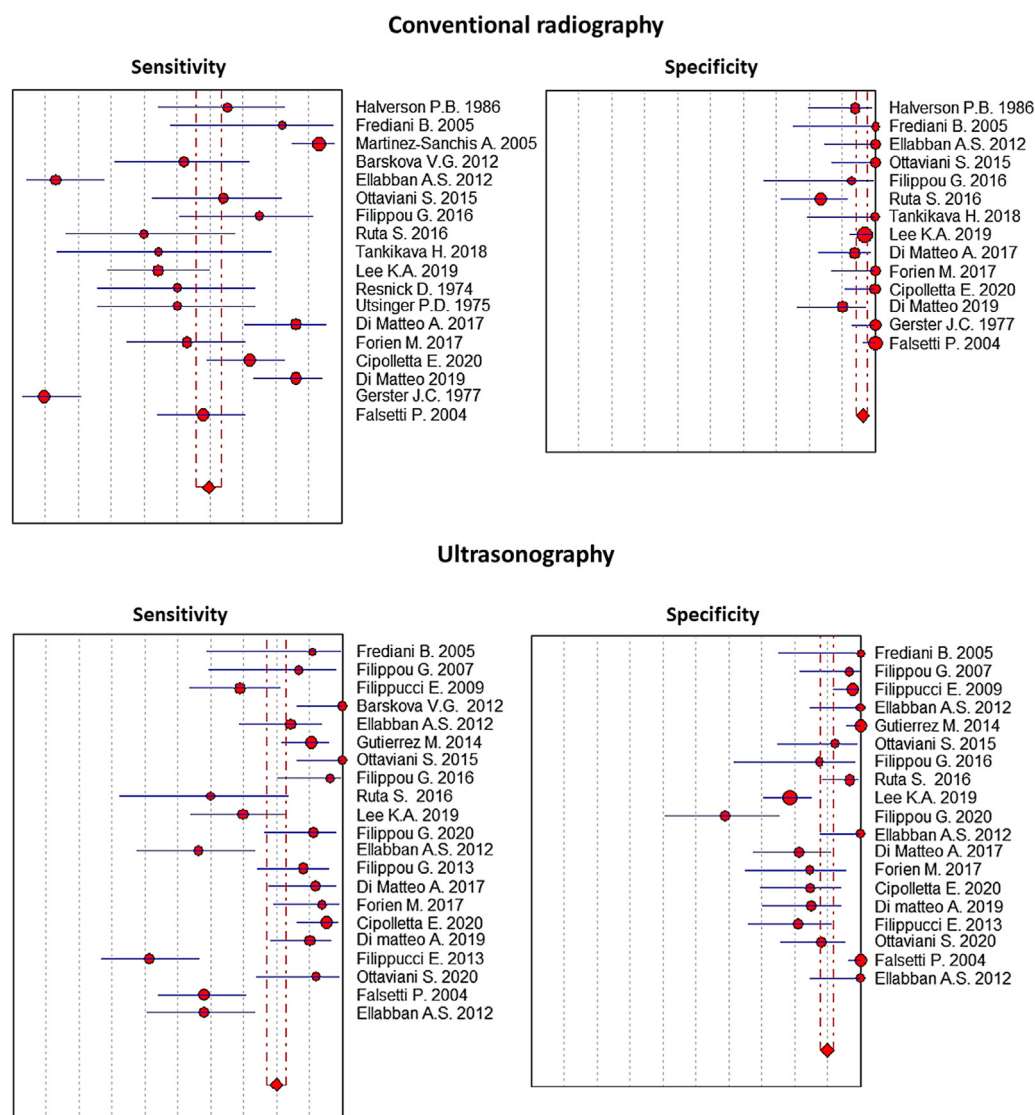


Fig. 2

Forest plots of the diagnostic performance of CR and US in the identification of CPP crystal deposits. Studies are organised according to anatomical sites as follows: knee, wrist, hip, shoulder, acromioclavicular joint and Achilles tendon, similarly to Tables II and IV. CR: pooled sensitivity = 0.60 (95%CI = 0.55–0.64); pooled specificity = 0.96 (95%CI = 0.94–0.98); heterogeneity $p < 0.01$, $I^2 = 69\%$. US: pooled sensitivity = 0.81 (95%CI = 0.78–0.84); pooled specificity = 0.90 (95%CI = 0.87–0.92); heterogeneity $p < 0.01$, $I^2 = 85\%$. Legend. **95%CI**: 95% confidence interval, **CR**: conventional radiography, **US**: ultrasonography.

and plantar fascia in 3^{43,44,51}, acromioclavicular joint in 1⁶⁰ and hip in 1⁴⁸).

A total of 1,230 (610 CPPD patients and 620 controls) and 1707 (821 CPPD patients and 886 controls) subjects were assessed by CR and US, respectively.

The mean age of CPPD patients was 68.9 and 66.7 years in CR and US groups, respectively. The female/male ratio was 1.4/1 in both groups.

Fig. 2 shows the forest plots of the diagnostic accuracy of CR and US.

Diagnostic accuracy of CR and US in the detection of CPP crystals at knee level

The diagnostic accuracy of CR and US in the detection of CPP crystals at knee level was investigated in 10 (38.5%)^{35,36,39,41,50,52,53,57–59} and in 12 (46.2%)^{36–40,42,50,53,54,57–59} studies, respectively. A total of 601 (286 CPPD patients and 315 controls) and 893 (396 CPPD patients and 497 controls) subjects were assessed by CR and US, respectively. The main characteristics of the studies evaluating

the diagnostic accuracy of CR and US in the detection of CPP crystals at knee level are reported in Table I and Table II.

Overall, the sensitivity, specificity, PPV and NPV of CR ranged from 0.13³⁹ to 0.93⁵², from 0.83⁵⁸ to 1.0^{36,39,41,59}, from 0.38⁵⁹ to 1.0^{36,39,41,59} and from 0.40³⁹ to 0.87³⁶, respectively, whereas the sensitivity, specificity, PPV and NPV of US ranged from 0.60⁵⁸ to 1.0^{53,59}, from 0.79⁵⁷ to 1.0^{36,39,40,50}, from 0.52⁵⁷ to 1.0^{36,39,40,50} and from 0.79^{39,50} to 1.0⁵⁹, respectively.

Considering SFA as the reference method, the pooled sensitivity, specificity, PPV, NPV and DOR were 0.59 (95%CI = 0.53–0.65), 0.95 (95%CI = 0.92–0.97), 0.83 (95%CI = 0.73–0.90), 0.76 (95%CI = 0.71–0.80) and 19.4 (95%CI = 7.9–47.4) for CR^{35,36,39,41,52,53,57–59}, and 0.85 (95%CI = 0.80–0.88), 0.91 (95%CI = 0.88–0.94), 0.86 (95%CI = 0.81–0.90), 0.90 (95%CI = 0.86–0.93) and 116.0 (95%CI = 24.1–558.2) for US^{36,37,39,40,50,53,57–59} (Table II).

