Diagnosis, prognosis and classification of early arthritis: results of a systematic literature informing the 2016 update of the EULAR recommendations for the management of early arthritis.

SUPPLEMENTARY MATERIALS

S1: Research questions

Question 1:

a) Can the recognition of arthritis by general practitioners (GPs) be trained, and if yes: how?
b) Which diagnostics should a GP perform in a patient with early arthritis?
c) How to recognize early arthritis (by the GP)?
d) Should all patients with early arthritis be referred to a medical specialist for further diagnosis and treatment? Or only patients with specific features (> 1 joint, rheumatoid factor positive)
e) How early should patients with arthritis be referred to a medical specialist? Or how early a patient with arthritis needs to be seen by the specialist?

Question 2:

a) Which is the place of laboratory tests such as RF, anti-CCP, ANA, new diagnostic tests (multibiomarker test..), etc in the diagnosis of early arthritis?
b) Which is the place of imaging such as plain X-rays, MRI, US, or other imaging modalities (Scintigraphy, PET scan, optical imaging methods: Xeralite Rheumascan; Hemics Handscan...) etc. in the diagnosis of early arthritis? Has US and MRI detected inflammation the same weight as clinical evaluation for the detection of synovitis at disease presentation?
c) Is there a minimum set of diagnostic procedures that need to be performed in a patient with early arthritis?

Question 3:

a) Which is the place of laboratory tests such as RF, anti-CCP, ANA, new diagnostic tests (multibiomarker test..), etc in the prognosis of early arthritis?
b) Which is the place of imaging such as plain X-rays, MRI, US, or other imaging modalities (Scintigraphy, PET scan, optical imaging methods: Xeralite Rheumascan; Hemics Handscan...) etc. in the prognosis of early arthritis? Has US and MRI detected inflammation the same weight as clinical evaluation for the detection of synovitis at disease presentation?

Question 4:

a) Which are relevant differential diagnostic considerations in patients referred with early undifferentiated arthritis in light of the epidemiology?

Question 5:

a) Is it still relevant to the individual patient to classify the disease according to recognised classification criteria?
S2: PICOTs

**Question 1:**

a) What is the sensitivity/specificity of any tools applied by a GP for patients with suspected early arthritis to distinguish those with confirmed early arthritis from those with no early arthritis confirmed?

**Population:** patients suspected to have early arthritis, with confirmed EA according to an external standard (eg. rheumatologist’s opinion)

**Intervention:** any tool applied by a GP to help diagnosing EA (questionnaires, algorithm, imaging, lab test, physical examination, etc.)

**Control:** patients suspected to have early arthritis in whom EA was not confirmed by an external standard (eg. rheumatologist’s opinion)

**Outcomes:** Sensitivity and specificity/ PPV and NPV (and 2-by-2 table with crude numbers)/ OR or RR

**Type of study:** diagnostic experiment

b) What is the RR (OR) of patients with (a suspicion of) arthritis referred by the GP to a specialist in comparison to those not referred by the GP with respect of final diagnosis of any inflammatory rheumatic disease and with respect to radiographic progression?

**Population:** patients with i) suspicion of arthritis by the GP or ii) arthritis diagnosed by the GP; that have been referred to the rheumatologist

**Intervention:** Any tool applied by a GP to distinguish between referral and non-referral (imaging, ACPA, RF, more than 1 joint affected, family history, etc.)/ GP’s clinical judgement/ No intervention defined

**Control:** patients with i) suspicion of arthritis by the GP or ii) arthritis diagnosed by the GP; that have not been referred to the rheumatologist

**Outcomes:** percentage of patients per group (or OR/RR) with i) diagnosis/classification of RA after x years; ii) a diagnosis/classification of any inflammatory rheumatic disease after x years; iii) radiographic progression after x years

**Type of study:** prognostic study with prospective follow-up

c) What is the RR (OR) of patients meeting remission or with non-radiographic progression when referred to specialist within x weeks compared to those referred beyond x weeks?

**Population:** patients with early arthritis that have been referred to specialist within x months after onset of arthritis

**Intervention:** Random allocation of early referral vs late referral/ The GP’s judgement (early vs late referral)/ Any test result that guides early or late referral (eg. ACPA)/ No intervention

**Control:** patients with early arthritis that have been referred to specialist beyond x months after onset of arthritis
Outcomes: percentage of patients per group or as OR/RR with: clinical remission after x years/ non radiographic progression after x years.

Type of study: RCT or prognostic study with prospective follow-up

**Question 2:**

What is the PPV/NPV of ACPA/RF/ANA... when tested in a population with patients with arthralgia or early arthritis with respect to a classification of RA or other inflammatory rheumatic disease after x years?

Population: Patients with i) early arthritis or with ii) arthralgia who will develop RA or any other inflammatory rheumatic disease according to classification criteria

Intervention: Any laboratory tool applied to help diagnosing RA or any inflammatory rheumatic disease (ACPA, RF, ANA, ANCA)

Control: Patients with i) early arthritis or with ii) arthralgia who will NOT develop a RA or any other inflammatory rheumatic disease according to classification criteria

Outcomes: Sensitivity and specificity of the tool to predict RA/other diagnosis/ PPV and NPV (and 2-by-2 table with crude numbers)/ OR or RR

Type of study: i) case control studies and ii) Prognostic studies with prospective follow up

b) What is the PPV/NPV of imaging exams when tested in a population with arthralgia or early arthritis with respect to a classification of RA or other inflammatory rheumatic disease after x years?

