

**ASSOCIATION BETWEEN SHARP'S RADIOGRAPHIC INDEX AND ACUTE PHASE REACTANTS IN RHEUMATOID ARTHRITIS**

## VEZA IZMEĐU SHARPOVOG RADIOGRAFSKOG INDEKSA I REAKTANATA AKUTNE FAZE KOD REUMATOIDNOG ARTRITISA

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**Summary:** The aim of this study was to evaluate the activity of rheumatoid arthritis (RA) by hand radiography (Sharp's radiographic index), and assessment of acute phase reactants – erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and rheumatoid factor (RF), and to determine their value as prognostic markers for disease outcome in patients with early RA treated with disease modifying antirheumatic drugs (DMARDs)-Methotrexate (MTH); to register and quantify clinical, radiographic and laboratorial differences in certain time intervals in a group of patients treated with immunomodulation therapy with MTH; to determine which of the acute phase reactants would be the most useful marker for evaluation of disease activity in long-term follow-up in RA patients; to select high-risk groups with aggressive course of disease, in order to emphasize the necessity of early and aggressive treatment. Thirty patients with early RA (disease evolution up to 1 year) were evaluated in several time intervals. The score of the Sharp's index showed greater radiographic progression of the joint damage of hands in time intervals between 0-time and 12 months ( $p=0.0167$ ) and between 0-time and 18 months ( $p=0.0089$ ). Statistical analysis showed differences in values of CRP in four time intervals ( $p=0.00002$ ). Considering CRP, there were statistically significant differences among mean values in four time intervals ( $p=0.0428$ ) (standard deviations showed greater variations). There were no statistically significant differences among mean values of RF in four time intervals ( $p=0.573$ ). At 0-time in 3 (10%) patients progression of the Sharp's index was found, after 6 months in 13 (39%)

**Kratak sadržaj:** Cilj ovog istraživanja bio je da se proceni aktivnost reumatoidnog artritisa (RA) pomoću radiografske procene šake (Sharpov radiografski indeks) i reaktanata akutne faze – sedimentacije (ESR), C reaktivnog proteina (CRP), reumatoidnog faktora (RF), i da se utvrdi njihov značaj kao prognostičkih markera za ishod bolesti kod pacijenata sa ranim RA, lečenih lekovima koji modifikuju progresiju bolesti (DMARDs-Metotreksat (MTX). Kliničke, rendgenološke i laboratorijske razlike su registrovane i kvantificirane u određenom vremenskom periodu u grupi pacijenata tretiranih imunomodulatornom terapijom sa MTX. Kako bi se utvrdilo koji bi od reaktanata akutne faze bio najkorisniji marker za procenu aktivnosti bolesti kod dugoročnog praćenja RA pacijenata, kao i da bi se selektovale visokorizične grupe sa agresivnim tokom bolesti gde se ukazuje potreba za ranim i agresivnim lečenjem, ispitivano je 30 pacijenata sa ranim RA i evolucijom bolesti do 1 godine. Isti pacijenti su praćeni u nekoliko vremenskih intervala. Sharpov indeks pokazao je veću radiološku progresiju zglobnog oštećenja šake u intervalima između 0 i 12 meseci ( $p=0,0167$ ) i 0 i 18 meseci ( $p=0,0089$ ). Postoje statistički značajne razlike između srednje vrednosti CRP u sva četiri vremenska intervala ( $p=0,0428$ ) (standardne devijacije imale su velike varijacije). Nisu otkrivene statistički značajne razlike između srednje vrednosti RF u sva 4 vremenska intervala ( $p=0,573$ ). U 0-vremenu kod 3 pacijenata (10%) registrovana je progresija Sharpovog indeksa, nakon 6 meseci kod 13 pacijenata (39%), a u 12. i 18. mesecu registrovana je kod identičnog broja pacijenata, 15 (50%). Kod velikog broja pacijenata registrovane su povišene vrednosti CRP i RF. Progresija radiološkog oštećenja posebno je izražena kod pacijenata sa visokim vrednostima ESR, CRP, RF, gde postoje prethodne erozije šake, koje su prediktori za agresivan tok bolesti. CRP je najkorisniji mar-

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patients, while after 12 and 18 months progression of the Sharp's index was found in an identical number of patients, 15 (50%). In most patients high values of CRP and RF were found. Progression of the radiographic damage is especially expressed in patients with high values of ESR, CRP, RF and existence of previous erosions of hands, which are predictors for aggressive course of disease. CRP is the most useful marker for the evaluation of RA activity in the long-term follow-up of RA patients.