When the reference method was the histological analysis, the pooled sensitivity, specificity, PPV, NPV and DOR of US were 0.93 (95%CI = 0.84–0.98), 0.68 (95%CI = 0.53–0.81), 0.73 (95%CI = 0.66–0.87), 0.85 (95%CI = 0.75–0.97) and 40.5 (95%CI = 3.7–438.3), respectively^{42,50}. Only one article evaluates the

| Authors | Year | Study design | Number of patients | Age (years) | Sex (F/M) | RS | Imaging techniques | US equipment | 2017–2018 OMERACT definitions ^{61,62} | Structure assessed by US/CR | SFA equipment |
|--|------|--------------------|------------------------|--------------------|-----------|--------|--------------------|--|--|-------------------------------|---------------|
| Halverson P.B. et al. ³⁵ | 1986 | Case control | 26 cases, 33 controls | 75.4 (range 52–80) | 14/12 | SFA | CR | / | / | / | NR |
| Frediani B. et al. ³⁶ | 2005 | Case control | 11 cases, 13 controls | 67.8 (range 61–79) | 9/2 | SFA | CR, US | 7.5–13 MHz linear probe | N | Menisci and hyaline cartilage | CPM |
| Martinez-Sanchis A. et al. ⁵² | 2005 | Cross sectional | 74 CPPD patients | 68.3 (range 40–90) | 47/27 | SFA | CR | / | / | / | CPM |
| Filippou G. et al. ³⁷ | 2007 | Case control | 14 cases, 29 controls | 69.0 (range 40–92) | NR | SFA | US | 7.5–13 MHz linear probe | N | Menisci and hyaline cartilage | CPM |
| Filippucci E. et al. ³⁸ | 2009 | Case control | 48 cases, 84 controls | 64.5 ± 10.3 | 37/11 | RMC | US | 6–18 MHz linear probe | N | Hyaline cartilage | NR |
| Barskova V.G. et al. ⁵³ | 2012 | Cross sectional | 25 CPPD patients | 49.8 (range 28–60) | 11/14 | SFA | CR, US | 4–13 MHz linear probe | N | Hyaline cartilage | NR |
| Ellaban A.S. et al. ³⁹ | 2012 | Case control | 32 cases, 28 controls | 53.5 ± 6.5 | 11/21 | SFA | CR, US | 7.5–12 MHz linear probe | N | Menisci and hyaline cartilage | PM |
| Filippou G. et al. ⁵⁴ | 2013 | Cross sectional | 42 CPPD patients | 64.0 ± 17.0 | 26/16 | RMC | US | 6–18 MHz linear probe | N | Menisci and hyaline cartilage | NR |
| Gutierrez M. et al. ⁴⁰ | 2014 | Case control | 74 cases, 83 controls | 69.3 ± 9.2 | NR | SFA | US | 9 MHz linear or 5–13 MHz linear probes | N | Menisci or hyaline cartilage | PM |
| Ottaviani S. et al. ⁵⁹ | 2015 | Prospective cohort | 26 cases, 25 controls | 66.1 ± 14.3 | NR | SFA | CR, US | 7.5–18 MHz linear probe | N | Menisci and hyaline cartilage | CPM |
| Filippou G. et al. ⁵⁰ | 2016 | Case control | 26 cases, 16 controls | 74.0 ± 8.4 | NR | H, SFA | CR, US | 7–13 MHz linear probe | N | Menisci and hyaline cartilage | CPM |
| Ruta S. et al. ⁵⁸ | 2016 | Prospective cohort | 15 cases, 60 controls | 67.5 ± 15.8 | NR | SFA | CR, US | 4–13 MHz linear probe | N | Menisci and hyaline cartilage | PM |
| Tanikawa H. et al. ⁴¹ | 2018 | Case control | 9 cases, 17 controls | NR | NR | SFA | CR | / | / | / | PM |
| Lee K.A. et al. ⁵⁷ | 2019 | Prospective cohort | 43 cases, 131 controls | 72.9 ± 15.5 | 30/13 | SFA | CR, US | 5–12 MHz linear probe | Y | Menisci and hyaline cartilage | CPM |
| Filippou G. et al. ⁴² | 2020 | Case control | 51 cases, 17 controls | 71.0 ± 8.0 | NR | H | US | NR | Y | Menisci and hyaline cartilage | NR |

Legend. CPM: compensated polarised microscope, CR: conventional radiography, F: female, H: histology, N: no, M: male, NR: not reported, OMERACT: Outcome Measure in Rheumatology, PM: polarised microscope, RMC: Ryan and McCarty criteria, RS: reference standard, SD: standard deviation; SFA: synovial fluid analysis, US: ultrasonography, Y: yes.

Table I

Main characteristics of the studies included in the systematic literature review evaluating CPPD at knee level

