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# Does non-erosive rheumatoid arthritis exist? A cross-sectional analysis and a systematic literature review

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ABSTRACT

*Objective:* To evaluate the prevalence and factors associated with non-erosive rheumatoid arthritis (RA).
*Methods:* First, a cross-sectional analytical study was performed. Non-erosive disease, defined as the absence of any erosion on X-rays after 5 years of RA, was evaluated in 500 patients. Further and additional evaluations including ultrasonography (US) and computed tomography (CT) were performed in those patients meeting the eligibility criteria. The Spearman correlation coefficient, kappa analysis, and Kendall's *W* test were used to analyze the data. Second, a systematic literature review (SLR) was performed following the PRISMA guidelines.
*Results:* Of a total of 40 patients meeting the eligibility criteria for non-erosive RA, eight patients were confirmed to have non-erosive RA by the three methods. A positive correlation between non-erosive RA and shorter disease duration, antinuclear antibodies positivity, lower rheumatoid factor (RF) and C-reactive protein titers, lower global visual analog scale values, toxic exposures, and lower disease activity-(RAPID3) was found. In addition, an inverse correlation with anticyclic citrullinated peptide antibodies (ACPA) positivity and medication use was observed. From the SLR, it was corroborated that factors associated with this subphenotype were shorter disease duration, younger disease onset, negative ACPA and RF titers, low cytokine levels, and some genetic markers.
*Conclusion:* Non-erosive RA is rare, occurring in less than 2% of cases. These findings improve on the understanding of RA patients who present without erosions and are likely to have less severe disease.


## Introduction

Rheumatoid arthritis (RA) is the most common inflammatory arthropathy worldwide. It is a chronic, multifactorial, and heterogeneous autoimmune disease (AD) characterized by the presence of long-standing inflammation of the diarthrodial joints, resulting in symmetric polyarthritis and systemic manifestations [1]. As with most ADs, it predominantly affects women, and its prevalence has been reported to be between 0.3% and 1.6% [2].

Chronic inflammation ultimately affects the joints, causing synovial membrane hypertrophy and bone and cartilage destruction. Erosion is the hallmark of the disease and is generally progressive and considered irreversible [1]. The presence of erosion at diagnosis is one of the factors most suggestive of a poor prognosis. Erosion reflects the cumulative history of the disease and correlates with deformity, disability (i.e., mainly in the hands [3] and the feet [4]), decreased functional work capacity, premature mortality, and reduced quality of life [5].

Radiographic assessment of joint damage is the most widely accepted standard tool for diagnosis, determination of disease extent, and RA follow-up. Despite demonstrating a high specificity in erosion detection, radiographs lack sensitivity in early disease [6]. Consequently, newer imaging techniques have been developed to improve diagnosis and follow-up of bone erosions [7].

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0049-0172/

Even though erosions may occur within 2–3 years of onset of the disease, their progression does not correlate with the duration of RA. The factors associated with radiological progression have to be identified to aid in starting early, appropriate, and aggressive therapy before radiographic damage occurs [8,9]. However, few studies have evaluated the factors associated with erosion-free status [10]. Therefore, predictive factors for non-erosive disease cannot be considered as the simple converse of those associated with erosive disease. Moreover, the reported information about non-erosive RA is ambiguous. Thus, the purposes of this study were to evaluate the prevalence and factors associated with non-erosive RA by means of a cross-sectional study and systematic literature review (SLR) and to examine the sensitivity and specificity of different erosion assessment methods in patients with RA.

## Material and methods

### *Study population*

This was a cross-sectional analytical study in which 500 consecutive patients fulfilling the 1987 American College of Rheumatology (ACR) classification criteria for RA [11] were included. Other causes of polyarthritis (i.e., chondrocalcinosis, spondyloarthropathies, and other ADs) were excluded following the international classification criteria (as shown in supplementary material). The subjects were examined at the Center for Autoimmune Diseases Research (CREA) in Bogota, Colombia. This study was undertaken between February 1996 and April 2012 and was conducted in compliance with Act 008430/1993 of the Ministry of Health of the Republic of Colombia. The Institutional Review Board of the Universidad del Rosario approved the study design. Each patient was evaluated by a rheumatologist. The information on patient sociodemographic and cumulative clinical and laboratory data was obtained by interview, physical examination, and chart review, as previously reported [12].

### *Radiological assessment*

As there is no agreement about the time lag interval for lack of erosions in RA, and there is no universally accepted definition for non-erosive RA, a zero score through an evaluation by two blinded researchers, a musculoskeletal radiologist (E.C.P.) and a rheumatologist (A.R.V.), according to a modified Sharp-van der Heijde (SvHD) method [13] in the last follow-up radiographs of the hand and the feet (posteroanterior view) in patients with a disease duration of more than 5 years of RA was considered as the eligibility criteria for such a condition. Last follow-up radiographs must meet the criteria of being taken in the last year of the disease. Eligible patients were invited for reassessment, which included new X-rays, ultrasound (US) imaging, and computed tomography (CT).

For qualified patients, radiography was conducted using an IEC Explorer Direct Capture, 1600 (Toshiba, Otawara, Japan). Posteroanterior radiographic projection of the hands and the feet was obtained. For CT examinations, a Toshiba Aquilion 64 CXL multidetector unit (Toshiba, Otawara, Japan) was used. Patients were examined, including their wrist, metacarpophalangeal (MCP), proximal interphalangeal (PIP) joints in the hands and the metatarsophalangeal (MTP) joints in the feet. Images with an in-plane resolution of 0.4 mm × 0.4 mm and slice thickness of 0.5 mm were obtained, and Quantum Denoising Software for multiplanar reconstruction created 3D reconstructions with a slice thickness of 0.5 mm, and these were used for image evaluation. To assess the inter-observer agreement, CT and X-ray images were evaluated independently by two blinded researchers (A.R.V. and E.C.P.). Prior to the evaluation, it was decided that E.C.P.'s scoring would be used for comparison with the results of the other imaging modalities.

US analyses were performed by a musculoskeletal radiologist (E.C.P.) with experience in the US of RA joints. The General Electric LOGIQ® E unit (General Electric Healthcare Medical Systems, Milwaukee, WI, USA), with a linear array transducer of 7–12 MHz, was used for all examinations. The dorsal and palmar aspects of the second and third MCP and IFP joints and second and fifth MTP joints were evaluated for synovitis, joint effusion, and inflammation. On the wrist, the dorsal, palmar, ulnar, and radial aspects were examined for the same parameters. Erosions were assessed on all joints (i.e., first to fifth MCP, PIP, MTF, and wrist).

All imaging modalities were evaluated with investigators blinded to clinical and other imaging data. On the X-rays, each joint quadrant was scored for the presence or absence of erosions following the SvHD method [13]. Erosions on CT were defined as a sharply demarcated area of focal bone loss observed in two planes, with a cortical break (loss of cortex) observed in at least one plane. These images were evaluated by using the rheumatoid arthritis magnetic resonance scoring system (RAMRIS) method [14]. US erosions were defined as irregularities of the bone surface of the area adjacent to the joint and observed in two planes, as suggested by the outcome measures in rheumatology (OMERACT) [15] (Fig. 1).