**Keywords:** rheumatoid arthritis, Sharp's radiographic index, acute phase reactants

## Introduction

Radiographic evaluation remains the most important tool for assessment of structural damage of the skeletal system. Progression of radiographic damage in hands and feet is a significant and objective variable for the evaluation of disease activity, as well as for the measurement of the outcome of treatment (1). Chronic synovitis is the most common reason for irreversible destructive changes of the cartilage of the joint and subchondral bone. Conventional anterior-posterior radiograms of the hands and feet are used for registration of structural changes that result in loss of joint-space and appearance of erosions, quantified with methods of counting and assembling, that should be reproducible and should allow dynamic follow-up of the changes. Radiographic evaluation of the joint damage is based on the standard methods for assessment of the effect of treatment in RA. In the past few decades a lot of numerical methods have been suggested – radiographic indexes for detection of radiographic abnormalities in the joints of hands, radiocarpal joints and feet (that refer to the counting of erosions, joint-space narrowing, or assessment of the degree of joint damage). Radiographic indexes are usually semi-quantitative methods that enable the showing of joint damages expressed with numeric values–scores, that directly estimate two anatomic characteristics of the joints in RA–cartilage damage and destruction of the joints. A lot of radiographic scores express the rate of progression of the joint damage and are predictors of the outcome of disease in RA. Evaluation of the rate of progression of joint damage enables the selection of groups at high-risk of an aggressive course of disease, and emphasizes the necessity for early and adequate treatment (2). Standard indexes for the evaluation of joint damage are Sharp's and Larsen's radiographic indexes (3). Both methods are modified several times (4–6).

Biochemical analyses (acute phase reactants such as ESR and CRP) indirectly reflect synovitis, but at the same time are sensitive tools for impartialness and measurement of immuno-mediated inflammatory responses in RA. Simultaneous tests are recommended especially for ESR, CRP and RF (which are reversible measures of inflammation), with clinical and radio-

ker za procenu aktivnosti RA kod dugoročnog praćenja pacijenata sa RA.

**Ključne reči:** reumatoidni artritis, Sharpov radiografski indeks, reaktanti akutne faze

graphic variables (irreversible) of the inflammatory synovitis, that make it possible to assess which of these three parameters correlates better with other joint and radiographic indexes of the disease activity. Taking into consideration the changeable course of disease activity, for reliable evaluation of RA, the most convenient are serial measurements of ESR and CRP (integrated in time) (7). Reports of the studies dealing with joint damage and inflammatory synovitis expressed with acute phase reactants are paradoxical. Although there is correlation between radiographic progression and acute phase reactants, some studies suggest that erosion progression continues, in spite of the suppression of joint inflammation (8).

Speaking of laboratory tests, anemia and thrombocytosis also reflect inflammation in RA. Rheumatoid factor (IgM-RF) is a serologic indicator which was included in the ACR (American College of Rheumatology) criteria for RA in 1987 (9) and is an anti-immunoglobulin antibody which directly acts on the Fc fragment of immunoglobulin G. RF is detected in 75–80% of patients with RA. High titer of RA is associated with a foudroyant course of the disease. Clinically, high disease activity at presentation and positive RF factor after one year of treatment with drugs that slow the course of disease – SAARDs (slow-acting anti-rheumatoid drugs) are the best predictors of bad prognosis, especially in patients with early RA. Nevertheless, the outcome of disease in individual patients with early RA could not be assessed with certainty (10).

The aim of the study was the evaluation of RA activity using hand radiography and assessment of acute phase reactants (ESR, CRP and RF), and their analysis, as prognostic markers for the outcome of disease in patients with early RA treated with MTH.