| Authors | Year | Sensitivity | Specificity | PPV | NPV | DOR |
|--|------|------------------|------------------|------------------|------------------|-------------------------|
| A Conventional Radiography | | | | | | |
| Halverson P.B. <i>et al</i> ³⁵ | 1986 | 0.65 (0.44–0.83) | 0.94 (0.80–0.99) | 0.90 (0.67–0.99) | 0.78 (0.62–0.89) | 29.3 (5.7–151.3) |
| Frediani B. <i>et al</i> ³⁶ | 2005 | 0.82 (0.48–0.98) | 1.0 (0.75–1.0) | 1.0 (0.66–1.0) | 0.87 (0.60–0.98) | 102.6 (4.4–2,389.0) |
| Martinez-Sanchis A. <i>et al</i> ⁵² | 2005 | 0.93 (0.85–0.98) | NR | NR | NR | NR |
| Barskova V.G. <i>et al</i> ⁵³ | 2012 | 0.52 (0.31–0.72) | NR | NR | NR | NR |
| Ellaban A.S. <i>et al</i> ³⁹ | 2012 | 0.13 (0.04–0.28) | 1.0 (0.85–1.0) | 1.0 (0.48–1.0) | 0.40 (0.27–0.54) | 7.4 (0.4–140.3) |
| Ottaviani S. <i>et al</i> ⁵⁹ | 2015 | 0.64 (0.43–0.82) | 1.0 (0.87–1.0) | 1.0 (0.79–1.0) | 0.74 (0.57–0.88) | 92.1 (5.0–1,688.9) |
| Ruta S. <i>et al</i> ⁵⁸ | 2016 | 0.40 (0.16–0.68) | 0.83 (0.72–0.92) | 0.38 (0.15–0.65) | 0.85 (0.73–0.93) | 3.3 (1.0–11.5) |
| Tanikawa H. <i>et al</i> ⁴¹ | 2018 | 0.44 (0.14–0.79) | 1.0 (0.79–1.0) | 1.0 (0.40–1.0) | 0.76 (0.53–0.92) | 27.0 (1.3–585.7) |
| Lee K.A. <i>et al</i> ⁵⁷ | 2019 | 0.44 (0.29–0.60) | 0.97 (0.92–0.99) | 0.83 (0.61–0.95) | 0.84 (0.77–0.90) | 25.1 (7.9–80.4) |
| Pooled results | | 0.59 (0.53–0.65) | 0.95 (0.92–0.97) | 0.83 (0.73–0.90) | 0.76 (0.71–0.80) | 19.4 (7.9–47.4) |
| Heterogeneity $p = 0.13$ and $I^2 = 37\%$ | | | | | | |
| Ultrasonography | | | | | | |
| Frediani B. <i>et al</i> ³⁶ | 2005 | 0.82 (0.48–0.98) | 1.0 (0.75–1.0) | 1.0 (0.69–1.0) | 0.93 (0.66–1.0) | 189.0 (7.0–5,127.7) |
| Filippou G. <i>et al</i> ³⁷ | 2007 | 0.87 (0.60–0.98) | 0.96 (0.82–1.0) | 0.93 (0.66–1.0) | 0.93 (0.77–0.99) | 175.5 (14.6–2,116.7) |
| Barskova V.G. <i>et al</i> ⁵³ | 2012 | 1.0 (0.86–1.0) | NR | NR | NR | NR |
| Ellaban A.S. <i>et al</i> ³⁹ | 2012 | 0.84 (0.69–0.94) | 1.0 (0.85–1.0) | 1.0 (0.89–1.0) | 0.79 (0.59–0.92) | 225.0 (12.1–4,197.9) |
| Gutierrez M. <i>et al</i> ⁴⁰ | 2014 | 0.91 (0.82–0.96) | 1.0 (0.96–1.0) | 1.0 (0.95–1.0) | 0.92 (0.85–0.97) | 1,503.0 (84.3–26,792.0) |
| Ottaviani S. <i>et al</i> ⁵⁹ | 2015 | 1.0 (0.86–1.0) | 0.92 (0.75–0.99) | 0.93 (0.76–0.99) | 1.0 (0.86–1.0) | 499.8 (22.8–10,946.7) |
| Filippou G. <i>et al</i> ⁵⁰ | 2016 | 0.78 (0.52–0.94) | 1.0 (0.78–1.0) | 1.0 (0.77–1.0) | 0.79 (0.54–0.94) | 99.9 (4.9–2022.9) |
| Ruta S. <i>et al</i> ⁵⁸ | 2016 | 0.60 (0.32–0.84) | 0.97 (0.89–1.0) | 0.82 (0.49–0.98) | 0.91 (0.81–0.97) | 43.5 (7.6–249.7) |
| Lee K.A. <i>et al</i> ⁵⁷ | 2019 | 0.70 (0.54–0.83) | 0.79 (0.71–0.85) | 0.52 (0.38–0.65) | 0.89 (0.82–0.94) | 8.5 (3.9–18.4) |
| Pooled results | | 0.85 (0.80–0.88) | 0.91 (0.88–0.94) | 0.86 (0.81–0.90) | 0.90 (0.86–0.93) | 116.0 (24.1–558.2) |
| Heterogeneity $p < 0.01$ and $I^2 = 75\%$ | | | | | | |
| B Conventional Radiography | | | | | | |
| Filippou G. <i>et al</i> ³⁰ | 2016 | 0.75 (0.51–0.91) | 0.93 (0.66–1.0) | 0.94 (0.78–1.0) | 0.72 (0.48–0.88) | 39.0 (4.0–378.2) |
| Ultrasonography | | | | | | |
| Filippou G. <i>et al</i> ⁵⁰ | 2016 | 0.96 (0.80–1.0) | 0.88 (0.62–0.98) | 0.93 (0.76–0.99) | 0.93 (0.68–1.0) | 175.0 (14.5–2,106.6) |
| Filippou G. <i>et al</i> ⁴² | 2020 | 0.91 (0.76–0.98) | 0.59 (0.41–0.75) | 0.69 (0.53–0.82) | 0.87 (0.66–0.97) | 14.8 (3.8–58.0) |
| Pooled results | | 0.93 (0.84–0.98) | 0.68 (0.53–0.81) | 0.73 (0.66–0.87) | 0.85 (0.75–0.97) | 40.5 (3.7–438.3) |
| Heterogeneity $p = 0.09$ and $I^2 = 66\%$ | | | | | | |
| C Ultrasonography | | | | | | |
| Filippucci E. <i>et al</i> ³⁸ | 2009 | 0.69 (0.54–0.81) | 0.98 (0.92–1.0) | 0.94 (0.81–0.99) | 0.85 (0.76–0.91) | 90.2 (19.5–416.5) |
| Filippou G. <i>et al</i> ⁵⁴ | 2013 | 0.98 (0.87–1.0) | NR | NR | NR | NR |

Legend. DOR: diagnostic odds ratio; NPV: negative predictive value, NR: not reported, PPV: positive predictive value, RMC: Ryan and McCarty criteria. Values in brackets refers to the 95% confidence interval.

Table II

Diagnostic performance of CR and US in the identification of CPP crystal deposits at knee level, using SFA (A), histology (B) and RMC (C) as reference standard

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diagnostic performance of CR in comparison with histology⁵⁰ [sensitivity = 0.75 (95%CI = 0.51–0.91); specificity = 0.93 (95% CI = 0.66–1.0), PPV = 0.94 (95%CI = 0.78–1.0), NPV = 0.72 (95% CI = 0.48–0.88) and DOR = 39.0 (95%CI = 4.0–378.2)], thus, there were insufficient data to calculate pooled results.

Diagnostic accuracy of CR and US in the detection of CPP crystals in different anatomic sites other than knees

The diagnostic accuracy of CR and US in the detection of CPP crystals in different anatomic sites other than knees was investigated in 8 (30.8%)^{43,44,46–49,55,56} and in 10 (38.5%)^{39,44–49,51,54,60} studies, respectively. Of the included, seven were focused on the wrist^{39,46,47,49,54–56}, two on the acromioclavicular joint^{45,60}, one on the hip joint⁴⁸, one on the shoulder⁴⁵ and four on tendons (i.e., Achilles tendon and plantar fascia)^{43,44,51,54}.

A total of 629 (324 CPPD patients and 305 controls) and 814 (425 CPPD patients and 389 controls) subjects were assessed by CR and US, respectively. The main characteristics of these studies are reported in Table III and Table IV.

Differently from the knee, studies comparing systematically imaging and SFA findings in the same joint were not found. In the great majority of the examined studies (84.6%), the Ryan and McCarty criteria were adopted as the reference method.

At joint level, for both CR and US, the highest diagnostic performances were obtained at wrist level with a pooled sensitivity of 0.67 (95%CI = 0.59–0.74) and 0.87 (95% CI = 0.81–0.91), a pooled specificity of 0.97 (95% CI = 0.92–0.99) and 0.87 (95%CI = 0.80–0.92), a pooled PPV of 0.97 (95%CI = 0.91–0.99) and 0.88 (95%CI = 0.82–0.93), a pooled NPV of 0.75 (95%CI = 0.67–0.82) and 0.85 (95% CI = 0.78–0.90) and a DOR of 98.9 (95%CI = 29.6–330.4) and 72.8 (95%CI = 31.5–167.9), respectively^{39,46,47,49,55,56}.