Population: Patients with i) early arthritis or with ii) arthralgia who will develop a confirmed RA or any other inflammatory rheumatic disease according to classification criteria

Intervention: Any imaging exam (plain X-rays, MRI, US, Scintigraphy, PET scan, optical imaging methods) applied to help diagnosing RA or any inflammatory rheumatic disease

Control: Patients with i) early arthritis or with ii) arthralgia who will NOT develop a confirmed RA or any other inflammatory rheumatic disease according to classification criteria

Outcomes: Sensitivity and specificity of the tool to predict a classification of RA/other inflammatory disease/ PPV and NPV (and 2-by-2 table with crude numbers)/ OR or RR

Type of study: i) case control studies and ii) Prognostic studies with prospective follow up.

c) What is the PPV/NPV of a sequence of diagnostic procedures for diagnosing a rheumatic disease in patients with early arthritis?

Population: Patients with undifferentiated early arthritis that will develop a rheumatic disease according to classification criteria after x years

Intervention: application of a pre-set sequence of diagnosis procedures

Control: Patients with undifferentiated early arthritis that have not developed a rheumatic disease according to classification criteria after x years

Outcomes: Sensitivity and specificity to diagnose RA or other rheumatological disease after x years/ PPV and NPV (and 2-by-2 table with crude numbers)/ OR or RR

Type of study: studies with prospective follow-up

**Question 3:**
a) What is the PPV/NPV of ACPA/RF/ANA... when tested in a population with arthralgia or early arthritis with respect to radiological outcome or functional outcome or remission outcome after x years?

Population: Patients with i) early arthritis or with ii) arthralgia who will develop a severe inflammatory rheumatic disease, in terms of functional outcome or radiological outcome or remission outcome

Intervention: Any laboratory tool (ACPA, RF, ANA., ANCA) applied to help diagnosing severe RA or any inflammatory rheumatic disease

Control: Patients with i) early arthritis or with ii) arthralgia who will NOT develop a severe inflammatory rheumatic disease, in terms of functional outcome or radiological outcome or remission outcome

Outcomes: Sensitivity and specificity of the tool to predict radiographic progression/functional disability/ PPV and NPV (and 2-by-2 table with crude numbers)/ OR or RR

Type of study: i) case control studies and ii) Prognostic studies with prospective follow up

b) What is the PPV/NPV of imaging exam when tested in a population with arthralgia or early arthritis with respect to radiological outcome or functional outcome after x years?

Population: Patients with i) early arthritis or with ii) arthralgia who will develop a severe inflammatory rheumatic disease, in terms of functional outcome or radiological outcome

Intervention: Any imaging exam (plain X-rays, MRI, US, Scintigraphy, PET scan, optical imaging methods) applied to help diagnosing severe RA or any inflammatory rheumatic disease

Control: Patients with i) early arthritis or with ii) arthralgia who will NOT develop a severe inflammatory rheumatic disease, in terms of functional outcome or radiological outcome

Outcomes: Sensitivity and specificity of the tool to predict radiographic progression/functional disability/ PPV and NPV (and 2-by-2 table with crude numbers)/ OR or RR

Type of study: i) case control studies and ii) Prognostic studies with prospective follow up

Question 4:

What is the frequency of rheumatic diseases toward which early arthritis evolve after x years?

Population: Patients presenting with undifferentiated early arthritis

Intervention: Follow-up during x years

Control: None

Outcome: Diagnosis of a specific rheumatic disease according to classification criteria

Type of study: Studies with prospective follow-up (inception cohorts)

Question 5:

a) Is the prognosis (in terms of radiographic progression or functionnal disability or persistent disease) of early RA responding to ACR/EULAR 2010 criteria better than the prognosis of early RA that are ACR/EULAR criteria negative?
Population: Patients with early rheumatoid arthritis diagnosed by the rheumatologist that are also ACR/EULAR 2010 criteria positive

Intervention: Application of the ACR/EULAR 2010 criteria

Control: Patients with early rheumatoid arthritis diagnosed by the rheumatologist that are (still) ACR/EULAR 2010 criteria negative

Outcomes: Percentage of patients (per group or as OR/RR) with persistent disease according to the rheumatologist: persistent synovitis/ persistent DMARDs treatment/ erosion

Type of study: Prognostic studies

b) Is the prognosis (in terms of radiographic progression or functional disability or persistent disease) of early PsA responding to CASPAR criteria better than the prognosis of early PsA that are CASPAR criteria negative?

Population: Patients with early psoriatic arthritis diagnosed by the rheumatologist that are also CASPAR criteria positive

Intervention: Application of the CASPAR criteria

Control: Patients with early psoriatic arthritis diagnosed by the rheumatologist that are (still) CASPAR criteria negative

Outcomes: Percentage of patients (per group or as OR/RR) with persistent PsA according to the rheumatologist: persistent synovitis/ persistent DMARD treatment/ radiographic abnormalities

Type of study: Prognostic studies

c) Is the prognosis (in terms of radiographic progression or functional disability or persistent disease) of early peripheral spondyloarthritis responding to ASAS 2009 criteria better than the prognosis of early peripheral spondyloarthritis that are ASAS2009 criteria negative?