### *Statistical analysis*

The Kendall's tau-*b* correlation coefficient was used in order to evaluate the categorical variables, while the Spearman's correlation test was used to analyze quantitative variables vs. categorical variable (i.e., non-erosive state). The inter-observer and intra-observer agreement between the two readers of the CT and X-ray images were calculated by agreement statistic (Kappa). Statistical significance was considered at 0.05. With CT as the standard reference method, the sensitivity and specificity of X-ray and US were calculated. Statistical analysis was performed in IBM SPSS Statistics 21.

### *Search strategy of systematic literature review*

The SLR of articles on non-erosive RA was conducted using the following databases: PubMed, Scopus, SciELO, and Virtual Health Library (VHL), which includes BIREME, LILACS, and many others LA sources (Fig. 2). The SLR included articles published between January 1971 and February 2014. Three reviewers did the search independently (J.A.A., O.J.C., and S.S.L.) while applying the same selection criteria described below. The search results were compared and disagreements were resolved by consensus. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed in data extraction, analysis, and reporting [16].

The search was performed in PubMed and Scopus, using the following medical subject headings (MeSH terms): “Arthritis, rheumatoid,” and “ultrasonography,” or “tomography, X-ray computed,” or “positron-emission tomography and computed tomography,” or “multidetector computed tomography,” or “radiography,” or “X-Rays,” or “magnetic resonance imaging.” Each term was cross-referenced with the following key words: “Non erosive,” or “without erosions,” or “no erosive.” No limits regarding language, period of publication, or publication type were used. A similar strategy was followed for the other databases. Each MeSH term was translated into DeCS (Health Sciences Descriptors) to explore sources of information in Portuguese, Spanish, and English from the SciELO and VHL databases. The following terms were selected: Artritis reumatoide or artrite reumatóide and ecografía, or ultrasonografía, or tomografía, or tomografia computarizada, or tomografia computarizada por emisión de positrones, or radiografía, or rayos X, or

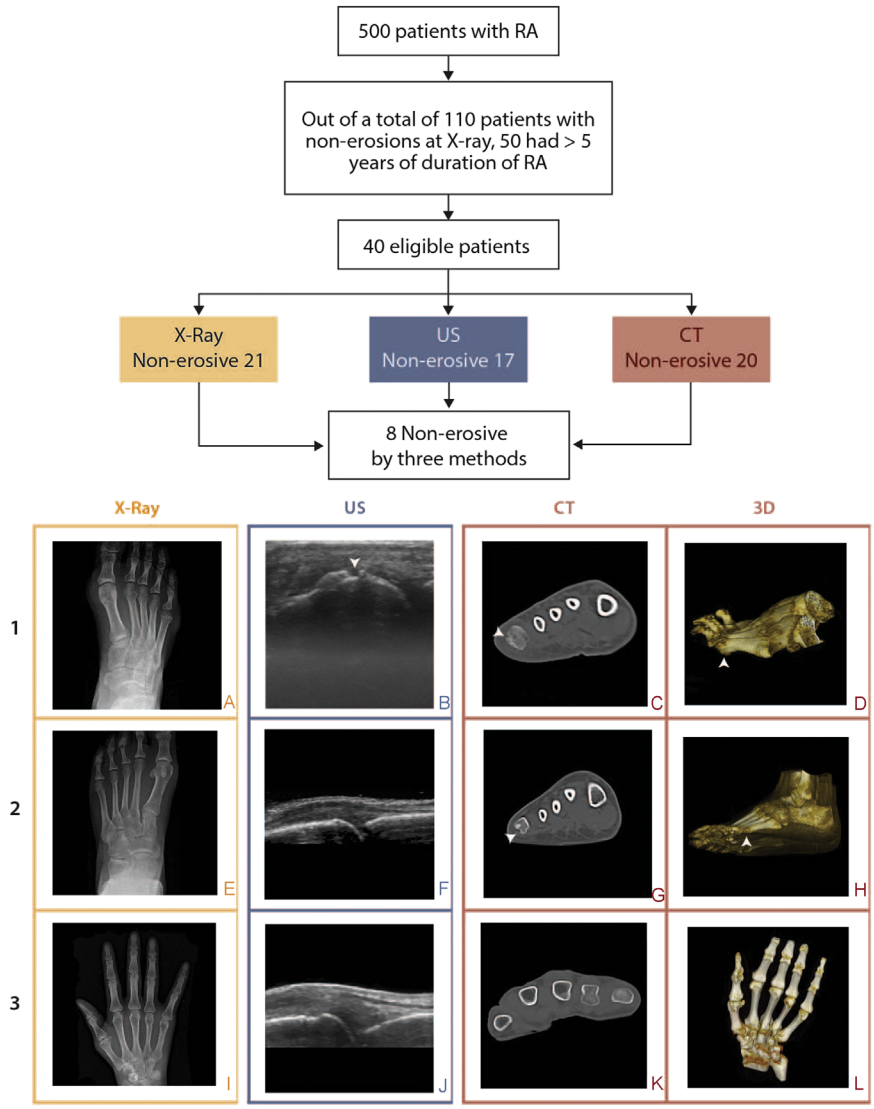


**Fig. 1.** Study flowchart of non-erosive rheumatoid arthritis and representative cases.
*Patient 1*: A 52-year-old male with 8-year duration of RA, he was seropositive for RF and ACPA. His treatment included methotrexate and hydroxychloroquine, with a functional class of I (HAQ) and presenting with low activity by RAPID3 index. (A) An X-ray image of a non-erosive left foot. (B) US shows an erosion on the fifth metatarsal head, confirmed by CT and CT-3D (C and D). Furthermore, erosions were also observed by US on the right wrist. The score by TAC was four in the hands and one in the feet. *Patient 2*: A 38-year-old female with 11-year duration of RA, still active with 20 tender and six swollen joints count. Both RF and ACPA were positive. She had taken methotrexate, sulfasalazine, gold salts, steroids, chloroquine, and biologics (infliximab and rituximab) as treatment. Her functional class was III (HAQ) and she presented a high activity by RAPID3 index. (E) An X-ray image of a non-erosive right foot. (F) Right foot US shows the absence of erosion in the fifth metatarsal head. (G and H) CT and CT-3D show the erosion on the fifth metatarsal head. The rest of the images were erosion-free.
*Patient 3*: A 52-year-old female with 10-year duration of RA. The patient had four tender and eight swollen joints count. Both RF and ACPA were positive. She had taken methotrexate, hydroxychloroquine, chloroquine, sulfasalazine, steroids, leflunomide, and biologics (etanercept) as treatment. Her functional class was I (HAQ) and she presented with low activity by RAPID3 index. (I) An X-ray of a non-erosive left hand. (J) US shows the absence of erosion in the metacarpal head. (K) CT does not show erosions at the level of metacarpals, and (L) 3D CT shows the erosion-free hand.
CT: computed tomography; RA: rheumatoid arthritis; US: ultrasonography.

resonancia magnética, or ultra-sonografíaa, or ultra-som, or tomografia computadorizada, or tomografia computadorizada de emissão de positrão, or ressonância magnética. Each term was cross-referenced with the following key words terms: No erosiva, or sin erosiones, or não erosiva or sem erosiones. Each term was cross-referenced for the greatest number of results.