## Material and Methods

To realize the aim, in the prospective study at the Clinic of Rheumatology, 30 patients with RA who fulfilled the criteria for disease classification according to ACR (American College of Rheumatology) from 1987 were followed, with disease evolution up to 1 year from diagnosis, with an average duration of RA of  $5.1 \pm 2.8$  months (range 2–11 months) and average age  $52.3 \pm$

11.2 (range 36–74 years). The dispersions were performed at the time of study entrance – 0-time, first control after 6 months, second control after 12 months and third control after 24 months. Immunomodulation therapy with MTH was initiated for the first time in patients (mean dose of 7.5 mg once weekly, besides non-steroid antiinflammatory drugs–NSAIDs). At the same time the preventing effect of therapy with MTH was evaluated, by measurement of the free interval from the moment of entering the study to the appearance of the first erosion.

#### Sharp's radiographic index

For a radiographic evaluation of disease progression at the appointed time intervals, in every patient the original Sharp's index was analyzed, which assesses 29 joint surfaces for bone erosions and destructions, and 27 joints with space narrowing on every hand and radio-carpal joint.

Joints which we evaluated are: 14 finger joints 5 bases of the metacarpal bones, 8 carpal bones, radius and ulna. Each one of them was individually evaluated for erosions, with scoring 0–5. The total sum of individually evaluated joints for erosions and destruction provides the cumulative sum of scores for erosions and joint damage in hands and radio-carpal joints (ES) which ranges from 0 to 290.

Score for joint-space narrowing (JSN) assesses JSN of 27 joints on every hand and radio-carpal joints (14 finger joints, 5 carpal-metacarpal, joint spaces between carpal bones, radio-carpal and radio-ulnar joints). Scoring is 0–4, depending on the narrowing of the joint space. The sum of individual scores provides the cumulative possible score of JSN which ranges from 0 to 216.

The sum of scores for erosions (ES) and scores for joint-space narrowing (JSN) defines the total score of joint damage (TC) which ranges from 0 to 506.

In every patient at identical periods in time the acute phase reactants were analyzed: ESR (mm/h) was determined according to the Westergren's method (reference values 4/10 mm/h), CRP was determined

with a nephelometric method (reference values 0–6 mg/L), values >6 mg/L signify positive CRP and rheumatoid factor (RF) which was determined by the agglutination test. Titer bigger than 1:30 IU/mL was taken for positive RF.

#### Statistical analysis

During data procession and analysis, statistical methods applied were: measures of central tendency (mean values) and measures of dispersion (standard deviation); testing the significance of differences among three or more arithmetical means in groups (dependant samples) was performed with Friedman's two-directional analysis of variance; testing the significance of differences between two arithmetical means in groups (dependant samples) was performed with Wilcoxon Matched Pairs Test. We used statistical software

**Table I** Sharp' index in patients with rheumatoid arthritis with disease evolution up to 1 year with mean values of joint-space narrowing (JSN), erosive score (ES) and total score (TS).

|                                   | 0-time | After 6 months | After 12 months | After 18 months |
|-----------------------------------|--------|----------------|-----------------|-----------------|
| Joint-space narrowing score (JSN) |        | 0–20           | 0–20            | 0–20            |
| Average number of JSN             | 6      | 11             | 13              | 14              |
| + Average number of JSN           |        | 5              | 2               | 1               |
| Erosive score (ES)                | 0–2    | 0–3            | 0–5             | 0–6             |
| Average number of ES              | 1      | 2              | 3               | 5               |
| + Average number of ES            |        | 1              | 1               | 2               |
| Total score of joint damage (TS)  | 0–18   | 0–23           | 0–25            | 0–26            |
| Average number of TS              | 7      | 13             | 16              | 19              |
| + Average number of TS            |        | 6              | 3               | 3               |

**Table II** Mean values of acute phase reactants (ESR, CRP and RF) in patients with RA.

|                           | 0-time      | After 6 months | After 12 months | After 18 months |
|---------------------------|-------------|----------------|-----------------|-----------------|
| Mean values of ESR (mm/h) | 59.9±27.7   | 31.6±16.9      | 31.4±17.4       | 25.0±11.6       |
| Range of ESR              | 34–111      | 14–85          | 20–90           | 10–50           |
| Mean values CRP (mg/L)    | 26.3±28.8   | 19.0 ±24.0     | 10.6±11.9       | 13.4±22.1       |
| Range of CRP + > 6 mg/L   | 0–128       | 0–96           | 0–61.2          | 0–96            |
| Mean values of RF (IU/mL) | 195.5±289.9 | 194.4±366.1    | 89.3±157.9      | 126±311.7       |
| Range of RF + > 30 IU/mL  | 0–1280      | 0–1536         | 0–1536          | 0–1536          |

Statistica, release 7.0 for data processing. Data are expressed as mean ± SD and range when appropriate. P values less than 0.05 were considered significant (11).