Tendon involvement (i.e., Achilles tendon and plantar fascia) showed a very high specificity (higher than 0.99 for both imaging techniques) and a very low sensitivity [up to 0.35 (95% CI = 0.26–0.45) for CR and to 0.57 (95%CI = 0.48–0.65) for US]^{43,44,51,54}.

There were insufficient data to calculate pooled results at hip and shoulder level.

| Authors | Year | Study design | Number of patients | Age (years) | Sex (F/M) | RS | Joint for SFA | Imaging techniques | US equipment | 2017–2018 OMERACT definitions ^{61,62} | Structure assessed by US/CR |
|---|------|--------------------|------------------------|--------------------|-----------|-----|---|--------------------|--|--|---|
| Resnick D. <i>et al.</i> ⁵⁶ | 1974 | Cross sectional | 18 CPPD patients | 71.0 | 2/16 | RMC | NR | CR | / | / | Wrist |
| Utsinger P.D. <i>et al.</i> ⁵⁵ | 1975 | Cross sectional | 18 CPPD patients | 71.3 ± 14.2 | 2/16 | RMC | NR | CR | / | / | Wrist |
| Gerster J.C. <i>et al.</i> ⁴³ | 1977 | Case control | 52 cases, 52 controls | 77.4 (range 54–93) | 41/11 | RMC | Knee | CR | / | / | Achilles tendon Plantar fascia |
| Falsetti P. <i>et al.</i> ⁴⁴ | 2004 | Case control | 57 cases, 100 controls | 69.4 (range 44–92) | 27/30 | RMC | NR | CR, US | 10–13 MHz linear probe | N | Achilles tendon, Plantar fascia |
| Ellabban S.A. <i>et al.</i> ⁵¹ | 2012 | Case control | 38 cases, 22 controls | 51.5 ± 8.7 | 15/23 | RMC | Knee | US | 7.5–12 MHz linear probe | N | Achilles tendon, Plantar fascia |
| Ellabban S.A. <i>et al.</i> ³⁹ | 2012 | Case control | 32 cases, 28 controls | 53.5 ± 6.5 | 11/21 | SFA | Knee | US | 7.5–12 MHz linear probe | N | TFCC |
| Filippucci E. <i>et al.</i> ⁴⁵ | 2013 | Case control | 46 cases, 42 controls | 73.6 ± 7.7 | 29/17 | RMC | NR | US | 4–13 MHz or 9–14 MHz linear probe | N | Rotator cuff tendons Acromio-clavicular joint Gleno-humeral joint |
| Filippou G. <i>et al.</i> ⁵⁴ | 2013 | Cross sectional | 42 CPPD patients | 64.0 ± 17.0 | 26/16 | RMC | NR | US | 6–18 MHz linear probe | N | TFCC, Achilles tendon, Plantar fascia |
| Di Matteo A. <i>et al.</i> ⁴⁶ | 2017 | Case control | 36 cases, 48 controls | 74.8 (range 56–80) | 29/7 | RMC | NR | CR, US | 15 MHz linear probe | N | TFCC |
| Forien M. <i>et al.</i> ⁴⁷ | 2017 | Case control | 32 cases, 26 controls | 67.1 ± 16.3 | NR | SFA | Knee (58.6%), wrist (25.9%), shoulder (5.2%), hip (5.2%), ankle (3.5%), elbow (1.7%) | CR, US | 10–18 MHz linear probe | N | TFCC, RCJ volar side |
| Di Matteo A. <i>et al.</i> ⁴⁸ | 2019 | Case control | 50 cases, 40 controls | 71.0 ± 10.2 | 27/23 | RMC | Knee (94.0%), hip (28.0%), wrist (12.0%), ankle (5.0%), shoulder (8.0%), elbow (4.0%) | CR, US | 3–13 MHz linear or 2–7 MHz convex probes | Y | Anterior labrum AC, Femoral head HC |
| Cipolletta E. <i>et al.</i> ⁴⁹ | 2020 | Case control | 61 cases, 39 controls | 73.7 ± 7.7 | 42/19 | RMC | Knee (73.8%), hip (26.2%), wrist (19.7%), shoulder (4.9%) | CR, US | 6–18 MHz linear probe | Y | TFCC, RCJ volar side, SLL dorsal side |
| Ottaviani S. <i>et al.</i> ⁶⁰ | 2020 | Prospective cohort | 25 cases, 50 controls | 79.8 ± 8.5 | 22/3 | SFA | Knee (52.0%), shoulder (32.0%), wrist (12.0%), ankle (4.0%) | US | 7.5–15 MHz linear probe | Y | Acromio-clavicular joint |

Legend. AC: acetabular fibrocartilage, CR: conventional radiography, F: female, HC: hyaline cartilage, M: male, N: no, NR: not reported, OMERACT: Outcome Measure in Rheumatology, RCJ: radio-carpal joint, RMC: Ryan and McCarty criteria, RS: reference standard, SD: standard deviation, SFA: synovial fluid analysis, SLL: scapholunate ligament, TFCC: triangular fibrocartilage complex of the wrist, US: ultrasonography, Y: yes.

Table III

Main characteristics of the studies included in the systematic literature review evaluating CPPD at different anatomic sites other than knees

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Diagnostic accuracy of CR and US in the detection of CPP crystals according to different reference standards

A subgroup analysis was conducted according to the reference test (Ryan and McCarty criteria vs SFA/histology). In studies that adopted SFA/histology as reference standard, the pooled sensitivity,

specificity, PPV, NPV and DOR were 0.47 (95%CI = 0.40–0.55), 0.95 (95%CI = 0.92–0.97), 0.85 (95%CI = 0.77–0.92), 0.74 (95%CI = 0.69–0.78) and 20.77 (95%CI = 8.94–48.23) for CR^{35,36,39,41,47,50,57–59}; and 0.87 (95%CI = 0.83–0.91), 0.88 (95%CI = 0.85–0.91), 0.83 (95%CI = 0.79–0.87), 0.91 (95%CI = 0.88–0.93) and 80.78 (95%CI = 28.31–230.52) for