Study selection, data extraction, and quality assessment. A study was included if (a) the abstract was available, (b) it contained original data, (c) it used accepted classification criteria for RA, and (d) it measured non-erosive disease. Articles were excluded from the analysis if they dealt with juvenile idiopathic arthritis or involved animal models. Studies were also excluded if they were reviews or case reports, if they discussed topics not related to image evaluation, and/or they were not focused on individuals (i.e., only joints assessment). Those references from the articles that appeared to be relevant for the present review were hand-searched and were included in the discussion. The authors of articles to which full-text access was not possible were contacted via e-mail. For articles in languages other than English or Spanish, translations of abstracts or full texts were reviewed to determine eligibility. Finally, the abstracts and full-text articles were reviewed to find eligible studies, and duplicates were excluded.

Three blinded reviewers (J.A.A., O.J.C., and S.S.L.) organized the selected articles on the basis of publication source, author, type of study, gender ratio, duration of the disease, frequency of non-erosive RA, ancestry, follow-up time, assessment method, non-erosion-associated factors, comparative population, erosion-associated factors, comparative population, and comments.

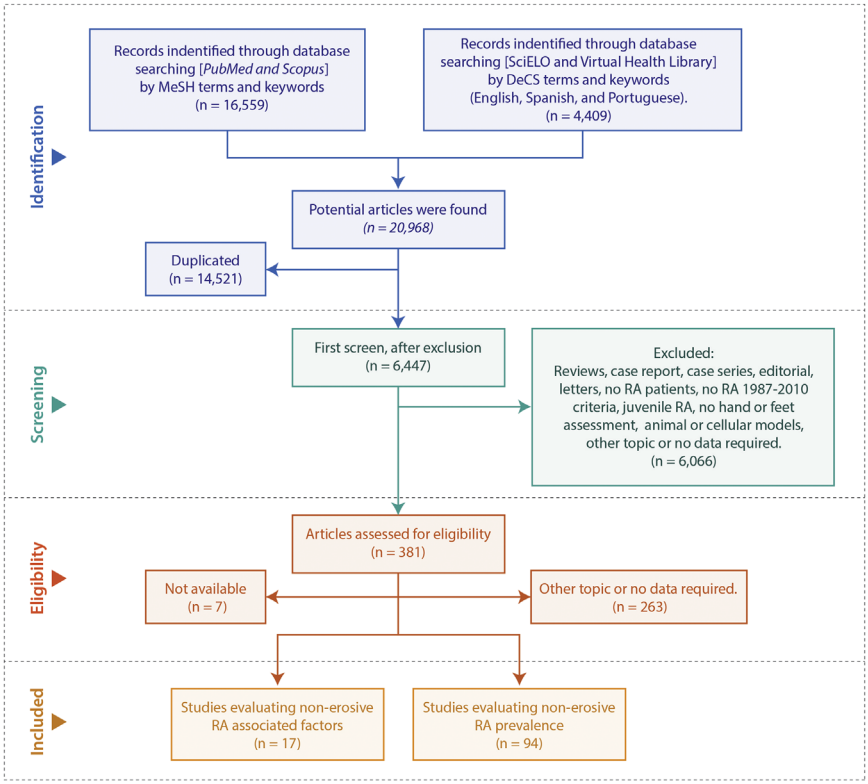


**Fig. 2.** Flowchart of the systematic literature review.

Moreover, a descriptive analysis from these data was completed. The articles were not included in the analysis when there was a lack of inclusion criteria, insufficient data, or lack of statistical significance. Disagreements between the reviewers were resolved by consensus. Each record was classified based on the quality score of the studies, which was assigned by applying the levels established by the Oxford Centre for Evidence-based Medicine 2011 to evaluate the risk of bias [17].

## Results

### *Colombian cohort*

Out of a total of 500 patients, 50 fulfilled the inclusion criteria, of whom 40 were recaptured and 10 were lost to follow-up. Most of the patients were women (75%). The median (range) values of the age and duration of the disease were 52 (14) and 10 (6) years, respectively. The percentage presence of antibodies was 90% for rheumatoid factor (RF) and 60% for anti-cyclic citrullinated peptide antibodies (ACPA). All characteristics of the patients are listed in Table 1.

Inter-observer and intra-observer concordance between the two evaluators of radiographs and CT images was high ($\kappa = 0.96$, $P < 0.001$). The new X-rays indicated that non-erosive disease persisted in 21 patients. Erosion-free status according to US and CT was observed in 17 (42.5%) and 20 (50%) cases, respectively. Non-erosive RA was confirmed by the three methods in eight patients. The characteristics of these eight patients are summarized in Figure 1 and Table 2.

There was no concordance between the three methods. For this sample, the sensitivity and specificity (CT as gold standard) were 65% and 50% for US and 60% and 65% for X-ray imaging, respectively. Regarding the US evaluation, there was not statistically significant correlation between synovitis, joint effusion, and inflammation with non-erosive disease.

The factors that positively and inversely correlated with non-erosive RA (on an X-ray basis) are listed in Table 3.

### *Systematic literature review*

There were 4550 articles identified in the PubMed database search. Additional records identified through other sources included 12,009 articles from Scopus, 4385 from VHL, and 24 from SciELO. Therefore, the database searches provided a total of 20,968 publications. Of these, 14,521 duplicates were identified. A total of 6447 were evaluated for meeting the eligibility criteria. Of these articles, 381 were selected for the analysis. We obtained 374 articles in full text, for a 1.83% loss. Finally, 17 articles [10,18–33] that had interpretable data and fulfilled the eligibility criteria were included. Of the selected articles, five were cross-sectional, five were cohort studies, four were case-controls, and two were inception cohorts. The flowchart for systematic literature review and articles included in the analysis is shown in Figure 2.

### *Prevalence of non-erosive RA*

The prevalence of non-erosive RA, considered as the absence of any cortical break on hand or feet images, ranged from 11% up to 85%. Within the studies analyzed, four studies were from the American population [10,19,21,26], including one from Latin American population [19]. In this area, the prevalence of non-erosive RA was reported to be 20% (Colombia) (our study) to 81.7% (Mexico) [19]. Similarly, from the seven studies evaluated, the prevalence in Europe ranged from 11% to 71.9% [18,20,25,28–30,32]. In the case of Asia, five studies were retrieved [22–24,31,33], where the prevalence of non-erosive RA was found to range from 31.7% [23] up to 69% [24]. Only one study from Africa reported non-erosive disease with a prevalence of 34.9% [27]. Table 4 gives a detailed view of the data. However, there were several articles in which the authors assessed the erosive state