**Results**

RA was evaluated following the dynamics of changes in mean values of the score of the radiographic index, mean values of ESR, CRP and RF.

Sharp's index in patients with RA with disease evolution up to 1 year with mean values of joint-space narrowing (JSN), erosive score (ES) and total score of joint damage (TC) are shown in Table I.

Mean values of the acute phase reactants (ESR, CRP and RF) in patients with RA are shown in Table II.

In relation to Sharp's radiographic index, Wilcoxon-Matched Pairs Test analysis shows that differences in the average number of joint-space narrowing are statistically significant between 0-time and after 12 months for  $p=0.0288$  (+7 JSN), as well as between 0-time and after 18 months for  $p=0.0205$  (+8 JSN). Differences in the average number of joint-space narrowing among other measurements were not statistically significant ( $p>0.05$ ).

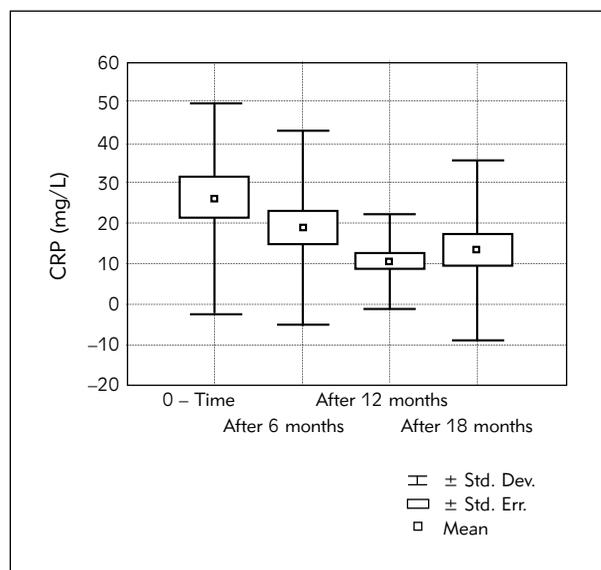
Differences in the average number of erosive changes are statistically significant between 0-time and after 12 months for  $p=0.0169$  (+2 ES), as well as between 0-time and after 18 months for  $p=0.0034$  (+4 ES). Differences in the average number of erosive changes among other measurements were not statistically significant ( $p>0.05$ ).

Differences in the average number of the total score are statistically significant between 0-time and 12 months for  $p=0.0167$  (+9 TS), as well as between 0-time and after 18 months for  $p=0.0089$  (+11 TS).

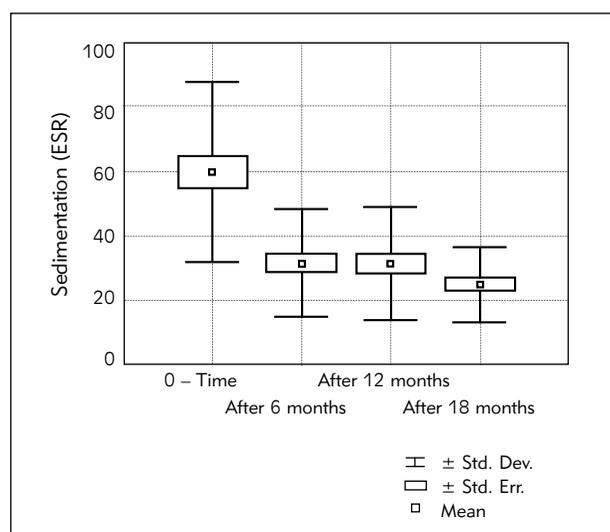
Differences in the average number of the total score among other measurements were not statistically significant ( $p>0.05$ ).

Wilcoxon Matched Pair Test analysis showed that differences in the average number of joint-space narrowing, erosive changes, as well as the total score, were not statistically significant among all measurements ( $p>0.05$ ).