Population: Patients with early peripheral spondyloarthritis diagnosed by the rheumatologist that are also ASAS 2009 criteria positive

Intervention: Application of the ASAS 2009 criteria

Control: Patients with early peripheral spondyloarthritis diagnosed by the rheumatologist that are (still) ASAS 2009 criteria negative

Outcomes: Percentage of patients (per group or as OR/RR) with persistent peripheral spondyloarthritis according to the rheumatologist

Type of study: Prognostic studies
S3: Search strategy

**Question 1 - Recognition of arthritis and referral to a medical specialist**

| MEDLINE | 1. exp Arthritis, Rheumatoid;/ 2. exp early diagnosis;/ 3. 1 and 2; 4. exp Arthritis, Rheumatoid/ and (early or recent).tw.; 5. ((early or recent$ or undifferentiated or persistent or unclassified) adj3 arthritis).tw.; 6. or/3-5; 7. exp "Referral and Consultation";/ 8. exp Mass Screening;/ 9. Physicians, Primary Care;/ 10. exp Primary Health Care;/ 11. General Practitioners;/ 12. Triage;/ 13. Population Surveillance/mt [Methods]; 14. exp "Predictive Value of Tests";/ 15. Primary Care.tw.; 16. General Practitioner$.tw.; 17. screen$.tw.; 18. refer$.tw.; 19. case finding.tw.; 20. consult$.tw.; 21. or/7-20; 22. 6 and 21; 23. (sensitiv: or diagnos:).mp. or di.fs.; 24. 6 and 23; 25. 22 or 24; 26. exp animals/ not humans.sh.; 27. 25 not 26; 28. limit 27 to "all adult (19 plus years)"; 29. limit 28 to yr="2010 -Current" |
|---|---|
| The Cochrane Library | #1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees; #2 MeSH descriptor: [Early Diagnosis] explode all trees; #3 #1 and #2; #4 (early or recent):ti,ab ; #5 #1 and #4 ; #6 ((early or recent$ or undifferentiated or persistent or unclassified) near/3 arthritis):ti,ab ; #7 #3 or #5 or #6 ; #8 MeSH descriptor: [Referral and Consultation] explode all trees; #9 MeSH descriptor: [Mass Screening] explode all trees; #10 MeSH descriptor: [Physicians, Primary Care] this term only; #11 MeSH descriptor: [Primary Health Care] explode all trees; #12 MeSH descriptor: [General Practitioners] this term only; #13 MeSH descriptor: [Triage] this term only; #14 MeSH descriptor: [Population Surveillance] this term only and with qualifier(s): [Methods - MT]; #15 MeSH descriptor: [Predictive Value of Tests] explode all trees; #16 "Primary Care":ti,ab; #17 "General Practitioner*":ti,ab ; #18 screen*:ti,ab ; #19 refer*:ti,ab ; #20 "case finding":ti,ab ; #21 consult*:ti,ab ; #22 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 ; #23 #7 and #22 ; #24 (sensitiv* or diagnos*) ; #25 Any MeSH descriptor with qualifier(s): [Diagnosis - DI]; #26 #24 or #25 ; #27 #7 and #26 ; #28 #23 or #27 Publication Year from 2010 to 2015 |
| EMBASE | #24. #23 AND [humans]/lim AND [embase]/lim AND ([adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim OR [young adult]/lim) AND (2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py); #23. #20 OR #22; #22. #6 AND #21; #21. 'diagnosis'/lnk OR predict*:ab,ti OR specificity:ab,ti; #20. #6 AND #19; #19. #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 ; #18. consult*:ab,ti ; #17. 'case finding':ab,ti; #16. refer*:ab,ti ; #15. screen*:ab,ti ; #14. 'general practitioner':ab,ti OR 'general practitioners':ab,ti ; #13. 'primary care':ab,ti ; #12. 'predictive value'/de; #11. 'health survey'/exp; #10. 'primary health care'/exp; #9. 'general practitioner'/de; #8. 'mass screening'/exp; #7. 'patient referral'/de; #6. #3 OR #4 OR #5 ; #5. ((early OR recent$ OR undifferentiated OR persistent OR unclassified) NEAR/3 arthritis):ab,ti; #4. 'rheumatoid arthritis'/exp AND (early:ab,ti OR recent:ab,ti); #3. #1 AND #2; #2. 'early diagnosis'/de; #1. 'rheumatoid arthritis'/exp |
### MEDLINE

1. exp Arthritis, Rheumatoid/
2. exp early diagnosis/
3. 1 and 2
4. exp Arthritis, Rheumatoid/ and (early or recent).tw.
5. ((early or recent$ or undifferentiated or persistent or unclassified) adj3 arthritis).tw.
6. exp Arthralgia/
7. arthralgi$.tw.
8. or/3-7
9. (sensitiv: or diagnos:).mp. or di.fs.
10. incidence.sh. or exp mortality/
11. follow-up studies.sh.
12. prognos:.tw.
13. predict:.tw.
14. course:.tw.
15. exp Classification/
16. classif$.tw.
17. Classification.fs.
18. or/9-18
19. 8 and 19
20. exp animals/ not humans.sh.
21. 19 not 20
22. limit 2 to "all adult (19 plus years)"
23. limit 22 to yr="2005 -Current";
24. limit 23 to english language

### The Cochrane Library

#1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees; #2 MeSH descriptor: [Early Diagnosis] explode all trees; #3 #1 and #2 ; #4 (early or recent):ti,ab ; #5 #1 and #4 ; #6 ((early or recent* or undifferentiated or persistent or unclassified) near/3 arthritis):ti,ab ; #7 MeSH descriptor: [Arthralgia] explode all trees; #8 arthralgi*:ti,ab ; #9 #3 or #5 or #6 or #7 or #8 ; #10 (sensitiv* or diagnos*) ; #11 Any MeSH descriptor with qualifier(s): [Diagnosis - DI]; #12 MeSH descriptor: [Incidence] this term only; #13 MeSH descriptor: [Mortality] explode all trees; #14 MeSH descriptor: [Follow-Up Studies] this term only; #15 prognos*:ti,ab ; #16 predict*:ti,ab ; #17 course*:ti,ab ; #18 MeSH descriptor: [Classification] explode all trees; #19 classif*:ti,ab ; #20 Any MeSH descriptor with qualifier(s): [Classification - CL]; #21 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 ; #22 #9 and #21 Publication Year from 2005 to 2015