**Table 1**
General characteristics of 40 patients with rheumatoid arthritis[a]

| | % (*n*/N) |
|---|---|
| Variable | |
| Age (years), median, IQR | 52 (14) |
| Age at onset (years), mean, SD | 39.25 ± 9.67 |
| Disease duration (years), median, IQR | 10 (6) |
| Sociodemographic characteristics | |
| Female | 75 (30/40) |
| High educational level | 90 (36/40) |
| High socioeconomic status | 84.2 (32/40) |
| Clinical characteristics | |
| Extra-articular manifestations | 15 (6/40) |
| VAS pain, median, IQR | 3.25 (4) |
| VAS global, median, IQR | 3 (4) |
| HAQ FC II[b] | 55 (22/40) |
| RAPID3: severe activity | 25 (10/40) |
| RAPID3: moderate activity | 30 (12/40) |
| RAPID3: low activity | 30 (12/40) |
| RAPID3: near remission | 15 (6/40) |
| Familial autoimmunity | 37.5(15/40) |
| Toxics[c] | 52.5 (21/40) |
| Cardiovascular risk | |
| Hypertension | 17.5 (7/40) |
| Ever smoking | 18 (45/38) |
| Coffee consumption | 85 (34/40) |
| Dyslipidemia | 10 (4/40) |
| Medication | |
| DMARDs[d] | 97.5 (39/40) |
| Corticosteroids[e] | 77.5 (31/40) |
| Antimalarial[f] | 85 (34/40) |
| Biological therapy[g] | 25 (10/40) |
| Aspirin intake | 10 (4/40) |
| Laboratory | |
| ANAs (+) | 47.5 (19/40) |
| RF (+) | 90 (36/40) |
| ACPA (+) | 60 (24/40) |

ACPA: anti-cyclic citrullinated peptide antibodies; ANAs: antinuclear antibodies; DMARD: disease-modifying antirheumatic drugs; FC: functional class; HAQ: health assessment questionnaire; IQR: interquartile range; RAPID: routine assessment of patient index data; RF: rheumatoid factor; SD: standard deviation; VAS: visual analog scale.

[a] Registered at the moment patients were recaptured.
[b] HAQ data correspond to the most frequent functional class.
[c] Exposure to any of the following: hair dyes, pesticides, organic solvents, and silicone implants.
[d] If the patient had consumed any of the following: methotrexate, sulfasalazine, D-penicillamine, cyclosporine, gold salts, and leflunomide.
[e] If the patient had consumed any of the following: prednisolone, methylprednisolone, and deflazacort.
[f] If the patient had consumed any of the following: chloroquine and hydroxychloroquine.
[g] If the patient had consumed any of the following: rituximab, infliximab, etanercept, abatacept, adalimumab, and tocilizumab.

and its associations, but they only provided the frequencies for non-erosive RA. In those circumstances, we could not infer inverse associations for the non-erosive state.

### *Factors associated with non-erosive RA*

Most studies in the literature explore the association with erosive outcomes, but research on the factors associated with non-erosive disease is scarce. Among the studies, we found different associated factors, including genetics [18,26–28,33] as well as being negative for RF and ACPA [10,18,21–23]. Similarly, younger age and a shorter duration of the disease have also been reported to be associated with non-erosive RA [10,19,20,24,25,30–32] (Table 4).

## Discussion

Our results indicate that non-erosive RA, although rare, may be observed in less than 2% of patients with established RA. Erosive disease has been recently defined as the presence of one erosion (cortical break) seen in at least three separate joints, with the goal of achieving higher specificity in early disease assessment (i.e., the 2010 ACR/EULAR rheumatoid arthritis classification criteria) [34]. Nevertheless, heterogeneous erosion assessment methods are still used. From our perspective, non-erosive disease should be considered as the absence of any erosion on radiological images, including different techniques to adequately assure non-erosiveness.

Radiographic assessment of joint damage remains a diagnostic tool for RA. The factors associated with erosions and radiological progression of bone damage in RA have been well recognized. On the contrary, the factors associated with non-erosive presentation of RA have not been systematically examined. We shall discuss further the factors that are positively and inversely correlated with non-erosive RA found in the SLR (Tables 3 and 4).

### *Radiological assessment*

Plain radiographs were the imaging assessment most reported in the articles included in the present SLR. The current "gold standard" for monitoring the progression of RA is plain film radiography [35]. Based on the measurement error, the smallest detectable difference (SDD) can be defined [36]. Nevertheless, additional tools such as CT and MRI are being increasingly used.

Currently, US has a higher reported sensitivity than conventional X-rays [37]. Recently, a meta-analysis including 913 patients concluded that US detects significantly more erosions than X-ray imaging [38]. US can be considered to have additional advantages compared with other imaging methods (i.e., non-invasiveness, easy accessibility, low cost, and the absence of radiation exposure). However, the specificity of US for bone erosions is low. In RA, the erosion diameter tends to be higher than in other diseases, such as psoriasis, gout, or osteoarthritis, and the smaller lesions observed with US do not always represent breaks in the cortical bone surface [39].

Although CT and MRI both allow visualization of soft tissues and a three-dimensional imaging of the assessed joint, unlike simple X-ray imaging, our group decided to perform CT instead of MRI in assessing patients involved in the study on account of several advantages of the former over the latter. CT is a radiological method that combines rapid acquisition of images with a detailed view of joint and bone structures and a lower cost and with greater sensibility in evaluating bone cortex than MRI. MRI is very sensitive in detecting bone marrow edema, but CT has been proven better for the detection of bone erosion [4], which was the main purpose of the study. MRI is an expensive test and requires the patient to remain perfectly still for an extended period of time to prevent distortion of joint image. In addition, orthopedic hardware such as plates or screws can also distort joint images [14].

### *Factors associated with non-erosive RA*

Bone erosions may occur during the first years of disease, in a generally progressive and irreversible manner [8,9,40]. However, some other results indicate that the progression rate is constant during the disease course [41]. Biomarkers and clinical variables associated with radiographic progression and erosive disease are well-documented [42].

We found that shorter disease duration correlates positively with non-erosive RA as observed by others [19]. Age is an

**Table 2**
Characteristics of eight patients with non-erosive rheumatoid arthritis through three imaging methods

| Patient no. | ACR criteria[a] | Gender | Age (yr) | Duration (yr) | MS | SJC | TJC | HAQ | RAPID3 (activity) | CRP (mg/dl) | ESR (mm/h) | ANA[b] titer | RF[b](UI/ml) | ACPA[b]UI | Toxics[c] | Medication[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 4 | F | 57 | 6 | No | 6 | 2 | I | Low | 6.41 | 41 | 1:320 | 384.2 | 210 | Yes | LFN and PDN |
| 2 | 5 | F | 39 | 6 | Yes | 0 | 0 | II | NR | 6.56 | 30 | 1:80 | 151.4 | 28 | Yes | MTX, HCQ, and PDN |
| 3 | 4 | F | 34 | 6 | Yes | 3 | 8 | III | Severe | 3.27 | 20 | 1:160 | 50 | 10 | No | MTX, CLQ, SSZ, PEN, and PDN |
| 4 | 4 | F | 62 | 7 | No | 1 | 1 | II | Moderate | 1.3 | 28 | 1:160 | 212 | 159 | Yes | MTX, CLQ, AZA, PEN, and PDN |
| 5 | 4 | F | 63 | 10 | Yes | 0 | 0 | I | NR | 10.4 | 8 | 1:320 | 90.1 | 1000 | Yes | MTX, LFN, and PDN |
| 6 | 4 | F | 52 | 10 | No | 8 | 4 | I | Low | 3.21 | 20 | 1:160 | 90 | 186 | Yes | MTX, CLQ, HCQ, SSZ, LFN, PDN, and ETA |
| 7 | 4 | F | 52 | 12 | No | 0 | 4 | I | Low | 13.6 | 36 | 1:320 | 67 | 500 | Yes | MTX, HCQ, LFN, PDN, and DFZ |
| 8 | 5 | F | 58 | 14 | Yes | 9 | 0 | II | Low | 2.1 | 34 | 1:80 | 101 | 165 | No | MTX, SSZ, LFN, PDN, and INF |

ACPA: anti-cyclic citrullinated peptide antibodies; ANA: antinuclear antibodies; AZA: azathioprine; CLQ: chloroquine; CRP: C-reactive protein; DFZ: deflazacort; ESR: erythrocyte sedimentation rate; ETA: etanercept; F: female; HAQ: Health Assessment Questionnaire; HCQ: hydroxychloroquine; INF: infliximab; LFN: leflunomide; MS: morning stiffness; MTX: methotrexate; NR: near remission; PDN: prednisolone; PEN: penicillamine; RAPID: routine assessment of patients index data; RF: rheumatoid factor; SJC: swollen joint count; SSZ: sulfasalazine; TJC: tender joint count; yr: year.

