Predictor of joint damage in rheumatoid arthritis

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ABSTRACT

Objective: This study was implemented to determine the joint damage predictor in rheumatoid arthritis (RA).

Methods: A cross-sectional study was conducted on outpatients of the rheumatology clinic at Cipto Mangunkusumo General Hospital who had suffered from RA for more than 2 years during the period from October 1, 1999 to June 30, 2000. During this period, we obtained 23 RA patients who fulfilled the inclusion and exclusion criteria. We evaluated the patients' medical data that included gender, education, age of onset, rheumatoid factor (RF), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Then we carried out examinations and tests including X-ray of hand and wrist joints, RF, CRP, and ESR. The degree of joint damage was evaluated using the Larsen score.

Results: Twenty three patients—all women, mean age of onset was 36.7 years, mean duration of disease was 62.8 months, educational level with high school degree or above were found in 19 cases (82.6%), and RF (+) at initial treatment were found in 10 cases (43.5%). The mean ESR at initial treatment was 77.9 mm/hr and CRP at initial treatment was between 0 and 768 mg/dL. The Larsen score ranged between 0 and 68 with a mean of 21.7. In bivariate analysis, the Larsen score was significantly higher in the group with positive RF at initial treatment compared to that in the group with negative RF at initial treatment ($p = 0.031$). C-reactive protein and ESR at initial treatment and the age of onset did not have any significant correlation with the Larsen score, but there was a significant correlation of CRP and ESR during the study with the the Larsen score.

Conclusion: RF level was the most significant predictor in determining the degree of joint damage according to the Larsen score while initial positive RF had lower significance level.

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease which has a variety of disease course and very unpredictable prognosis ranging from mild to severe outcome.[1,2] The natural course of RA disease could be categorized into 3 types: (1) monocyclic, characterized by one attack cycle followed by remission; (2) polycyclic, consisting of intermittent subtype and continuous subtype; and (3) progressive, characterized by spreading involvement to other joints.[3] Most RA course of disease is chronic and fluctuative so that, if not treated, can cause progressive joint damage, deformity, disability, and early death.[4] According to Fuch, of the medically-treated RA patients, only 15% had remission or had normal functional status after 10 years of disease onset, while according to Edward D, of the RA patients studied during a mean of 11.9 years, only 17% were without disability.[5] The joint damage in RA occurs mostly in the first two years of the disease.[6,7]

The prognosis of the disease can be evaluated with some parameters, such as remission level, functional status, and the degree of joint damage.[8-10] The above three parameters are not always correlated with each other. An RA patient may have a severe joint damage with an impaired functional status although it is in complete remission. The opposite could also occur, in which an RA patient with a minimum joint damage may not be in remission or may be in flare-up but has impaired functional status. Radiographic image is believed to be "the true biological endpoint" of inflammation and enzymatic degradation of cartilage and subchondral bone.[11] In addition, evaluation for prognosis using the output of degree of joint damage is an objective method that can be calculated.[7]

Today there are some theories and studies attempting to determine factors that can predict the RA joint damage. Factors that are strongly suspected include rheumatoid factor (RF), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), presence of early joint erosion, human leukocyte antigen (HLA) associated with RA, and shared epitope.[2,3,7,8,12-18] Other factors are disease activity score, gender, disability index, age of onset, type of onset, extra-articular symptoms, thrombocyte, hemoglobin, matrix metalloproteinase, anti-cyclic citrulinated peptide, and educational level.[5,7,8,17-20]

To the extent of our knowledge, until today there has not been any research on predictor of RA joint damage in Indonesia; thereby, we conducted a study to determine the factors that can predict the RA joint damage of patients in Jakarta.

METHODS

This is a cross sectional study conducted at the Division of Rheumatology of the Department of Internal Medicine, University of Indonesia School of Medicine/Cipto Mangunkusumo General Hospital (CMGH), Jakarta from October 1, 1999 until June 30, 2000. The inclusion criteria included RA patients who fulfilled the 1987 American College of Rheumatology (ACR) criteria, underwent treatment at the rheumatology clinic at CMGH, suffered RA for more than two years, had age of onset of more than 16 years old, was either in polycyclic or

progressive category, had laboratory test result of ESR and or CRP and or RF during initial treatment, and gave consent to be part of the study. The exclusion criteria included those who suffered from other types of arthritis or refused to take part in the study.