| | Authors | Year | Sensitivity | Specificity | PPV | NPV | DOR |
|-----------------|---|------|------------------|------------------|------------------|------------------|----------------------|
| Wrist | Conventional Radiography | | | | | | |
| | Resnick D. <i>et al.</i> ⁵⁶ | 1974 | 0.50 (0.26–0.74) | NR | NR | NR | NR |
| | Utsinger P.D. <i>et al.</i> ⁵⁵ | 1975 | 0.50 (0.26–0.74) | NR | NR | NR | NR |
| | Di Matteo A. <i>et al.</i> ⁴⁶ | 2017 | 0.86 (0.71–0.95) | 0.94 (0.83–0.99) | 0.91 (0.76–0.98) | 0.90 (0.78–0.97) | 93.0 (20.7–417.9) |
| | Forien M. <i>et al.</i> ⁴⁷ | 2019 | 0.53 (0.35–0.71) | 1.0 (0.87–1.0) | 1.0 (0.81–1.0) | 0.63 (0.47–0.78) | 59.8 (3.4–1,066.1) |
| | Cipolletta E. <i>et al.</i> ⁴⁹ | 2020 | 0.72 (0.26–0.74) | 1.0 (0.91–1.0) | 1.0 (0.92–1.0) | 0.70 (0.56–0.81) | 200.9 (11.7–3,450.7) |
| | Pooled results | | 0.67 (0.59–0.74) | 0.97 (0.92–0.99) | 0.97 (0.91–0.99) | 0.75 (0.67–0.82) | 98.9 (29.6–330.4) |
| | Heterogeneity $p = 0.83$ and $I^2 = 10\%$ | | | | | | |
| | Ultrasonography | | | | | | |
| | Ellabban S.A. <i>et al.</i> ³⁹ | 2012 | 0.56 (0.38–0.74) | 1.0 (0.88–1.0) | 1.0 (0.82–1.0) | 0.67 (0.51–0.80) | 72.7 (4.1–1,294.6) |
| | Filippou G. <i>et al.</i> ⁵⁴ | 2013 | 0.88 (0.74–0.96) | NR | NR | NR | NR |
| | Di Matteo A. <i>et al.</i> ⁴⁶ | 2017 | 0.92 (0.78–0.98) | 0.81 (0.67–0.91) | 0.79 (0.63–0.90) | 0.93 (0.81–0.99) | 47.7 (11.9–190.7) |
| | Forien M. <i>et al.</i> ⁴⁷ | 2017 | 0.94 (0.79–0.99) | 0.85 (0.65–0.96) | 0.88 (0.73–0.97) | 0.92 (0.73–0.99) | 82.5 (13.9–491.3) |
| | Cipolletta E. <i>et al.</i> ⁴⁹ | 2020 | 0.95 (0.86–0.99) | 0.85 (0.70–0.94) | 0.91 (0.81–0.97) | 0.92 (0.78–0.98) | 106.3 (24.9–453.5) |
| | Pooled results | | 0.87 (0.81–0.91) | 0.87 (0.80–0.92) | 0.88 (0.82–0.93) | 0.85 (0.78–0.90) | 72.8 (31.5–167.9) |
| | Heterogeneity $p = 0.88$ and $I^2 = 3\%$ | | | | | | |
| Achilles tendon | Conventional Radiography | | | | | | |
| | Gerster J.C. <i>et al.</i> ⁴³ | 1977 | 0.10 (0.03–0.21) | 1.0 (0.93–1.0) | 1.0 (0.48–1.0) | 0.81 (0.73–0.87) | 12.2 (0.7–225.8) |
| | Falsetti P. <i>et al.</i> ⁴⁴ | 2004 | 0.53 (0.39–0.66) | 1.0 (0.93–1.0) | 1.0 (0.89–1.0) | 0.53 (0.42–0.63) | 238.9 (14.2–4,033.8) |
| | Pooled results | | 0.35 (0.26–0.45) | 1.0 (0.98–1.0) | 1.0 (0.91–1.0) | 0.68 (0.62–0.74) | 55.2 (2.9–1,068.0) |
| | Heterogeneity $p = 0.13$ and $I^2 = 57\%$ | | | | | | |
| | Ultrasonography | | | | | | |
| | Falsetti P. <i>et al.</i> ⁴⁴ | 2004 | 0.58 (0.44–0.71) | 1.0 (0.96–1.0) | 1.0 (0.89–1.0) | 0.81 (0.73–0.87) | 274.8 (16.3–4,643.9) |
| | Ellabban S.A. <i>et al.</i> ⁵¹ | 2012 | 0.58 (0.41–0.74) | 1.0 (0.85–1.0) | 1.0 (0.85–1.0) | 0.58 (0.41–0.74) | 61.4 (3.5–1,086.1) |
| | Filippou G. <i>et al.</i> ⁵⁴ | 2013 | 0.55 (0.39–0.70) | NR | NR | NR | NR |
| | Pooled results | | 0.57 (0.48–0.65) | 1.0 (0.97–1.0) | 1.0 (0.94–1.0) | 0.75 (0.70–0.82) | 131.5 (17.5–986.3) |
| | Heterogeneity $p = 0.47$ and $I^2 = 3\%$ | | | | | | |
| | Conventional Radiography | | | | | | |
| | Gerster J.C. <i>et al.</i> ⁴³ | 1977 | 0.02 (0.00–0.10) | 1.0 (0.93–1.0) | 1.0 (0.30–1.0) | 0.51 (0.41–0.61) | 3.1 (0.1–76.8) |
| | Falsetti P. <i>et al.</i> ⁴⁴ | 2004 | 0.16 (0.08–0.28) | 0.99 (0.95–1.0) | 0.90 (0.56–1.0) | 0.67 (0.59–0.75) | 18.6 (2.3–150.8) |
| | Pooled results | | 0.09 (0.05–0.16) | 1.0 (0.98–1.0) | 0.91 (0.59–1.0) | 0.60 (0.54–0.67) | 10.9 (1.9–62.9) |
| | Heterogeneity $p = 0.36$ and $I^2 = 13\%$ | | | | | | |
| | Ultrasonography | | | | | | |
| | Falsetti P. <i>et al.</i> ⁴⁴ | 2004 | 0.16 (0.08–0.28) | 0.99 (0.95–1.0) | 0.99 (0.95–1.0) | 0.67 (0.59–0.75) | 18.6 (2.3–150.8) |
| | Ellabban S.A. <i>et al.</i> ⁵¹ | 2012 | 0.16 (0.06–0.31) | 1.0 (0.85–1.0) | 1.0 (0.85–1.0) | 0.41 (0.28–0.55) | 9.0 (0.5–167.9) |
| | Filippou G. <i>et al.</i> ⁵⁴ | 2013 | 0.26 (0.14–0.42) | NR | NR | NR | NR |
| | Pooled results | | 0.19 (0.13–0.27) | 0.99 (0.96–1.0) | 0.99 (0.96–1.0) | 0.60 (0.53–0.67) | 14.5 (2.7–79.8) |
| | Heterogeneity $p = 0.29$ and $I^2 = 12\%$ | | | | | | |
| Hip | Conventional Radiography | | | | | | |
| | Di Matteo A. <i>et al.</i> ⁴⁸ | 2019 | 0.86 (0.73–0.94) | 0.90 (0.76–0.97) | 0.92 (0.80–0.98) | 0.84 (0.69–0.93) | 55.3 (15.0–204.1) |
| Shoulder | Ultrasonography | | | | | | |
| | Di Matteo A. <i>et al.</i> ⁴⁸ | 2019 | 0.90 (0.78–0.97) | 0.85 (0.70–0.94) | 0.88 (0.76–0.96) | 0.87 (0.73–0.96) | 51.0 (14.4–181.2) |
| AC | Ultrasonography | | | | | | |
| | Filippucci E. <i>et al.</i> ⁴⁵ | 2013 | 0.15 (0.06–0.29) | 0.95 (0.84–0.99) | 0.78 (0.40–0.97) | 0.51 (0.39–0.62) | 3.9 (0.8–19.9) |
| AC | Ultrasonography | | | | | | |
| | Filippucci E. <i>et al.</i> ⁴⁵ | 2013 | 0.41 (0.27–0.57) | 0.81 (0.66–0.91) | 0.70 (0.50–0.86) | 0.56 (0.42–0.69) | 3.0 (1.1–7.9) |
| | Ottaviani S. <i>et al.</i> ⁵⁰ | 2020 | 0.92 (0.74–0.99) | 0.88 (0.77–0.96) | 0.79 (0.60–0.92) | 0.96 (0.85–1.0) | 84.3 (15.8–451.5) |
| | Pooled results | | 0.59 (0.47–0.71) | 0.85 (0.76–0.91) | 0.75 (0.62–0.86) | 0.73 (0.63–0.81) | 14.8 (0.6–394.9) |
| | Heterogeneity $p = 0.15$ and $I^2 = 32\%$ | | | | | | |