[a] Classification criteria, American College Rheumatology (ACR) 1987.
[b] The positive cutoff values were $>40$ UI for RF, $>60$ UI for ACPA, and $\geq 1/80$ titers for ANA.
[c] Exposure to any of the following: hair dyes, pesticides, organic solvents, and silicone implants.
[d] Medication over time: from the onset of the disease to the present.

additional predictor of radiographic involvement in RA, with a 22% increase per decade of age in Caucasians [43]. Younger age at onset and short disease duration have been associated with non-erosive disease in large cohort studies [10].

Disability and quality of life have been previously associated with radiographic damage in prospective longitudinal studies in patients with established RA. A significant correlation between function, disease activity, and radiographic damage has been shown [44]. In addition, erosive RA has been predicted by the area under the curve for number of swollen joints, DAS28, SDAI, and CDAI for 3 years [45]. However, HAQ has not been associated with non-erosive disease [46]. Regarding disease activity scores, we found an association with the RAPID3 score. A lower RAPID3 score correlates positively with non-erosive disease. It is noteworthy that this finding indicates the higher the functional class is, the lower the erosive status is. Furthermore, VAS pain score was predictive for 3-year radiographic scores [9]. Interestingly, a low VAS pain score can be a consequence of a lower RAPID3 score, indicating that the patient's perception of pain will decrease in the context of lower disease activity and conjunctively less bone erosion.

**Table 3**
Associated factors with non-erosive RA

| Variable | *r* | *P* value[a] |
|---|---|---|
| ANA (+)[b] | 0.462 | 0.012 |
| Shorter disease duration[c] | 0.438 | 0.005 |
| Lower titers of RF[c] | 0.383 | 0.021 |
| Lower G-VAS[b] | 0.358 | 0.023 |
| Toxic exposure[b,d] | 0.350 | 0.027 |
| Lower titers of CRP[c] | 0.350 | 0.034 |
| Lower RAPID[b] | 0.328 | 0.039 |
| ACPA (+)[b] | −0.439 | 0.020 |
| Aspirin intake[b] | −0.378 | 0.021 |
| Biological therapy[b,e] | −0.346 | 0.029 |
| Antimalarial[b,f] | −0.315 | 0.048 |

ACPA: anti-cyclic citrullinated peptide antibody; ANA: antinuclear antibodies; CRP: C-reactive protein; G-VAS: global visual analog scale; RA: rheumatoid arthritis; RAPID: routine assessment of patients index data; RF: rheumatoid factor.

[a] The statistical significance was considered $P < 0.05$.
[b] The Kendall's tau-*b* correlation coefficient was used in order to evaluate the categorical variables.
[c] Spearman's correlation coefficient was used in order to evaluate the quantitative variables.
[d] Exposure to any of the following: hair dyes, pesticides, organic solvents, and silicone implants.
[e] If the patient had consumed any of the following: rituximab, infliximab, etanercept, abatacept, adalimumab, and tocilizumab.
[f] If the patient had consumed any of the following: chloroquine and hydroxychloroquine.

Simultaneous RF and ACPA negativity proved to be a strong predictive factor for non-erosive disease [22]. Negative RF was associated with a non-erosive radiological presentation of RA in studies conducted in the United States [21] and Sweden [18]. In addition, ACPA negativity was also found to be related with non-erosive disease in other studies [10,22]. Furthermore, a cross-sectional study from Israel noted that the titers of RF, CRP, and ACPA in patients with non-erosive disease differed from those found in erosive RA [22].

Compellingly, a correlation between non-erosive disease and ANA positivity was found in our cohort. ANAs may be a surrogate of the presence of SLE. The coexistence of SLE in RA is known to be associated with a non-erosive state; however, in the present study, the presence of SLE was an exclusion criterion. ANAs may be observed frequently in RA regardless of the coexistence of SLE [47]. To our knowledge, there are no studies exploring the association between the presence of ANAs and bone erosions.

Cytokines influence the erosive status of RA. Elevated serum levels of IL-4 and IL-8 have been found in non-erosive RA patients [24]. IL-4 not only correlated with non-erosive disease but also with female gender, milder disease, and earlier age at onset [24]. Some studies have proved IL-10 impedes joint destruction [32]. Data on IL-2 is inconclusive [25].

Genetics factors have been reported to be associated with erosive RA. The presence of HLA–DRB1 shared epitope (SE) is the most strong genetic factor associated with RA pathogenicity and is considered to be a predictive marker of rapid radiologic damage progression [48], regardless of the status of RF [49]. Weyand et al. [26] previously reported that a gene dosage effect for HLA–DRB1 alleles is functional in RA patients. Patients who have inherited disease-associated alleles on both haplotypes tend to develop more aggressive disease than patients with a single copy. However, there is little information about the influence of genetics on non-erosive disease. Fex et al. [18] observed that patients with early erosive disease predominantly carried HLA–DRB1*04 alleles, whereas patients with late or non-erosive RA were more seronegative for RF, as well as less frequently carrying both HLA-DR4 alleles and hyper variable region 3.