### EMBASE

#17. #16 AND [embase]/lim AND [humans]/lim AND [english]/lim AND ([adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim OR [young adult]/lim) AND (2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py) AND ('article'/it OR 'article in press'/it); #16. #8 AND #15; #15. #9 OR #10 OR #11 OR #12 OR #13 OR #14; #14. classif*:ab,ti ; #13. 'classification/exp ; #12. prognos*:ab,ti ; #11. epidemiology/lnk ; #10. 'follow up'; #9. 'diagnosis'/lnk OR predict*:ab,ti OR specificity:ab,ti; #8. #3 OR #4 OR #5 OR #6 OR #7; #7. arthralgi*:ab,ti ; #6. 'arthralgia'/de ; #5. ((early or recent* OR undifferentiated OR persistent OR unclassified) NEAR/3 arthritis):ab,ti; #4. 'rheumatoid arthritis/exp AND (early:ab,ti OR recent:ab,ti); #3. #1 AND #2; #2. 'early diagnosis/de ; #1. 'rheumatoid arthritis/exp
S4: Studies design. (A) For the diagnosis part and (B) for the prognosis part.

A.

Baseline \[\rightarrow\] End of follow-up

**Undifferentiated arthritis:**
- RF +/-
- Anti-CCP +/-

| RA       | Not RA       | Sensitivity  | Specificity |
|----------|--------------|--------------|-------------|
| RF/Anti-CCP + | True Positive | False Positive | Sensitivity= TP/TP+FN |
| RF/Anti-CCP - | False negative | True Negative       | Specificity= TN/TN+FP   |

**OR, Multivariate**

B.

Baseline \[\rightarrow\] End of follow-up

**Early Rheumatoid arthritis (ERA):**
- RF +/-
- Anti-CCP +/-

| ERA       | Severe RA       | Sensitivity  | Specificity |
|----------|-----------------|--------------|-------------|
| RF/Anti-CCP + | True Positive | False Positive | Sensitivity= TP/TP+FN |
| RF/Anti-CCP - | False negative | True Negative       | Specificity= TN/TN+FP   |

**OR, Multivariate**

**Severe Rheumatoid arthritis:**
- Radiographic progression
- No remission
- High HAQ score
S5: (A) Value of laboratory tests in EA diagnosis and (B) Value of imaging tests in EA diagnosis.

A.