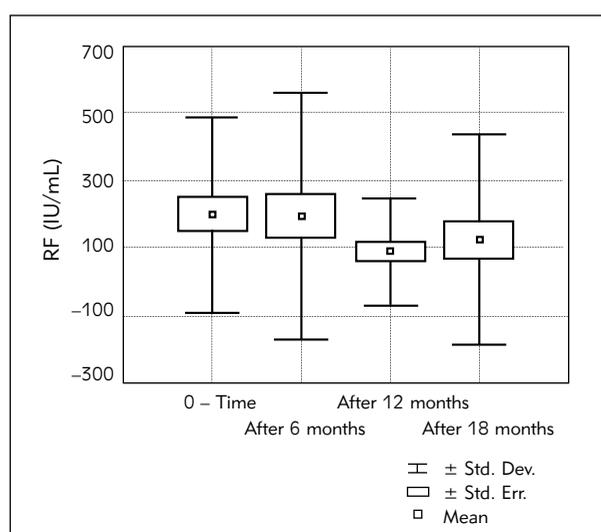
Considering the acute phase reactants, Friedman's two-directional analysis of variance showed that there were statistically significant differences among mean values of ESR in the four time intervals  $F\chi^2 = 19.485$ ,  $p=0.00002$  (Figure 1). Wilcoxon Matched Pair test showed statistically significant differences of



**Figure 2** Mean values of CRP in patients with early RA.



**Figure 1** Mean values of ESR in patients with early RA.



**Figure 3** Mean values of RF in patients with early RA.

mean values of ESR at the period of time between 0-time and 6 months ( $p=0.00014$ ); between 0-time and 12 months ( $p=0.00014$ ); 0-time and 18 months ( $p=0.00010$ ).

Friedman's two-directional analysis of variance showed that there were statistically significant differences among mean values of CRP at the four time intervals. For  $\chi^2 = 2.804$ ,  $p=0.0428$  (standard deviations showed greater variations). Concerning the distribution analysis of patients with values of CRP above and below 6 mg/L,  $\chi^2$ -test showed that the number of patients in whom the values of CRP were negative increased in time, and the differences were statistically significant ( $\chi^2=11.35$ ,  $df=3$ ,  $p=0.0099$ ) (Figure 2).

Friedman's two-directional analysis of variance showed that there were no statistically significant differences among mean values of RF at the four time intervals. For  $\chi^2=1.017$ ,  $p=0.3875$  (standard deviations showed great variations).

Analysis with  $\chi^2$ -test showed that the number of patients in whom the values of RF were negative increased in time, but the differences were not statistically significant ( $\chi^2=1.99$ ,  $df=3$ ,  $p=0.573$ ) (Figure 3).

At 0-time in 3 (10%) patients changes in Sharp's index were registered, in 2 of them changes considering the score of joint-space narrowing were registered and in 1 considering the erosive score. Two of the patients had high values of RF and CRP, while in one negative values of RF and CRP were noted.

After 6 months of treatment with MTH, in 12 patients progression of the score of joint-space narrowing was found, while in 13 (44%) patients it was TS. In four patients negative values of RF and CRP were found. In the rest of the patients high values of RF and CRP were noted.

After 12 months of treatment with MTH in 14 patients progression of the score of joint-space narrowing, and in 15 (50%) patients progression of the total score were found. In 9 patients high values of RF were registered and high values of CRP in 6.

After 18 months of treatment with MTH, the number of patients, in view of the score of joint-space narrowing and the erosive score, was identical with the previous control (after 12 months) i.e. in 15 (50%) patients progression of the score of the Sharp's index was found. In 9 of them high values of RF and in 9 negative CRP were found.

Considering ESR, consecutive decrease in values at every following control was registered, and at four time intervals in most of the patients progression of the Sharp's radiographic score was found.

## Discussion

Evaluation of the disease activity and effect of treatment with MTH is performed by follow-up of the dynamics of radiographic progression and reactants

acute phase (ESR, CRP, RF). Our results show radiographic progression (without radiographic improvement, presence of periarticular soft tissue swelling and juxtaarticular osteoporosis), in spite of clinical improvement in most patients.