**Table 4**
Factors associated with non-erosive RA (systematic literature review)

| References | Country | Type of study | Level of evidence | Women, *n* (%) | Duration of the disease | RA Non-erosive % (*n*/N) | Follow-up time (yr) | Assessment method 1 | Assessment method 2 | Non-erosive assessment (erosive or score) | Non-erosive associated factors | Conclusions |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Amaya-Amaya et al. (current report) | Colombia | Cross-sectional | 2 | 30 (75) | 10 (6) yr | 20 (8/40) | 0 | X-ray | US, CT | Erosion absent | Positively: shorter disease duration, ANA positivity, lower RF and CRP titers, lower G-VAS, toxic exposures, and lower disease activity (RAPID3); inversely: ACPA positivity, biological therapy, aspirin and antimalarial intake | Non-erosive RA is an uncommon condition (8/500). There is a high variability and lack of concordance among the imagining techniques. The highest sensitivity was calculated for X-Ray imaging, and the highest specificity was calculated for US. |
| Slobodin et al. [31] | Israel | Cross-sectional | 2 | 23 (85.2) | > 2 yr | 37 (10/27) | 0 | X-ray | ND | Erosive score 0 | High LAP expression on peripheral blood monocytes | Increases in LAP as TGF-β1 marker can be associated with protection against erosion formation. |
| Bang et al. [33] | Korea | Inception cohort | 2 | 1347 (88.4) | 11.3 ± 8.4 yr[a] | 56.6 (864/1524) | 0 | X-ray | ND | Steinbroker class I–II | Brachydactyly | Brachydactyly may have a protective effect on global erosive changes due to mutational changes of *HOXD13* gene. |
| Hussein et al. [27] | Egypt | Cross-sectional | 2 | 172 (100) | 10.6 ± 7.9 yr[a] | 65.1 (112/172) | 0 | X-ray | ND | Erosion absent | IL-4Rα Q576R QR haplotype | Subjects carrying QR genotype were significantly decreased in patients with erosive RA compared to patients with non-erosive RA. |
| Bosello et al. [20] | Italy | Cohort | 3 | 92 (76.0) | 5.22 ± 3.4 mo[a] | Baseline: 71.9 (87/121); 1 yr: 60.3 (73/121) | 1 | X-ray | ND | Erosive score < 1 | Very early RA | Very early RA represents the best therapeutic opportunity in clinical practice to achieve a complete remission and to stop the erosive course. |
| Dawidowicz et al. [28] | France | Case–control | 4 | 328 (86.3) | 9.7 ± 8.5 yr[a] | 25 (95/380) | 0 | X-ray | ND | Erosion absent | *IRF5* CTA *RR* haplotype | The haplotype–phenotype correlation analysis revealed that *IRF5* influences both the erosive and the RF status in RA patients (i.e., CTA predictor for non-erosive RA and the AGG predictor for erosive RA). |
| Liao et al. [10] | United States | Cohort | 3 | 219 (80.8) | 4.5 ± 3.1 yr[a] | 20.7 (56/271) | 2 | X-ray | ND | Erosive score 0 | Younger AOD, shorter disease duration, and negative ACPA | Younger age and disease duration were consistent, significant clinical predictors of erosion-free status. ACPA may play a less prominent role in predicting erosion-free RA compared with erosive disease. |
| Rossol et al. [29] | Germany | Inception cohort | 2 | 369 (73.4) | 16 (2–70) yr[b] | 19.3 (97/503) | 0 | X-ray | ND | Erosion absent | CCR5d32 deletion | Carriers of the deletion were protected from joint erosions, were less frequently affected by EAM, and had lower CRP levels. |

**Table 4** (*continued*)

| References | Country | Type of study | Level of evidence | Women, *n* (%) | Duration of the disease | RA Non-erosive % (*n*/N) | Follow-up time (yr) | Assessment method 1 | Assessment method 2 | Non-erosive assessment (erosive or score) | Non-erosive associated factors | Conclusions |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pascual-Ramos et al. [19] | Mexico | Cohort | 3 | ND | ND | 81.7 (58/71) | 2 | X-ray | US | Erosion absent | Shorter disease duration, lower number of RA ACR classification criteria, and fewer ultrasound synovitis detected | RA patients with erosive disease have similar characteristics, although they accumulated more hyperv-ascular synovitis at baseline than non-erosive patients. |
| Uppal et al. [24] | Kuwait | Case–control | 4 | 27 (64.3) | < 3– > 24 mo | 69 (29/42) | 0 | X-ray | ND | ND | Higher levels of IL-4 and IL-18 | IL-4 and IL-18 correlate with non-erosive disease and earlier AOD. Furthermore, IL-4 correlates with gender female and milder disease. |
| Shankar et al. [23] | India | Cross-sectional | 2 | 88 (187) | 5 (3–8) yr[b] | 31.7 (67/211) | 0 | X-ray | ND | Erosive score 0 | Seronegativity for both RF and ACPA | Seronegativity for RF and ACPA had a strong negative predictive value for erosive disease, suggesting that if a patient is negative for both, the chances of developing erosive disease are significantly lesser. |
| Bokarewa et al. [30] | Sweden | Case–control | 4 | 93 (70.9) | 8 ± 1.4 yr[d,a] | 32.8 (43/131) | 0 | X-ray | ND | Erosion absent | Survivin antibodies IgG and IgM | Higher levels of survivin antibodies were found in patients with non-erosive RA. These findings suggest that survivin regulates the inflammatory and destructive process inside the joints. |
| Shovman et al. [22] | Israel | Cross-sectional | 2 | 44 (73.3) | 5–10 yr | 61.7 (37/60) | 0 | X-ray | ND | Erosion absent | Low titers of RF, ACPA, and CRP | The diagnostic utility of ACPA and RF were superior to other markers for non-erosive RA. |
| Huizinga et al. [32] | The Netherlands | Cohort | 3 | ND | ND | 46,1 (6/13) | 12 (10-14)[b] | X-ray | ND | Erosive score 0 | Greater IL-10/GAPDH mRNA ratio | IL-10 mRNA was higher in synovial biopsies from patients with non-erosive RA. It is suggestive that IL-10 inhibits joint destruction. |
| Fex et al. [18] | Sweden | Cohort | 3 | 75 (66.3) | 11.4 ± 6.6 yr[a] | Baseline: 53 (60/113); 5 y: 8.8 (10/113) | 5 | X-ray | ND | Erosive score 0 | Short disease duration, RF negative, less HLA–DRB1*04, and HVR3 positive | Disease duration, genetic factors, and RF had a predictive value of non-erosive disease. |
| Weyand et al. [26] | United States | Case–control | 4 | ND | > 5 yr | 46.6 (28/60)[c] | 0 | X-ray | ND | Erosion absent | Lacked an RA-linked haplotype (HLA–DRB1*X/X) | Patients with early erosive disease predominantly expressed HLA–DRB1*04 allele, whereas patients with late or non-erosive RA frequently lacked an RA-linked haplotype (HLA–DRB1*X/X). |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Jokinen et al. [25] | Finland | Cohort | 3 | 41 (70.7)[e] | 8 (2–24) mo[b] | Baseline: 70.7 (41/58); 2 yr: 31 (18/58) | 2 | X-ray | ND | Erosive score 0 | Higher levels of IL-2 | Altered immune functions—manifested as decreased production of IgM and IL-2—are involved in the progression of the disease and affect the outcome of patients and, thus, represent an unfavorable prognostic feature. |
| Burns and Calin [21] | United States | Case–control | 4 | 40 (86.9) | 8.9 yr | 45.6 (21/46) | 0 | X-ray | ND | Erosion absent | Seronegative disease[c] | The X-rays of patients with seronegative disease had an average score lower than those with seropositive disease. |

ACPA: anti-cyclic citrullinated peptide antibody; ANA: antinuclear antibody; CRP: C-reactive protein; CT: computed tomography; EAM: extra-articular manifestations; G-VAS: global visual analog scale; HVR3: hyper variable region 3; mo: months; IL: interleukin; LAP: latency-associated peptide; MDHAQ: multi-dimensional health assessment questionnaire; ND: no data; RA: rheumatoid arthritis; RAPID: routine assessment of patients index data; RF: rheumatoid factor; US: ultrasound; US: ultrasonography; yr: years.

[a] Mean ± (standard deviation).
[b] Median (range).
[c] Seronegative RA (RF−).
[d] Information of non-erosive group.
[e] The American Rheumatism Association (ARA) 1958 diagnostic criteria.