| Study [LoE]          | Population at baseline | Time for RA diagnosis (outcome) | % of pts achieving outcome | Laboratory test (+ vs -) | Sens | Spec | PPV | NPV | OR (95% CI) |
|----------------------|------------------------|--------------------------------|---------------------------|--------------------------|------|------|-----|-----|-------------|
| Raza [2b] [22]       | EA (n= 97)             | 1 year                         | 25                        | Anti-CCP                 | 63   | 94   | 79  | 88  | NR          |
|                      |                        |                                |                           | RF                       | 63   | 99   | 94  | 89  | NR          |
|                      |                        |                                |                           | Anti-CCP and RF          | 58   | 100  | 100 | 88  | NR          |
|                      |                        |                                |                           | Anti-CCP or RF           | 67   | 97   | 76  | 89  | NR          |
| van Gaalen [2b] [23] | EA (n= 467)            | 1 year                         | 33                        | Anti-CCP                 | 54   | 96   | 86  | 81  | NR          |
|                      |                        |                                |                           | RF                       | 55   | 89   | 84  | 65  | NR          |
|                      |                        |                                |                           | RF, high titer           | 41   | 98   | 92  | 63  | NR          |
|                      |                        |                                |                           | Anti-RA33                | 28   | 90   | 74  | 55  | NR          |
| Nell [2b] [24]       | EA (n= 200)            | 1 year                         | 51                        | Anti-CCP                 | 41   | 98   | 96  | 62  | NR          |
|                      |                        |                                |                           | RF                       | 55   | 89   | 84  | 65  | NR          |
|                      |                        |                                |                           | RF, high titer           | 41   | 98   | 92  | 63  | NR          |
|                      |                        |                                |                           | Anti-RA33                | 28   | 90   | 74  | 55  | NR          |
| Boire [2b] [25]      | EA (n= 149)            | 30 months                      | 19                        | Anti-CCP                 | 39   | 67   | NR  | NR  | NR          |
|                      |                        |                                |                           | RF                       | 57   | 63   | NR  | NR  | NR          |
|                      |                        |                                |                           | Anti-cit-vim             | 39   | 73   | NR  | NR  | NR          |
| Fernandez-Suarez [2b] [26] | EA (n= 78)     | 1 year                         | 68                        | Anti-CCP                 | 53   | 100  | 100 | 58  | NR          |
|                      |                        |                                |                           | RF                       | 57   | 97   | 97  | 60  | NR          |
|                      |                        |                                |                           | Anti-CCP or RF           | 68   | 97   | 97  | 67  | NR          |
|                      |                        |                                |                           | Anti-CCP and RF          | 42   | 100  | 100 | 53  | NR          |
| Kudo-Tanaka [2b] [27] | EA (n= 146)            | 1 year                         | 12                        | Anti-CCP                 | 83   | 93   | 65  | 97  | NR          |
|                      |                        |                                |                           | RF                       | 78   | 68   | 30  | 98  | NR          |
|                      |                        |                                |                           | Anti-CCP and RF          | 72   | 96   | 72  | 96  | NR          |
|                      |                        |                                |                           | MMP-3                    | 60   | 71   | 25  | 92  | NR          |
| Ateş [2b] [28]       | EA (n= 64)             | 9 months                       | 50                        | Anti-CCP                 | 44   | 97   | 92  | 71  | NR          |
|                      |                        |                                |                           | RF                       | 41   | 95   | 85  | 69  | NR          |
|                      |                        |                                |                           | Anti-CCP and RF          | 33   | 100  | 100 | 67  | NR          |
|                      |                        |                                |                           | Anti-CCP or RF           | 52   | 92   | 82  | 72  | NR          |
| Study                  | EA (n) | Duration | Anti-CCP | RF | Anti-MCV | Anti-CCP, low titers | RF or Anti-CCP, high titers | RF or Anti-CCP and RF |
|------------------------|--------|----------|----------|----|----------|-----------------------|-----------------------------|------------------------|
| Kondo [2b] [29]        | 70     | 1 year   | 31       |    |          |                       |                             |                        |
| Ursum [2b] [44]        | 162    | 1 year   | 76       |    |          |                       |                             |                        |
| Mjaavatten [2b] [30]   | 384    | 1 year   | 18       |    |          |                       |                             |                        |
| van der Linden [2b] [31] | 625  | 1 year   | 32       |    |          |                       |                             |                        |
| Funovits [2b] [32]     | 3115   | 1 year   | NR       |    |          |                       |                             |                        |
| Damjanovska [4] [46]   | 917    | NR       | 62       |    |          |                       |                             |                        |
| Emad [2b] [33]         | 69     | 1 year   | 26       |    |          |                       |                             |                        |
| Gossec [2b] [34]       | 731    | 1 year   | 51       |    |          |                       |                             |                        |
| Duer-Jensen [2b] [35]  | 116    | 12 to 23 months | 23   |    |          |                       |                             |                        |
| Pratt [2b] [36]        | 75     | Median of 28 months | 39   |    |          |                       |                             |                        |
| Bizzaro [2b] [37]      | 192    | 2 years  | 38       |    |          |                       |                             |                        |
| Study               | Cohort (n) | Follow-up | Anti-CCP, high titers | RF, low titers | RF, high titers | Anti-CCP and RF |
|---------------------|------------|-----------|------------------------|---------------|---------------|-----------------|
| Chen [2b] [38]      | EA (n= 218)| 2 years   | 64 83 69 79            | 63 72 57 76   | 15 86 42 63    | 60 83 67 77     |
| Hiura [2b] [39]     | EA (n= 99) | 1 year    | 34 94 56 85            | 41 79 33 84   | 9 98 50 81     | 41 81 35 84     |
| Goëb [2b] [47]      | EA (n= 250)| Approx. 5 years | 35 94 NR NR NR       | 35 94 NR NR NR | 47 93 84 70  
| Moghimi [4] [40]    | EA (n= 193)| NR  NR  | 47 93 84 70            | 57 84 73 72   | 39 97 89 68     |
| Nicaise-Roland [2b] [48]² | EA (n= 188)| 2 years | 30 93 80 56            | 31 88 73 55   | 32 87 71 56    |
| Regueiro [2b] [41]  | EA (n= 552)| 2 years | 53 80 NR NR NR         | NR NR 69 80   | NR NR 68 82    |
LoE, Level of Evidence; RA, rheumatoid arthritis; Pts, patients; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; These values are in percentages. OR, Odds-ratio; CI, confidence interval; NR, not reported; EA, early arthritis; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide antibodies; MMP-3, matrix metalloproteinase 3; anti-MCV, anti-mutated citrullinated vimentine antibodies; cit-vim, citrullinated vimentin; anti-CarP, anti-carbamylated protein antibodies;

1Studies with this footnote were conducted in the same cohort: the Leiden Early Arthritis cohort. 2Studies with this footnote were conducted in the same cohort: the ESPOIR cohort