Although therapy with MTH resulted with clinical suppression of RA after 6 months, radiographic progression of joint damage continued besides the decrease of the mediators of inflammation. Other studies also show existence of a more expressed radiographic progression of the erosions after 6 and 12 months from treatment in comparison with the first 6 months in early RA, with linear progression of the erosions (12).

Besides mutual dependence among the variables of inflammation and acute phase reactants on one hand, and radiographic joint damage on the other hand (13, 14), significant difference considering inflammatory variables and joint destruction, recently proved with experimental models of arthritis (15, 16), seems to be present only in the early stages of disease, when inflammation is active, but cartilage and bone structures are not yet attacked. So, data suggest that, if inflammation stops in a similar way in early stage RA, joint damage improvement is partly »autonomous«. During the follow-up of patients at four time intervals, those with high values of RF and CRP in all time intervals showed greater progression of joint damage.

A lot of clinical studies and published reports suggest the difficulty of assessing which factors are of primary importance as predictors of the therapeutic response, and the reason are different definitions of responses to therapy and the investigation of different predictors of disease, in different clinical studies. On the other hand, of relative influence is the different approach to treatment of RA with DMARDs alone, or the combination with several DMARDs (17, 18).

Studies that evaluate disease activity as a predictor for the therapeutic response are inconsistent in their reports. Relatively recent studies point out that positive RF is a predictor for disease activity and radiographic progression, i.e. high titer of RA is a predictor for further joint damage (19). That was proved also in this study. Some patients had enormously high values of RF. According to the values of RF, patients were divided into those above and those below 30 IU/mL. The number of patients in who the values of RF were negative increased over time, but the differences were not statistically significant. Particularly in patients with high values of RF higher progression of joint damage was noted at the next time interval of the follow-up of RA activity.

Some studies point out that markers of inflammation manifested at the beginning of RA with the introduction of therapy do not have predictive importance for further therapeutic responses i.e. RF status is not a predictor of the therapeutic response of a drug (20). In some studies RF is a consistent indicator of the severity of disease, while other clinical variables measured at the beginning of disease that assess disease activity

with the counting of inflammatory joints as well as with reactants acute phase are variable in their influence on further joint damage (21).

In the study of patients with early stage disease and intensive therapy, positive RF at the beginning of the study is shown to be a bad predictor for disease outcome, but positive RF in the course of one year has shown to have prognostic significance for disease outcome (10), which is also confirmed in this study.

Chronically active disease RA is a reflection of the elevated values of CRP, ESR and rapid radiographic progression (22). This study emphasizes the superiority of CRP in comparison with ESR as a predictor for radiographic progression, and points to a much greater correlation between CRP and radiographic progression than with the number of sensitive joints, Ritchie's articular index or number of inflammatory joints. Superiority of CRP compared with ESR is explained with a higher sensitivity of CRP in relation to the inflammatory state, and in contrast with ESR, CRP is resistant to the influence of sex, age, anemia or other serum proteins, which is also confirmed in this study. Considering radiographic progression, this study shows that it correlates much better with serial measurements of CRP than of ESR and/or articular indexes, and that the combination of CRP and ESR does not have any additional advan-

tage in the evaluation of radiographic progression in comparison to CRP alone.

Radiographic progression is noticed also with normal values of CRP (23) with a tendency towards bigger progression in already damaged joints, with a smaller number of newly involved joints. Determination of the values of CRP and ESR for disease evaluation, defined with radiographically detectable damages, selects CRP as a priority indicator, because it is a direct and sensitive marker which gives quick response to the changes in the inflammatory synovitis in comparison with ESR, which is an indirect marker of inflammation. CRP reflects the changes in disease activity more precisely, and in shorter time in comparison with ESR, which registers changes in RA activity after few weeks. However, the decrease of the values of CRP in the following controls at the four time intervals in the group, confirms the sensitivity of CRP in relation to joint inflammation.

Besides the therapy with MTH, the radiographic damage continues especially in patients with high values of ESR, CRP, RF and previous existence of erosions in the hands, which are shown to be predictors of an aggressive course of disease. They enable selection of groups at high-risk for aggressive course of disease and suggest the necessity of early and aggressive treatment in selected patients.

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