

Diagnostic issues in difficult-to-treat rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of difficult-to-treat rheumatoid arthritis

SUPPLEMENTARY

Supplementary file

1. The confirmation of the diagnosis of RA or relevant differential diagnoses of an alternative or mimicking disease

Clinical question

How do we optimally confirm an RA diagnosis?

Epidemiological question

How can we confirm a diagnosis of RA in difficult-to-treat RA patients?

- P: Difficult-to-treat RA patients with doubt about diagnosis or doubt about RA as origin of complaints
- I: Diagnostic 'tests' for RA as well as differential diagnoses
- C: RA or non-RA/relevant differential diagnosis
- O: Diagnostic test value of 'tests' to establish RA/relevant differential diagnosis

Search in short

Rheumatoid arthritis AND Terms for misdiagnosis and common mimicking diseases (gout, CPPD, PsA, SpA, fibromyalgia, OA, PMR, SLE, paraneoplastic syndromes, reactive arthritis) AND Terms for diagnostic outcomes/association measures

Search in full

PubMed: (RA[tiab] OR "rheumatoid arthritis"[tiab] OR "arthritis, rheumatoid"[Mesh]) **AND** (Misdiagnosis[tiab] OR "Diagnostic Errors"[Mesh] OR Gout[tiab] OR "Gouty arthritis"[tiab] OR Gout[Mesh] OR Pseudogout[tiab] OR CPPD[tiab] OR "Calcium pyrophosphate disease"[tiab] OR PsA[tiab] OR "Psoriatic arthritis"[tiab] OR "Arthritis, Psoriatic"[Mesh] OR Spondylarthropathy[tiab] OR "Bechterew"[tiab] OR "Spondylarthropathies"[Mesh] OR AxSpA[tiab] OR Spa[tiab] OR "Ankylosing spondylitis"[tiab] OR Spondylarthritis[tiab] OR FM[tiab] OR Fibromyalgia[tiab] OR "Fibromyalgia"[Mesh] OR "Widespread pain"[tiab] OR "Widespread musculoskeletal pain"[tiab] OR "Pain syndrome"[tiab] OR "Pain syndromes"[tiab] OR OA[tiab] OR Osteoarthritis[tiab] OR Osteoarthritis [Mesh] OR PMR[tiab] OR "Polymyalgia rheumatic"[tiab] OR SLE[tiab] OR "systemic lupus erythematosus"[tiab] OR "Lupus Erythematosus, Systemic"[Mesh] OR "paraneoplastic syndrome"[tiab] OR "paraneoplastic syndromes"[tiab] OR "Paraneoplastic Syndromes"[Mesh] OR "reactive arthritis"[tiab] OR "post-infectious arthritis"[tiab] OR "postinfectious arthritis"[tiab] OR Reiter[tiab] OR "Arthritis,

Reactive"[Mesh]) **AND** (sensitivity[Title/Abstract] OR "sensitivity and specificity"[MeSH] OR "diagnosis,differential"[MeSH] OR specificity[tiab])

Search in Embase is available on request.

Exclusion criteria

- Duplicate
- Language other than English
- Animal study
- Wrong publication type (e.g., Editorial, case report or case series, abstract not of ACR or EULAR of past 2 years, narrative review)
- No patients with (or suspected of) RA
- No evaluation of a diagnostic test (test should be meant as diagnostic test in paper):
 1. Evaluation of a (single) diagnostic test for RA in a population suspected of RA, but not satisfying classification criteria
 2. Evaluation of the added diagnostic value of a 'new' diagnostic test for RA over the 'classification criteria' in patients suspected of RA
 3. Patients (clinically) diagnosed with RA in which a diagnostic test for a (group of) mimicking diseases is evaluated (either as diagnosis (i.e. misdiagnosis RA) or as comorbidity)
- No diagnostic test value (sensitivity, specificity, PPV, NPV or calculation possible, AUC, LR, OR) for RA or mimicking disease reported/calculable
- Other

Predetermined items for data extraction

- Study:
 - o 1st Author
 - o Title
 - o Publication year
 - o Publication type (original study/SLR/abstract)
 - o Country where study was performed
 - o Setting (general practitioner/secondary care/tertiary care)
 - o Study design
 - o General description of population
- Baseline characteristics:
 - o RA patients without mimicking disease:
 - Number of patients
 - Gender (female)
 - Age (years)
 - DAS28 (or another composite index)
 - RF positivity
 - ACPA positivity
 - Disease duration (days/months/years)
 - DMARD history
 - Current DMARD therapy