Due to limitation of space, we decided to present in this table only the studies for which either Sens, Spec, PPV, NPV or multivariate OR were available. Moreover, we decided to present only the studies evaluating a laboratory tools studied more than once. Details of non-presented studies are available on request.
| Study [LoE] | Population at baseline | Time for RA diagnosis (outcome) | % of pts achieving outcome | Imaging test | Evaluated parameter | Topography | Sens | Spec | PPV | NPV | OR (95% CI) |
|-------------|------------------------|-------------------------------|---------------------------|--------------|----------------------|------------|------|------|------|------|-------------|
| de Rooy [2b] [52] | EA (n= 80) | 1 year | 44 | DXR on hands XR | Elevated BMD loss\(^6\) at 6 months | Hand | 26 | 95 | 85 | 52 | NR |
| Duer-Jensen [2b] [35] | EA (n= 116) | 12 to 23 months | 23 | MRI | Bone edema, RAMRIS System | Wrist | 33 | 82 | 36 | 80 | NR |
| | | | | | | MCP | 0 | 94 | 0 | 76 | NR |
| | | | | | PIP | 0 | 100 | 1 | 77 | NR |
| | | | | | MTP | 15 | 97 | 57 | 79 | NR |
| | | | | | Wrist + MTP | NR | NR | NR | NR | 1.4 (1.0–2.0)* |
| | | | | | TS | Hand | 30 | 89 | 44 | 81 | NR |
| Nieuwenhuis [2b][49] | EA (n= 178) | 1 year | 39 | MRI | TS | MCP 5 flexor | 20 | 92 | 61 | 65 | 4.2 (1.4–12.9)* |
| | | | | | | | MCP 2 extensor | 14 | 98 | 83 | 64 | 9.4 (2.0–45.8)* |
| | | | | | | | MCP 4 extensor | 12 | 99 | 89 | 64 | 20.1 (2.2–186.0)* |
| | | | | | | | Compartment 1 wrist extensor | 19 | 94 | 68 | 65 | 3.7 (1.3–10.4)* |
| Study | Type | Duration | Sample Size | Imaging Method | Compartment | Sensitivity | Specificity | PPV | NPV | Odds Ratio | 95% CI |
|-------|------|----------|-------------|----------------|-------------|-------------|-------------|-----|-----|-------------|--------|
| Nieuwenhuis [2b] [50] | EA (n=202) | 1 year | 14 | MRI | Any MRI inflammation, RAMRIS system | Compartmen 2 wrist extensor | 19 | 92 | 59 | 64 | 2.3 (0.90–6.0) § |
| | | | | | | Compartmen 4 wrist extensor | 33 | 82 | 53 | 66 | 2.1 (1.0–4.5) § |
| Sahbudin [2b] [51] | EA (n=107) | 18 months | 40 | US | TS, OMERACT recommendations | Extensor carpi ulnaris | NR | NR | NR | NR | 5.5 (2.3–13.4) § |
| | | | | | | Hand extensor | NR | NR | NR | NR | 4.8 (1.8–13.1) § |
| | | | | | | PD TS symmetry | Hand flexor or extensor | NR | NR | NR | NR | 6.3 (2.2–17.9) § |
| | | | | | | Wrist extensor | | | | | 6.3 (2.1–19.1) § |

LoE, Level of Evidence; RA, rheumatoid arthritis; Pts, patients; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; These values are in percentages. OR, Odds-ratio; CI, confidence interval; NR, not reported; MRI, Magnetic Resonance Imaging; RAMRIS, Rheumatoid Arthritis Magnetic Resonance Imagins Score; MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint; MTP, metatarsophalangeal joint; TS, tenosynovitis; DXR, digital x-ray radiogrammetry; XR, x-rays; BMD, bone marrow density; US, ultrasonography; PD, power Doppler; OMERACT, Outcome Measures in Rheumatoid Arthritis Clinical Trials

*Elevated BMD loss means a change ≥ 2.5mg/cm²/month.
Studies with this footnote were conducted in the same cohort.

*The OR for MRI bone marrow edema of the wrist and MTP are for the per unit of change in the RAMRIS system. The scale of this score for wrist + MTP is 0-66.

$The OR for MRI Tenosynovitis or MRI inflammation (bone edema or synovitis or tenosynovitis) are for presence vs absence.

§The OR of US Tenosynovitis are for presence vs absence
S6: (A) Value of laboratory tests in EA prognosis and (B) Value of imaging tests in EA prognosis.

A.