Genetic factors related to cytokine receptors have been associated with erosive status in RA. IL-2RB [50] and IL4R polymorphisms [27] are associated with erosive disease. Interestingly, *IL-4Rα Q576R* has been observed to be significantly decreased in erosive RA compared to non-erosive disease [27]. In addition, the haplotype–phenotype correlation analysis revealed that *IRF*5 influences both the erosive and the RF status of RA. There is evidence for the involvement of *IRF*5 in RA heterogeneity, notably the non-erosive and RF-negative phenotypes. This evidence suggests that information from common risk polymorphisms could improve disease prediction and may be useful for risk stratification of a given disease [28]. Moreover, in patients without radiographic evidence of bone erosions, the *CCR5d*32 deletion was present more frequently than in patients with erosive disease [29]. Furthermore, carriers of the deletion were less frequently affected by extra-articular manifestations of the disease and had lower cumulative CRP levels. This association indicates the clinical usefulness of this deletion as a prognostic diagnostic marker [29].

Other associated factors with non-erosive disease identified through SLR include the presence of antibodies against survivin, which is a member of the inhibitor of apoptosis family [30], higher expression of latency-associated peptide (LAP) [31], greater IL-10/GAPDH ratio in synovial tissue [32], and presence of brachydactyly [33]. The influence of medications on erosive RA is challenging to determine because confounding by indication should be considered.

### *Limitations of the study*

The main purpose of this study was to define and document the existence of non-erosive RA. The percentage of non-erosive RA may vary depending on the population evaluated (i.e., outpatients vs. inpatients, primary care vs. specialty care, and public vs. private healthcare). The low number of studies addressing non-erosive RA explains the heterogeneous results and the lack of reproducibility of major findings observed in the SLR. Lastly, most of studies evaluated erosive disease, and the articles reporting the prevalence of non-erosive involvement reported short disease duration, in most cases no longer than 3–5 years and short periods of follow-up. The cross-sectional nature of our study does not allow us to infer the causality of the associated factors found.

### *Conclusions*

A new subphenotype of RA is defined. Its physiopathology will deserve a place in the research agenda and its treatment approach should be delineated. In addition, non-erosive RA should be considered when interpreting the results of future clinical trials in order to not overestimate any results.

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## Appendix A. Supporting information

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## References

[1] Sanmartí R, Ruiz-Esquide V, Hernández MV. Rheumatoid arthritis: a clinical overview of new diagnostic and treatment approaches. Curr Top Med Chem 2013;13:698–704.