Legend. AC: acromioclavicular, **DOR:** diagnostic odds ratio; **NPV:** negative predictive value, **NR:** not reported; **PPV:** positive predictive value. Values in brackets refers to the 95% confidence interval.

Table IV Diagnostic performance of CR and US in the identification of CPP crystals at different anatomic sites other than knees

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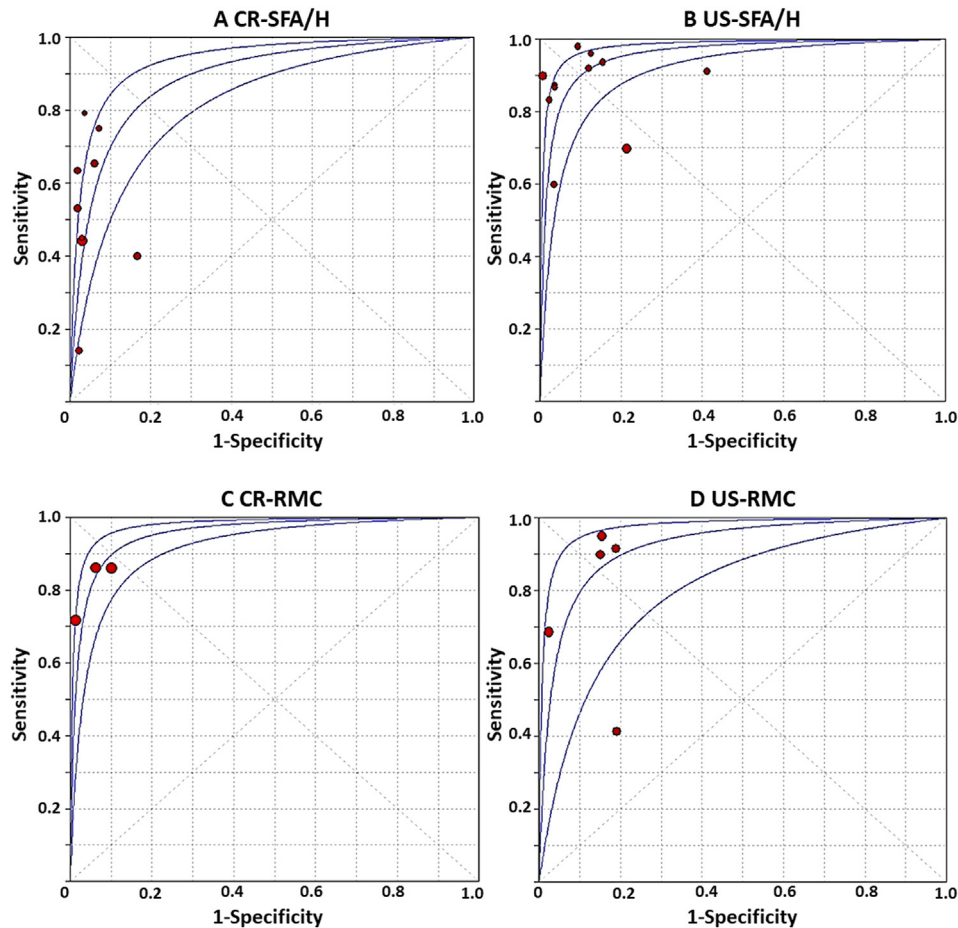
US^{36,37,39,40,42,47,50,57–60}. On the other hand, when Ryan and McCarty criteria were considered the reference standard, the pooled sensitivity, specificity, PPV, NPV and DOR were 0.80 (95% CI = 0.73–0.86), 0.95 (95%CI = 0.89–0.98), 0.94 (95% CI = 0.89–0.98), 0.81 (95%CI = 0.73–0.87) and 77.53 (95% CI = 30.55–196.76) for CR^{46,48,49}; and 0.78 (95%CI = 0.72–0.83), 0.88 (95%CI = 0.83–0.92), 0.86 (95%CI = 0.81–0.90), 0.81 (95% CI = 0.76–0.85) and 35.09 (95%CI = 7.79–158.01) for US^{38,45,46,48,49}.

The SROC curves for the diagnostic performance of CR and US are reported in Fig. 3.

The diagnostic performance of CR varied significantly adopting different reference tests, being higher using Ryan and McCarty criteria than SFA/histology ($p < 0.01$). On the other hand, no significant difference was observed in the US accuracy using either Ryan and McCarty criteria or SFA/histology ($p = 0.08$).

Comparison of US and CR diagnostic performance

A total of seven studies were eligible: six evaluated the knee^{36,39,50,57–59} whereas only one the wrist⁴⁷. The pooled

**Fig. 3**

SROC curves showing the diagnostic performance of CR and US in the detection of CPP deposits using SFA/histology (A–B), and RMC (C–D). **A** CR: AUC = 0.889, SE (AUC) = 0.031, $Q = 0.820$, SE(Q) = 0.032. **B** US: AUC = 0.957, SE (AUC) = 0.017, $Q = 0.900$, SE(Q) = 0.024. **C** CR: AUC = 0.956, SE (AUC) = 0.016, $Q = 0.898$, SE(Q) = 0.022. **D** US: AUC = 0.922, SE (AUC) = 0.041, $Q = 0.856$, SE(Q) = 0.047. **Legend.** AUC: area under the curve, **CR**: conventional radiography, **RMC**: Ryan and McCarty criteria, **SE**: standard error, **US**: ultrasonography.