- RA patients with mimicking coexisting disease, or patients without RA and with alternative disease:
 - Name of mimicking disease
 - Number of patients
 - Gender (female)
 - Age (years)
 - DAS28 (or another composite index)
 - RF positivity
 - ACPA positivity
 - Disease duration (days/months/years)
 - DMARD history
 - Current DMARD therapy
- Determinant:
 - Diagnostic test:
 - Name/description
 - Cut-off (if applicable)
 - Reference standard:
 - Name/description
 - Cut-off (if applicable)
 - Time interval between diagnostic test and reference standard
- Outcome:
 - Diagnostic test value to establish RA (without mimicking disease):
 - Diagnostic OR (95%CI, p-value)
 - AUC-ROC (95%CI, p-value)
 - PPV (95%CI)
 - NPV (95%CI)
 - Sensitivity (95%CI)
 - Specificity (95%CI)
 - LR+ (95%CI)
 - LR- (95%CI)
 - Other
 - Diagnostic test value to establish mimicking disease (with RA as coexisting disease, or without RA as alternative disease):
 - Diagnostic OR (95%CI, p-value)
 - AUC-ROC (95%CI, p-value)
 - PPV (95%CI)
 - NPV (95%CI)
 - Sensitivity (95%CI)
 - Specificity (95%CI)
 - LR+ (95%CI)
 - LR- (95%CI)
 - Other
 - Calculable test value
 - Number of RA patients without mimicking disease with positive test

- Number of RA patients without mimicking disease with negative test
 - Number of patients with mimicking disease with positive test
 - Number of patients with mimicking disease with negative test
- Other remarks (e.g. funding, conflicts of interest, things that stand out)
- Additional items for SLRs:
 - Number of studies included in qualitative analysis
 - Number of studies included in quantitative analysis (meta-analysis)
 - Narrative summary of baseline characteristics
 - Narrative summary of results
 - Measure to assess risk of bias
 - Outcome of risk of bias (range)
 - Narrative summary of risk of bias
 - References of included studies

2. The assessment of inflammatory activity in RA patients

2a. The assessment of inflammatory activity in RA patients

Clinical question

How do we evaluate the level of inflammation of RA activity in difficult-to-treat RA patients?

Epidemiological question

How can we evaluate the presence of inflammatory RA activity in difficult-to-treat RA?

- P: Difficult-to-treat RA patients
- I: Diagnostic 'tests' to establish inflammatory activity
- C: Inflammatory activity or not (remission) according to a reference standard
- O: Diagnostic test value of the 'test(s)' to establish inflammatory activity

2b. The assessment of inflammatory activity in RA patients with comorbidities that might influence the assessment

Clinical question

How do comorbidities influence the assessment of RA?

Epidemiological question

How do comorbidities influence the assessment of RA disease activity?

- P: Difficult-to-treat RA patients
- I: Comorbidities (that may influence disease activity assessment)
- C: No comorbidities
- O: Diagnostic test value of combined disease activity score, APR or imaging to establish disease activity/comparison with reference standard in those with/without comorbidity

Search in short

Rheumatoid arthritis AND Terms for difficult-to-treat RA and comorbidities that may influence disease activity assessment AND General terms for inflammation AND Specific tests to assess inflammation AND Diagnostic query of PubMed extended with relevant diagnostic terms