[2] Chopra A. The WHO ILAR COPCORD Latin America: consistent with the world and setting a new perspective. J Clin Rheumatol 2012;18:167–9.
[3] Henry J, Roulot E, Gaujoux-Viala C. The rheumatoid hand. Presse Med 2013;42:1607–15.
[4] Chan PS, Kong KO. Natural history and imaging of subtalar and midfoot joint disease in rheumatoid arthritis. Int J Rheum Dis 2013;16:14–8.
[5] Ollier WE, Harrison B, Symmons D. What is the natural history of rheumatoid arthritis? Best Pract Res Clin Rheumatol 2001;15:27–48.
[6] Lillegraven S, Prince FH, Shadick NA, Bykerk VP, Lu B, Frits ML, et al. Remission and radiographic outcome in rheumatoid arthritis: application of the 2011 ACR/EULAR remission criteria in an observational cohort. Ann Rheum Dis 2012;71:681–6.
[7] Fouque-aubert A, Chapurlat R, Miossec P, Delmas PD. A comparative review of the different techniques to assess hand bone damage in rheumatoid arthritis. Joint Bone Spine 2010;77:212–7.
[8] Lindqvist E, Jonsson K, Saxne T, Eberhardt K. Course of radiographic damage over 10 years in a cohort with early rheumatoid arthritis. Ann Rheum Dis 2003;62:611–6.
[9] Combe B, Dougados M, Goupille P, Cantagrel A, Eliaou JF, Sibilia J, et al. Prognostic factors for radiographic damage in early rheumatoid arthritis: a multiparameter prospective study. Arthritis Rheum 2001;44:1736–1743.
[10] Liao KP, Weinblatt ME, Cui J, Iannaccone C, Chibnik LLB, Lu B, et al. Clinical predictors of erosion-free status in rheumatoid arthritis: a prospective cohort study. Rheumatology (Oxford) 2011;50:1473–9.
[11] Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
[12] Amaya-Amaya J, Sarmiento-Monroy JC, Mantilla RD, Pineda-Tamayo R, Rojas-Villarraga A, Anaya JM. Novel risk factors for cardiovascular disease in rheumatoid arthritis. Immunol Res 2013;56:267–86.
[13] Van der Heijde DM. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 2000;27:261–3.
[14] Døhn UM, Conaghan PG, Eshed I, Boonen A, Boyesen P, Peterfy CG, et al. The OMERACT-RAMRIS rheumatoid arthritis magnetic resonance imaging joint space narrowing score: intrareader and Interreader reliability and agreement with computed tomography and conventional radiography. J Rheumatol 2014;41:392–7.
[15] Wakefield RJ, Balint PV, Szkudlarek M, Filippucci E, Backhaus M, D'Agostino MA, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. J Rheumatol 2005;32:2485–7.
[16] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009;62:e1–34.
[17] Oxford Centre for Evidence-Based Medicine. OCEBM Levels of Evidence Working Group*."The Oxford Levels of Evidence 2", ⟨http://www.cebm.net/index.aspx?o=5653⟩.
[18] Fex E, Jonsson K, Johnson U, Eberhardt K. Development of radiographic damage during the first 5–6 yr of rheumatoid arthritis. A prospective follow-up study of a Swedish cohort. Br J Rheumatol 1996;35:1106–15.
[19] Pascual-Ramos V, Contreras-Yañez I, Cabiedes-Contreras J, Rull-Gabayet M, Villa AR, Vázquez-Lamadrid J, et al. Hypervascular synovitis and American College of Rheumatology classification criteria as predictors of radiographic damage in early rheumatoid arthritis. Ultrasound Q 2009;25:31–8.
[20] Bosello S, Fedele AL, Peluso G, Gremese E, Tolusso B, Ferraccioli G. Very early rheumatoid arthritis is the major predictor of major outcomes: clinical ACR remission and radiographic non-progression. Ann Rheum Dis 2011;70:1292–5.
[21] Burns TM, Calin A. The hand radiograph as a diagnostic discriminant between seropositive and seronegative "rheumatoid arthritis": a controlled study. Ann Rheum Dis 1983;42:605–12.
[22] Shovman O, Gilburd B, Sherer Y, Orbach H, Zandman-Goddard G, Gerli R, et al. The diagnostic utility of anti-cyclic citrullinated peptide antibodies, matrix metalloproteinase-3, rheumatoid factor, erythrocyte sedimentation rate, and C-reactive protein in patients with erosive and non-erosive rheumatoid arthritis. Clin Dev Immunol 2005;12:197–202.
[23] Shankar S, Grover R, Handa R. Role of anti cyclic citrullinated peptide antibodies in erosive disease in patients with rheumatoid arthritis. Indian J Med Res 2006;124:689–96.
[24] Uppal SS, Raghupathy R, Hayat SJ, Chowdhury RI, Abraham M, Rawoot P. Patient demographics and disease variables correlate with distinct cytokine patterns in mitogen-stimulated peripheral blood mononuclear cells from rheumatoid arthritis patients. Rheumatol Int 2008;28:533–9.
[25] Jokinen EI, Möttönen TT, Hannonen PJ, Arvilommi HS. Association of in vitro immune functions with the severity of the disease in rheumatoid arthritis. Br J Rheumatol 1993;32:550–5.
[26] Weyand CM, McCarthy TG, Goronzy JJ. Correlation between disease phenotype and genetic heterogeneity in rheumatoid arthritis. J Clin Invest 1995;95:2120–6.
[27] Hussein Y, El-Tarhouny S, Mohamed R, Pasha H, Abul-Saoud A. Association of interleukin-4 receptor gene polymorphisms with rheumatoid arthritis in Egyptian female patients. Joint Bone Spine 2012;79:38–42.
[28] Dawidowicz K, Allanore Y, Guedj M, Pierlot C, Bombardieri S, Balsa A, et al. The interferon regulatory factor 5 gene confers susceptibility to rheumatoid arthritis and influences its erosive phenotype. Ann Rheum Dis 2011;70:117–21.
[29] Rossol M, Pierer M, Arnold S, Keysser G, Burkhardt H, Baerwald C, et al. Negative association of the chemokine receptor CCR5 d32 polymorphism with systemic inflammatory response, extra-articular symptoms and joint erosion in rheumatoid arthritis. Arthritis Res Ther 2009;11:R91.
[30] Bokarewa M, Lindblad S, Bokarew D, Tarkowski A. Balance between survivin, a key member of the apoptosis inhibitor family, and its specific antibodies determines erosivity in rheumatoid arthritis. Arthritis Res Ther 2005;7:R349–58.
[31] Slobodin G, Kaly L, Peri R, Kessel A, Rosner I, Toubi E, et al. Higher expression of latency-associated peptide on the surface of peripheral blood monocytes in patients with rheumatoid arthritis may be protective against articular erosions. Inflammation 2013;36:1075–8.
[32] Huizinga TW, Keijsers V, Yanni G, Hall M, Ramage W, Lanchbury J, et al. Are differences in interleukin 10 production associated with joint damage? Rheumatology (Oxford) 2000;39:1180–8.
[33] Bang SY, Kim TH, Bae SC, Jun JB. Does brachydactyly have a protective effect on the erosive changes in rheumatoid arthritis? Joint Bone Spine 2012;79:271–273.
[34] van der Heijde D, van der Helm-van Mil AH, Aletaha D, Bingham CO, Burmester GR, Dougados M, et al. EULAR definition of erosive disease in light of the 2010 ACR/EULAR rheumatoid arthritis classification criteria. Ann Rheum Dis 2013;72:479–81.
[35] van der Heijde DM. Radiographic imaging: the "gold standard" for assessment of disease progression in rheumatoid arthritis. Rheumatology (Oxford) 2000;39(Suppl. 1):9–16.
[36] van der Heijde D, Lassere M, Edmonds J, Kirwan J, Strand V, Boers M. Minimal clinically important difference in plain films in RA: group discussions, conclusions, and recommendations. OMERACT imaging task force. J Rheumatol 2001;28:914–7.
[37] Funck-Brentano T, Gandjbakhch F, Etchepare F, Jousse-Joulin S, Miquel A, Cyteval C, et al. Prediction of radiographic damage in early arthritis by sonographic erosions and power Doppler signal: a longitudinal observational study. Arthritis Care Res (Hoboken) 2013;65:896–902.
[38] Baillet A, Gaujoux-Viala C, Mouterde G, Pham T, Tebib J, Saraux A, et al. Comparison of the efficacy of sonography, magnetic resonance imaging and conventional radiography for the detection of bone erosions in rheumatoid arthritis patients: a systematic review and meta-analysis. Rheumatology (Oxford) 2011;50:1137–47.
[39] Finzel S, Ohrndorf S, Englbrecht M, Stach C, Messerschmidt J, Schett G, et al. A detailed comparative study of high-resolution ultrasound and micro-computed tomography for detection of arthritic bone erosions. Arthritis Rheum 2011;63:1231–6.
[40] Guillemin F, Gérard N, van Leeuwen M, Smedstad LM, Kvien TK, van den Heuvel W. Prognostic factors for joint destruction in rheumatoid arthritis: a prospective longitudinal study of 318 patients. J Rheumatol 2003;30:2585–9.
[41] Wolfe F, Sharp JT. Radiographic outcome of recent-onset rheumatoid arthritis: a 19-year study of radiographic progression. Arthritis Rheum 1998;41:1571–82.
[42] Markatseli TE, Papagoras C, Drosos AA. Prognostic factors for erosive rheumatoid arthritis. Clin Exp Rheumatol 2009;28:114–23.
[43] Bukhari M, Lunt M, Harrison BJ, Scott DG, Symmons DP, Silman AJ. Rheumatoid factor is the major predictor of increasing severity of radiographic erosions in rheumatoid arthritis results from the norfolk arthritis register study, a large inception cohort. Arthritis Rheum 2002;46:906–12.
[44] Scott DL, Smith C, Kingsley G. Joint damage and disability in rheumatoid arthritis: an updated systematic review. Clin Exp Rheumatol 2003;21:S20–7.
[45] Stockman A, Tait BD, Wolfe R, Brand CA, Rowley MJ, Varney MD, et al. Clinical, laboratory and genetic markers associated with erosions and remission in patients with early inflammatory arthritis: a prospective cohort study. Rheumatol Int 2006;26:500–9.
[46] Syversen SW, Gaarder PI, Goll GL, Ødegård S, Haavardsholm EA, Mowinckel P, et al. High anti-cyclic citrullinated peptide levels and an algorithm of four variables predict radiographic progression in patients with rheumatoid arthritis: results from a 10-year longitudinal study. Ann Rheum Dis 2008;67:212–7.
[47] Ohmura K, Terao C, Maruya E, Katayama M, Matoba K, Shimada K, et al. Anti-citrullinated peptide antibody-negative RA is a genetically distinct subset: a definitive study using only bone-erosive ACPA-negative rheumatoid arthritis. Rheumatology (Oxford) 2010;49:2298–304.
[48] Rojas-Villarraga A, Diaz Francisco J, Calvo-Páramo E, Salazar JC, Iglesias-Gamarra A, Mantilla RD, et al. Familial disease, the HLA–DRB1 shared epitope and anti-CCP antibodies influence time at appearance of substantial joint damage in rheumatoid arthritis. J Autoimmun 2009;32:64–9.
[49] Massardo L, Gareca N, Cartes MA, Cervilla V, González A, Jacobelli S. The presence of the HLA–DRB1 shared epitope correlates with erosive disease in Chilean patients with rheumatoid arthritis. Rheumatol (Oxford) 2002;41:153–6.
[50] Ruyssen-Witrand A, Lukas C, Nigon D, Dawidowicz K, Morel J, Sibilia J, et al. Association of IL-2RA and IL-2RB genes with erosive status in early rheumatoid arthritis patients (ESPOIR and RMP cohorts). Joint Bone Spine 2014;81:228–34.