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sensitivity, specificity, PPV, NPV and DOR were 0.47 (95% CI = 0.40–0.55), 0.95 (95%CI = 0.92–0.97), 0.85 (95% CI = 0.77–0.92), 0.74 (95%CI = 0.69–0.78) and 20.77 (95% CI = 6.95–61.10) for CR and 0.85 (95%CI = 0.79–0.90), 0.87 (95% CI = 0.83–0.91), 0.81 (95%CI = 0.75–0.86), 0.90 (95% CI = 0.86–0.93) and 73.57 (95%CI = 18.75–288.64) for US. US showed a significantly better diagnostic accuracy than CR both including and excluding the single study focused on the wrist ($p < 0.01$). The SROC curves for the diagnostic performance of CR and US are reported in Fig. 4.

Methodological quality assessment

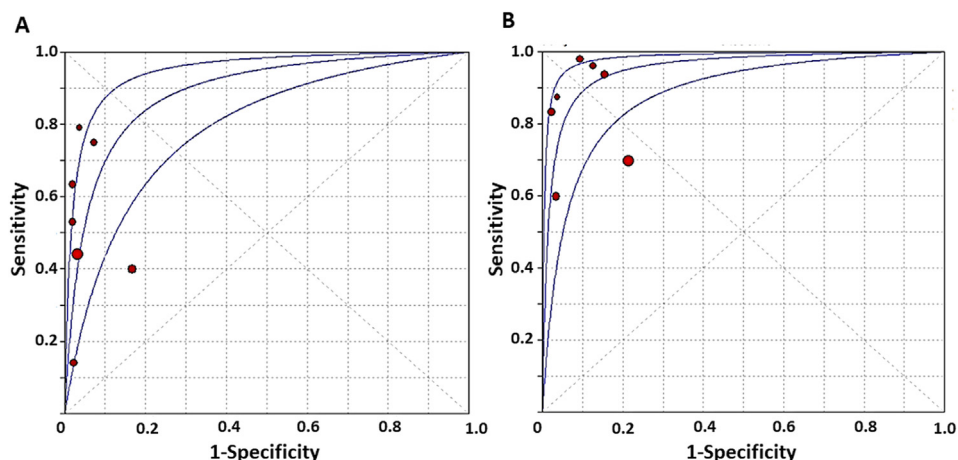
The great majority of the studies (80.8%) had a low risk of bias in most of the items evaluated, and the overall quality was acceptable. However, a high risk of verification bias was reported in two articles^{36,38}. In 5 studies, the time between the index and the reference tests was described^{36,37,50,57,58}, in one article an excessive time interval between two tests was observed (i.e., patients with a historical SFA recorded in a database underwent US)⁴⁰ and in the

remaining studies the time between the index and the reference tests was not mentioned. In addition, some of the studies did not report the blinding of the index and the reference tests^{36–40,44,51,53}. Moreover, except for three articles^{42,52,60}, most articles did not describe the withdrawal of patients. A detailed evaluation of the methodological quality of the articles is shown in Fig. 5.

Egger's regression asymmetry test did not reveal any publication bias neither for CR ($p = 0.15$) nor for US ($p = 0.14$).

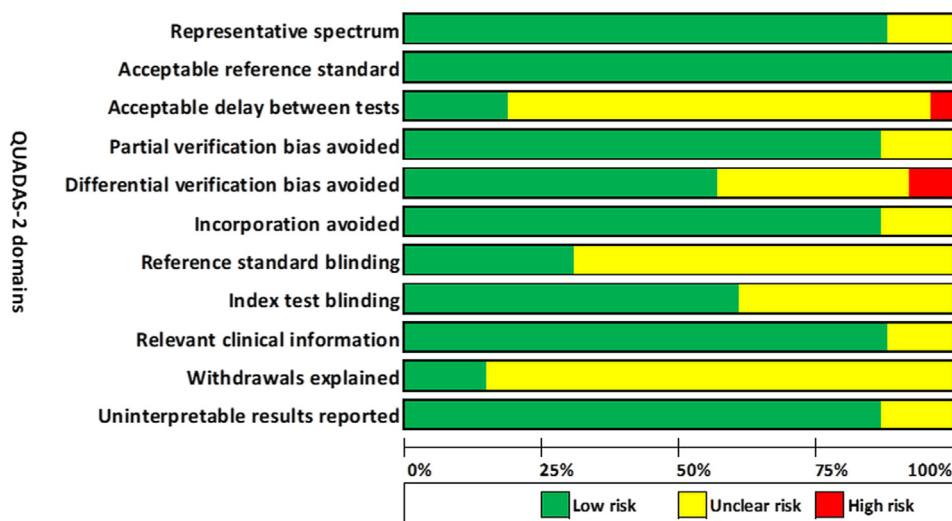
Discussion

This is not the first systematic literature review analysing the diagnostic accuracy of US in patients with CPPD. In fact, other systematic literature reviews have been performed analysing the value of US in the evaluation of the different potential targets of CPPD^{10,11,63} and the last one dates back to 2016. However, this is the first systematic literature review and meta-analysis which evaluate and compare the diagnostic accuracy of CR and US. Moreover, the present article provides an updated overview of the recent progresses of imaging of CPPD, as 10 new studies were published from

**Fig. 4**

SROC curves showing the diagnostic performance of CR and US in the detection of CPP deposits. **A** CR: AUC = 0.889, SE (AUC) = 0.040, Q = 0.820, SE(Q) = 0.041. **B** US: AUC = 0.954, SE (AUC) = 0.024, Q = 0.896, SE(Q) = 0.033. **Legend.** AUC: area under the curve, **CR**: conventional radiography, **SE**: standard error, **US**: ultrasonography.

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**Fig. 5**

Evaluation of the methodological quality of the included studies. **Legend.** QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies 2.

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2016^{41,42,46–50,57,58,60}, and five of them explored anatomic sites other than knees, such as wrists, shoulders, and hips^{46–49,60}. In addition, differently to the previous systematic literature reviews, we carried out several subgroups analyses to investigate the influence of reference standards and anatomic sites in the diagnostic performance of each imaging technique.

According to our results, CR and US showed an excellent (CR AUC = 0.889) and an outstanding (US AUC = 0.954) diagnostic accuracy using SFA/histology as the reference standard, respectively. Of note, the present meta-analysis indicates that US resulted more accurate than CR for the detection of CPP crystal deposits

($p < 0.01$). In fact, a higher sensitivity of US in comparison with CR [0.85 (95%CI = 0.79–0.90) vs 0.47 (95%CI = 0.40–0.55)], and only a little lower specificity [0.87 (95%CI = 0.83–0.91) vs 0.95 (95%CI = 0.92–0.97)] were found. These results support the validity of these imaging techniques in the diagnosis of CPPD and its early and correct identification may prevent unnecessary and potentially harmful treatments.^{74–77}

Among the included studies, a great heterogeneity was found in relation to the adopted reference standard. At knee level, CR and US were tested against all the different reference tests, whereas in other anatomic sites, the Ryan and McCarty criteria were mainly

used as reference test. This is primarily due to the fact that the knee is the most accessible joint to perform the synovial fluid aspiration and, therefore, the SFA.

At knee level, the diagnostic performance of CR and US varied adopting different reference tests.