Search in full

PubMed: (RA[Title/Abstract] OR Rheumatoid arthritis[Title/Abstract] OR "arthritis, rheumatoid"[MeSH]) **AND** (Established[Title/Abstract] OR Previously treated[Title/Abstract] OR Failed[Title/Abstract] OR Failure[Title/Abstract] OR Refractoriness[Title/Abstract] OR Refractory[Title/Abstract] OR Difficult-to-treat[Title/Abstract] OR Irresponsive[Title/Abstract] OR Irresponsiveness[Title/Abstract] OR Resistant[Title/Abstract] OR Resistance[Title/Abstract] OR Unsuccessful[Title/Abstract] OR comorbidity[Title/Abstract] OR "comorbidity"[MeSH Terms] OR Comorbidities[Title/Abstract] OR Co-morbidity[Title/Abstract] OR Co-morbidities[Title/Abstract] OR Multi-morbidity[Title/Abstract] OR Multi-morbidities[Title/Abstract] OR Multimorbidity[Title/Abstract] OR "multimorbidity"[MeSH Terms] OR Multimorbidities[Title/Abstract] OR Infection[Title/Abstract] OR Infections[Title/Abstract] OR "infection"[MeSH Terms] OR Hepatitis[Title/Abstract] OR "hepatitis"[MeSH Terms] OR HIV[Title/Abstract] OR Human Immunodeficiency Virus[Title/Abstract] OR "hiv"[MeSH Terms] OR TBC[Title/Abstract] OR "tuberculosis"[MeSH Terms] OR "latent tuberculosis"[MeSH Terms] OR Malignancy[Title/Abstract] OR Malignancies[Title/Abstract] OR "neoplasms"[MeSH Terms] OR Tumor[Title/Abstract] OR Tumors[Title/Abstract] OR Cancer[Title/Abstract] OR "obesity"[MeSH Terms] OR Obesity[Title/Abstract] OR "obesity, morbid"[MeSH Terms] OR Overweight[Title/Abstract] OR "overweight"[MeSH Terms] OR BMI[Title/Abstract] OR "Body Mass Index"[MeSH Terms] OR FM[Title/Abstract] OR Fibromyalgia[Title/Abstract] OR "fibromyalgia"[MeSH Terms] OR Widespread pain[Title/Abstract] OR Widespread musculoskeletal pain[Title/Abstract] OR Pain syndrome[Title/Abstract] OR Pain syndromes[Title/Abstract] OR "somatoform disorders"[MeSH Terms] OR OA[Title/Abstract] OR Osteoarthritis[Title/Abstract] OR "osteoarthritis"[MeSH Terms] OR Subluxation[Title/Abstract] OR "joint dislocations"[MeSH Terms]) **AND** (inflammation[Title/Abstract] OR inflammatory[Title/Abstract] OR remission[Title/Abstract] OR disease activity[Title/Abstract] OR synovitis[Title/Abstract] OR tenosynovitis[Title/Abstract] OR "tenosynovitis"[MeSH Terms]) **AND** ("Clinical characteristics"[Title/Abstract] OR "patient characteristics"[Title/Abstract] OR CRP[Title/Abstract] OR C-reactive protein[Title/Abstract] OR "c-reactive protein"[MeSH Terms] OR ACPA[Title/Abstract] OR Anti-CCP[Title/Abstract] OR Anti-Citrullinated Protein Antibodies[Title/Abstract] OR RF[Title/Abstract] OR Rheumatoid factor[Title/Abstract] OR "rheumatoid factor"[MeSH Terms] OR ESR[Title/Abstract] OR Erythrocyte sedimentation rate[Title/Abstract] OR Blood sedimentation[Title/Abstract] OR "blood sedimentation"[MeSH Terms] OR Interleukin[Title/Abstract] OR Interleukins[Title/Abstract] OR "interleukins"[MeSH Terms] OR IL[Title/Abstract] OR Cell migration[Title/Abstract] OR Cytokine[Title/Abstract] OR Cytokines[Title/Abstract] OR "cytokines"[MeSH Terms] OR Biomarker[Title/Abstract] OR Biomarkers[Title/Abstract] OR "biomarkers"[MeSH Terms] OR imaging methods[Title/Abstract] OR "diagnostic imaging"[MeSH Terms] OR bone marrow oedema[Title/Abstract] OR MRI[Title/Abstract] OR Magnetic resonance imaging[Title/Abstract] OR "magnetic resonance imaging"[MeSH Terms] OR Ultrasound[Title/Abstract] OR Ultrasonography[Title/Abstract] OR US[Title/Abstract] OR "ultrasonography"[MeSH Terms]) **AND** (sensitiv*[Title/Abstract] OR

sensitivity and specificity[MeSH Terms] OR diagnose[Title/Abstract] OR diagnosed[Title/Abstract] OR diagnoses[Title/Abstract] OR diagnosing[Title/Abstract] OR diagnosis[Title/Abstract] OR diagnostic[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic * [MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp] OR Predictive value[Title/Abstract] OR PPV[Title/Abstract] OR NPV[Title/Abstract] OR Predictive Value of Tests[Mesh] OR Receiver operating characteristic curve[Title/Abstract] OR ROC[Title/Abstract] OR ROC curve[Mesh] OR Odds ratio[Title/Abstract] OR Odds ratio[Mesh] OR specificity[Title/Abstract])
Search in Embase is available on request.