| Study [LoE]          | Population at baseline | Outcome                  | Definition of outcome* | Time for outcome evaluation | % of pts achieving outcome | Laboratory test (+ vs -) | Sens | Spec | PPV | NPV | OR (95% CI) |
|----------------------|------------------------|--------------------------|------------------------|-----------------------------|---------------------------|--------------------------|------|------|-----|-----|-------------|
| Boire [1b] [25]      | EA (n=165)             | Presence of severity criteria | M-HAQ ≥1 and/or total SvH > 15 | 30 months                  | 38                        | Anti-CCP                 | 43   | 71   | NR  | NR  | 0.90 (0.30-3.0) |
|                      |                        |                          |                        |                             |                           | Anti-CCP high titers     | NR   | NR   | NR  | NR  | 1.7 (0.60-5.2)  |
|                      |                        |                          |                        |                             |                           | RF                       | 55   | 63   | NR  | NR  | 1.8 (0.60-5.8)  |
|                      |                        |                          |                        |                             |                           | Anti-cit-vim             | 45   | 79   | NR  | NR  | 8.8 (2.1-36.4)  |
| Goldbach-Mansky [1b] [53] | ERA (n=98)           | Structural damage        | ≥1 erosion             | 1 year                      | 44                        | RF                       | NR   | NR   | NR  | NR  | 1.4 (0.60-3.1)  |
|                      |                        |                          |                        |                             |                           | SE                       | NR   | NR   | NR  | NR  | 2.4 (1.0-5.9)   |
| Nell [1b] [24]       | ERA (n=66)             | Structural damage        | ≥2 erosions            | 1 year                      | 55                        | Anti-CCP                 | 61   | 90   | 88  | 66  | NR          |
|                      |                        |                          |                        |                             |                           | RF high titers           | 58   | 80   | 78  | 62  | NR          |
|                      |                        |                          |                        |                             |                           | Anti-Ra33                | 31   | 77   | 61  | 48  | NR          |
| Young-Min [1b] [54]  | ERA (n=118)            | XR progression           | Change in Larsen score | 2 years                     | 42                        | RF                       | NR   | NR   | 46  | 68  | NR          |
|                      |                        |                          |                        |                             |                           | SE                       | NR   | NR   | 52  | 67  | NR          |
| Study                                      | Design   | Criteria         | Follow-up | Outcome 1 | MMP-3   | Anti-CCP | RF   | Anti-CCP, high titers | RF   | Anti-Ra33 | RF   | Anti-Ra33, high titers | RF   |
|------------------------------------------|----------|------------------|-----------|-----------|---------|----------|------|------------------------|------|-----------|------|------------------------|------|
| Machold [1b] [55]                        | ERA (n=55)| Structural damage≥1 erosion | 3 years   | 64        |         | Anti-CCP | NR   | NR                     | 95   | 96        | NR   | NR                     | NR   |
| Hetland [1b] [71]                        | ERA (n=139)| XR progression Change in total SvH > 0 | 5 years   | 53        |         | Anti-CCP | NR   | NR                     | NR   | NR        | NR   | NR                     | NR   |
| Nell-Duxneuner [1b] [56]1                | EA (n=66)| Structural damage≥2 erosions | 5 years   | 55        |         | Anti-CCP | 61   | 90                     | 88   | 66        | NR   | NR                     | NR   |
| Mouterde [1b] [72]2                      | EA (n=736)| XR progression Change in total SvH ≥ 1 | 1 year    | 28        |         | Anti-CCP | NR   | NR                     | NR   | NR        | NR   | NR                     | NR   |
| Burr [1b] [57]                           | EA (n=487)| Structural damage≥1 erosion | 5 years   | 43        |         | Anti-CCP | 53   | 90                     | NR   | NR        | NR   | NR                     | NR   |
| Burr [1b] [57]                           | EA        | Larsen score > 15 | 5 years   | 31        |         | Anti-CCP | 61   | 86                     | NR   | NR        | NR   | NR                     | NR   |
| Study                  | Study Type | Study Size | XR Progression | Time Period | Change in Total SvH ≥ 5 | Anti-CCP | RF | NR | Anti-CCP and/or RF | NR |
|------------------------|------------|------------|----------------|-------------|-------------------------|----------|----|----|-------------------|----|
| van den Broek [1b] [58]| ERA (n=465)| XR progression | Change in total SvH ≥ 5 | 1 year | 22 | Anti-CCP: 77, RF: 82, NR: 87 | | | | |
| van den Broek [1b] [73]| ERA (n=484)| XR progression | Change in total SvH > 5 | 8 years | NR | Anti-CCP: NR, RF: 3.8 (2.5-5.0) | | | | |
| Tobon [1b] [59]        | EA (n=500) | XR progression | Change in total SvH > 5 | 2-3 years | 18 | Anti-CCP: 62, RF: 65, NR: 88 | | | | |
| Andersson [1b] [74]    | ERA (n=349)| XR progression | Change in total SvH ≥ 5.8 | 5 years | 56 | Anti-CCP: NR, RF: 67, NR: 97 | COMP: 3.1 (1.2-7.8) | | | |
| Combe [1b][75]         | EA (n=813) | XR progression | Change in total SvH ≥ 1 | 3 years | 79 | Anti-CCP: NR, RF: 68, NR: 96 | | | | |
| Wevers-de Boer [1b] [60]| EA (n=428)| XR progression | Change in total SvH ≥ 0.5 | 1 year | 7 | Anti-CCP: 82, RF: 64, NR: 95 | | | | |
| Barra [1b] [61]        | EA (n=841) | XR progression | Apparition of ≥ 1 erosion | 1 year | 28 | Anti-CCP: 15, RF: 40, NR: 73 | | | | |
| Study                          | ERA (n=) | XR progression | Change in total SvH | Duration | 2 years | 1 year | MBDA (per unit of increase) | MBDA (per unit of increase) |
|-------------------------------|----------|----------------|---------------------|----------|---------|--------|----------------------------|----------------------------|
| **Hafstrom [1b]** [62]        | (117)    |                |                     |          | 39      |        |                            |                            |
| **Markusse [1b]** [78]        | (125)    |                |                     |          | 42      |        |                            |                            |
| **Hambardzumyan [1b] [79]**   | (235)    |                |                     |          | 18      |        |                            |                            |
| **Degboé [1b] [63]**          | (566)    |                |                     |          | 26      |        |                            |                            |
| **Fedele [1b] [76]**          | (386)    |                |                     |          | 13      |        |                            |                            |

**Hafstrom [1b]**: Change in total SvH ≥ 5.8 after 2 years.
**Markusse [1b]**: Change in total SvH > 0 after 1 year.
**Hambardzumyan [1b]**: Change in total SvH ≥ 5 after 1 year.
**Degboé [1b]**: Change in total SvH ≥ 5 after 1 year.
**Fedele [1b]**: Apparition of ≥ 1 erosion or change in.
### Table 1: Association of Anti-CCP and Anti-CarP with Radiographic Progression

| Study | Cohort | XR Progression | Outcome | Sens | Spec | PPV | NPV | OR (CI) |
|-------|--------|----------------|---------|------|------|-----|-----|---------|
| Akdemir [1b] [68] | EA (n=488) | XR progression | Change in total SvH ≥ 0.5 | 2 years | 10 | Anti-CCP | 70 | 45 | 13 | 93 | 1.4 (0.60-3.5) |
| | | | | | | RF | 62 | 45 | 11 | 87 | NR |
| | | | | | | Anti-CarP | 44 | 73 | 16 | 92 | 1.1 (0.10-9.7) |
| | | | | | | Anti-CCP and anti-CarP | NR | NR | NR | NR | 2.5 (1.2-5.6) |

LoE, Level of Evidence; ERA, early rheumatoid arthritis; Pts, patients; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; These values are in percentages. OR, Odds-ratio; CI, confidence interval; NR, not reported; SvH, Sharp-van der Heijde score; HAQ, health assessment questionnaire; RF, rheumatoid factor; anti-CCP, anti-citrullinated antigen antibodies; SE, shared epitope; COMP, cartilage oligomeric matrix protein; anti-CarP, anti-CarP, anticarbamylated protein antibodies; MBDA, multi-biomarker disease activity; XR, x-rays; XR progression, radiographic progression.