Using the SFA as reference standard, the pooled sensitivity and specificity were 0.59 (95%CI = 0.53–0.65) and 0.95 (95%CI = 0.92–0.97) for CR and 0.85 (95%CI = 0.80–0.88) and 0.91 (95%CI = 0.88–0.94) for US. When histology was considered as reference standard, the pooled sensitivity and specificity of US were 0.93 (95%CI = 0.84–0.98) and 0.68 (95%CI = 0.53–0.81), while no pooled results were available for CR. The sensitivity of US remains high despite changing the reference standard (Table II). On the other hand, the specificity of US was higher when SFA was adopted as reference standard compared with histology. This could be explained by the different sample size (651 patients in the SFA group and 110 in the histology group), as well as by the different study populations evaluated (e.g., patients with acute CPP crystal arthritis in the SFA group vs patients with severe osteoarthritis waiting for joint replacement in the histology group). In fact, meniscal degeneration may occur in the latter condition and it may appear as hyperechoic areas within the meniscal fibrocartilage^{64,65}.

In addition, these results should be interpreted in the light of the fact that SFA represent an imperfect gold standard, since the diagnostic accuracy and the reproducibility of SFA in CPP crystal identification have been questioned^{50,66,67}. Thus, other diagnostic methods such as Raman spectroscopy, histology or advanced imaging techniques (e.g., multi-energy Spectral Photon-Counting CT) should be used to further validate conventional imaging techniques^{10–12}.

Variable results of US accuracy were found in the evaluation of a specific joint, also when the same reference standard was used. For instance, at knee level the sensitivity and the specificity ranged from 0.13 to 0.93 and 0.83 to 1.0 for CR and from 0.60 to 1.0 and 0.79 to 1.0 for US using SFA as the reference test (Table II). Possible explanations include: first, the adopted US definition of CPP crystal deposits (e.g., OMERACT definitions vs previous ones); second, the assessment of different anatomic targets within the same joint (e.g., at knee level: meniscal fibrocartilage and/or femoral condyles' hyaline cartilage; at wrist level: triangular fibrocartilage and/or volar side of the radio-carpal joint and/or dorsal part of the scapholunate ligament); third, the use of different US equipment (e.g., 13 vs 18 MHz transducers). In addition, there are several factors that may influence the diagnostic value of CR in detecting chondrocalcinosis: localization of CPP crystal deposits, significant cartilage loss or bone superimposition or the technique used⁶⁸. Finally, the enrolment of patients with different demographic and clinical characteristics could have contributed to determine the different diagnostic performance in both imaging techniques.

In anatomic sites other than knees, the most adopted reference method was the Ryan and McCarty criteria: in this way CR has been used both as index test and as reference test, thus generating a verification bias. Moreover, the use of Ryan and McCarty criteria may have led to an overestimation of the diagnostic accuracy of CR. In fact, according to our results, the diagnostic accuracy of CR was significantly higher in the studies that adopted the Ryan and McCarty criteria than in those that used SFA/histology ($p = 0.01$). Conversely, the diagnostic accuracy of US was not significantly influenced by the adopted reference standard ($p = 0.08$).

Future researches should evaluate the diagnostic accuracy of imaging techniques assessing the joints in which the reference test was performed.

Despite the knee is by far the most commonly involved area in patients with CPPD, the isolated involvement of hip, wrist and metacarpophalangeal joints has been found by CR in 45.9%, 44.4%

and 31.3% of the patients with CPPD, respectively⁶⁹. Further studies are needed to provide more robust evidence regarding the role of US in the detection of CPP crystal deposits in these not enough studied, but equally important, targets of the disease.

The present systematic literature review has some drawbacks. First, the moderate to high heterogeneity between the studies could be explained by the low sample size of the great majority of the studies, as well as the differences in design, population, and reference standards characterising these studies. However, some degree of heterogeneity could be expected as this is a frequent finding in meta-analysis⁷⁰. In addition, as shown in Tables II and IV, subgroup analyses displayed only a low to moderate heterogeneity and confirmed that reference standard and anatomic site are ones of the main sources of heterogeneity. Second, only few data were available in anatomic sites other than knees and wrists. Thus, more studies are warranted to support the accuracy of CR and US in the identification of CPP crystal deposits at those levels. Third, in anatomic sites other than knees, the Ryan and McCarty criteria were the most adopted gold standard. Thus, the diagnostic performance of CR may be misestimated by the fact that CR was included in both the index and reference tests. This limitation should be considered in the interpretation of the results at these anatomic sites. Fourth, we did not perform a subgroup analysis to evaluate the diagnostic accuracy of CR and US in different age-groups. However, the great majority of the studies (73.1%) included subjects aged between 64 and 75 years and the age of the population in both the CR and US groups were similar (68.9 vs 66.7 years). Thus, we can reasonably exclude a sampling bias. Finally, other imaging techniques such as CT and dual energy CT were not included in the present systematic literature review. In fact, despite being promising, only a few data exploring their diagnostic accuracy were available^{12–14,31,43,55,71–73}.

In conclusion, our results support the diagnostic accuracy of both CR and US in patients with CPPD. CR has the advantages to be a well-established, widely available imaging tool, which provides a comprehensive visualization of calcium-containing crystal deposits as well as features of osteoarthritis. US offers a radiation-free, repeatable, multi-planar and multi-tissue assessment and the possibility to evaluate both crystal deposits and soft tissues inflammatory abnormalities. Although US is more sensitive and a little less specific than CR for identifying CPP crystal, both these two techniques should be regarded as complementary to each other in the diagnostic work-up in patients with CPPD.

Contributions

Dr. Edoardo Cipolletta (edoardocipolletta@gmail.com) and Dr. Andrea Di Matteo (andreadimatteo@hotmail.com) take the responsibility for the integrity of the work as a whole, from inception to finished article.

Study conception and design. Dr. Edoardo Cipolletta, Dr. Andrea Di Matteo, Dr. Emilio Filippucci.

Acquisition of data. Dr. Edoardo Cipolletta and Dr. Jacopo Di Battista.

Analysis and interpretation of data. Dr. Edoardo Cipolletta, Dr. Jacopo Di Battista, Dr. Andrea Di Matteo, Dr. Georgios Filippou, Dr. Emilio Filippucci, Prof. Walter Grassi, Prof. Fausto Salaffi and Prof. Carlo Alberto Scirè.

Statistical analysis. Dr. Edoardo Cipolletta, Prof. Fausto Salaffi and Prof. Carlo Alberto Scirè.

All authors have drafted the article, revised it critically for important intellectual content and read and approved the final version of the manuscript.

Competing interests

E.F. has received speaking fees from AbbVie, Bristol-Myers Squibb, Celgene, Novartis, Pfizer, Roche and Union Chimique Belge Pharma. W.G. has received speaking fees from AbbVie, Celgene, Grünenthal, Pfizer and Union Chimique Belge Pharma. All other authors have declared no conflict of interest.

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Supplementary data

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