Exclusion criteria

- Duplicate
- Language other than English
- Animal study
- Wrong publication type (e.g., Editorial, case report or case series, abstract not of ACR or EULAR of past 2 years, narrative review)
- No RA patients who received any treatment before (i.e. non-treatment naïve)
- No diagnostic test beyond currently used reference standards
- No quantitative information about diagnostic test value
- 2b only: No quantitative comparison of disease activity or diagnostic test value with a reference standard between RA patients with and without comorbidities
- Already included in SLR
- Other

Predetermined items for data extraction

- Study:
 - o 1st Author
 - o Title
 - o Publication year
 - o Publication type (original study/SLR/abstract)
 - o Country where study was performed
 - o Setting (general practitioner/secondary care/tertiary care)
 - o Study design
 - o RA diagnosis according to [classification criteria]
 - o General description of population
- Baseline characteristics:
 - o 2a: RA patients:
 - Number of patients
 - Gender (female)
 - Age (years)
 - DAS28 (or another composite index)
 - RF positivity
 - ACPA positivity
 - Disease duration (days/months/years)

- DMARD history
 - Current DMARD therapy
- 2b:
 - RA patients without comorbidity:
 - Number of patients
 - Gender (female)
 - Age (years)
 - DAS28 (or another composite index)
 - RF positivity
 - ACPA positivity
 - Disease duration (days/months/years)
 - DMARD history
 - Current DMARD therapy
 - RA patients with comorbidity:
 - Name of comorbidity
 - Diagnostic criteria used for comorbidity
 - Number of patients
 - Gender (female)
 - Age (years)
 - DAS28 (or another composite index)
 - RF positivity
 - ACPA positivity
 - Disease duration (days/months/years)
 - DMARD history
 - Current DMARD therapy
- Determinant:
 - Diagnostic test:
 - Name/description
 - Cut-off (if applicable)
 - Reference standard:
 - Name/description
 - Cut-off (if applicable)
 - Time interval between diagnostic test and reference standard
- Outcome:
 - 2a:
 - Diagnostic test value to establish presence/level of inflammation:
 - Diagnostic OR (95%CI, p-value)
 - AUC-ROC (95%CI, p-value)
 - PPV (95%CI)
 - NPV (95%CI)
 - Sensitivity (95%CI)
 - Specificity (95%CI)
 - LR+ (95%CI)

- LR- (95%CI)
- Correlation coefficient (95%CI, p-value)
- Other
- Calculable test value
 - Number of RA patients with inflammation and with positive test
 - Number of RA patients with inflammation and with negative test
 - Number of RA patients without inflammation and with positive test
 - Number of RA patients without inflammation and with negative test
- 2b:
 - Diagnostic test value to establish presence/level of inflammation in RA patients without comorbidity:
 - Diagnostic OR (95%CI, p-value)
 - AUC-ROC (95%CI, p-value)
 - PPV (95%CI)
 - NPV (95%CI)
 - Sensitivity (95%CI)
 - Specificity (95%CI)
 - LR+ (95%CI)
 - LR- (95%CI)
 - Correlation coefficient (95%CI, p-value)
 - Other
 - Diagnostic test value to establish presence/level of inflammation in RA patients with comorbidity:
 - Diagnostic OR (95%CI, p-value)
 - AUC-ROC (95%CI, p-value)
 - PPV (95%CI)
 - NPV (95%CI)
 - Sensitivity (95%CI)
 - Specificity (95%CI)
 - LR+ (95%CI)
 - LR- (95%CI)
 - Correlation coefficient (95%CI, p-value)
 - Other
 - Diagnostic test value (association measure) to establish disease activity in RA patients with versus without comorbidity:
 - Description of analysis
 - Mean difference (95%CI, p-value)
 - Other
 - Calculable test value:
 - Number of RA patients without comorbidity and with positive test
 - Number of RA patients without comorbidity and with negative test

- Number of RA patients with comorbidity and with positive test
 - Number of RA patients with comorbidity and with negative test
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