1 Studies with this footnote were conducted in the same cohort: the Austrian Early Arthritis Action cohort.
2 Studies with this footnote were conducted in the same cohort: the ESPOIR cohort.
3 Studies with this footnote were conducted in the same cohort: the BeST cohort.
4 Studies with this footnote were conducted in patients from the same trial: the BARFOT study.
5 Studies with this footnote were conducted in patients from the same trial: the IMPROVED study.

* In all studies, radiographic outcomes were evaluated from hands and feet X-Rays.

Due to limitation of space, we decided to present in this table only the studies for which either Sens, Spec, PPV, NPV or multivariate OR were available. Moreover, we decided to present only the studies evaluating a laboratory tools studied more than once and only studies using structural data as outcome. Details of non-presented studies are available on request.
| Study                  | Population at baseline | Outcome       | Definition of outcome* | Time for outcome evaluation | % of pts achieving outcome | Imaging test       | Evaluated parameter | Sens | Spec | PPV | NPV | OR (95% CI) |
|------------------------|------------------------|---------------|-------------------------|------------------------------|----------------------------|----------------------|---------------------|------|------|-----|-----|-------------|
| Forslind [1b] [106]    | ERA (n=379)            | XR progression| Change in total SvH ≥ 5.8 | 2 years                      | 41                         | DXR on hands XR     | BMD loss at 1 year | 67   | 60   | 49  | 76  | NR          |
| Wevers-de Boer [1b]    | EA (n=428)             | XR progression| Change in total SvH ≥ 0.5 | 1 year                       | 7                          | DXR on hands XR     | BMD loss at 4 months | NR   | NR   | NR  | NR  | 1.4 (1.1-1.7) |
| van den Broek [1b] [73]| ERA (n=465)            | XR progression| Change in total SvH ≥ 5  | Years 1-8                    | 22                         | XR                    | Change in total SvH ≥ 5 at 1 year | NR   | NR   | NR  | NR  | 2.0 (1.0-4.2) |
| Combe [2b] [75]        | EA (n=813)             | XR progression| Change in total SvH ≥ 1  | 3 years                      | 79                         | XR                    | Erosion SvH > 0 at baseline | NR   | NR   | NR  | NR  | 2.3 (1.4-3.8) |
| Tobon [2b] [59]        | EA (n=500)             | XR progression| Change in total SvH > 5  | 2-3 years                    | 18                         | XR                    | Erosion SvH at baseline | 54   | 71   | 30  | 87  | NR          |
|                        |                        |               |                         |                              |                            |                       | Change in total SvH > 5 at 1 year | 53   | 25   | 32  | 88  | NR          |
| Funck-Brentano [2b] [81]| EA (n=127)            | XR progression| Change in Erosion SvH ≥ 5 | 1 year                       | 9                          | US on MCP/MTP        | PD score at baseline | NR   | NR   | NR  | NR  | 1.2 (1.0-1.4) |
|                        |                        |               |                         |                              |                            |                       | Presence of erosions at baseline | NR   | NR   | NR  | NR  | 1.4 (1.0-2.0) |
| Study | Cohort | Disease | XR progression | Outcome | 1 year | MRI of hand and/or foot | US PD score | GS score | Sens | Spec | PPV | NPV | Notes |
|-------|--------|---------|----------------|---------|--------|-------------------------|-------------|----------|------|------|-----|-----|-------|
| Miedany [2b] [82] | EPsA (n=126) | XR progression | Apparition of JSN and/or erosions | 1 year | NR | US of hands and feet | PD score ≥ 2 at baseline | NR | NR | NR | NR | 2.7 (1.1-2.8) |
| Yoshikazu [2b] [80] | ERA (n=76) | XR progression | Change in total SG > 3 | 1 year | 16 | MRI of wrist and fingers | MRI bone edema, RAMRIS system | NR | NR | NR | NR | 1.1 (1.0-1.2)* |

LoE, Level of Evidence; RA, rheumatoid arthritis; Pts, patients; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; These values are in percentages. NR, not reported; XR, x-rays; XR progression, radiographic progression; SvH, Sharp-van der Heijde score; SG, Genant modified Sharp score; US, ultrasound; MRI, magnetic resonance imaging; ERA, early rheumatoid arthritis; EPsA, early psoriatic arthritis; JSN, joint space narrowing. GS, gray scale

1Studies with this footnote were conducted in the same cohort: the ESPOIR cohort.

2In all studies evaluating x-rays parameters, x-rays were performed on hands and feet.

3BMD loss means a change ≥ 2.5mg/cm² at 1 year.

4BMD loss means a change ≥ 1.5mg/cm² at 4 months.

5The ORs for US PD score of MCP and MTP are for the per unit of change in the OMERACT PD score. The scale of this score is 0-3 for each joint.

6The ORs for MRI bone marrow edema of the wrist and fingers are for 5 units of change in the RAMRIS system. The scale of this score for wrist + MCP + PIP is 0-90.

Due to limitation of space, we decided to present in this table only the studies for which either Sens, Spec, PPV, NPV or multivariate OR were available. Moreover, we present only studies using structural data as outcome. Details of non-presented studies are available on request.