Based on the medical records in the rheumatology clinic at CMGH, patients' medical records with diagnosis of RA were selected. An evaluation was carried out based on the medical record. If it met the 1987 RA criteria according to the ACR, the patient was asked to perform a follow-up at or visit the rheumatology clinic at CMGH. If it was not possible, the patients would be visited at their home. The patient's history was taken and physical examination was performed. If the patient obviously met the inclusion criteria and did not meet the exclusion criteria, she would be included as sample in the study. The medical data recorded were (1) name, age, gender, address, and education level; (2) age of onset; and (3) RF, ESR, and CRP at the initial treatment. During the study, RF, CRP, ESR, and radiograph of left and right hand and wrist joints were examined and later Larsen score was determined.

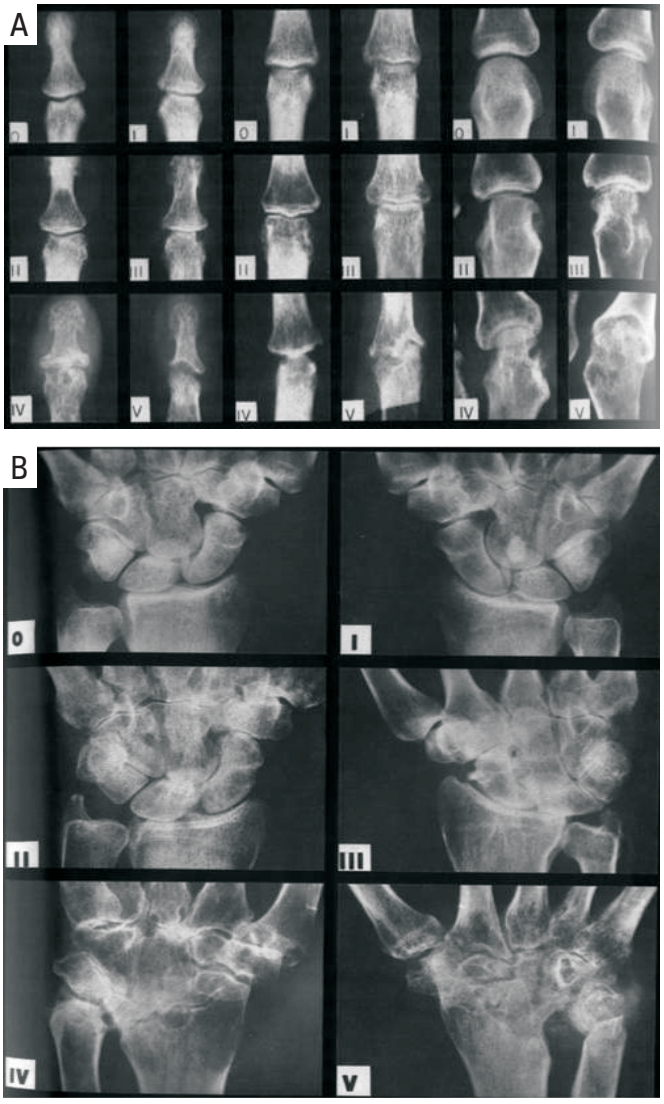


Figure 1 Radiographic grading of Larsen score: (A) interphalangeal joint; (B) metacarpophalangeal joint. (Adapted from Larsen et al, 1977)[21]

Positivity and level of rheumatoid factor at the initial treatment was taken from the patient's medical record. Rheumatoid factor test at the initial treatment used a semiquantitative method using dilutions. It was positive if the dilution factor was > or = 160. During this study, RF test was conducted using RapiTex RF, a semiquantitative method for RF examination in which the value is positive when RF is greater than or equal to 20 IU/mL.

Table 1 Rheumatoid factor changes from initial treatment to the time of the study

Group	Rheumatoid factor I	Rheumatoid factor II
1	negative	negative
2	positive	negative
	negative	positive
3	positive	positive

C-reactive protein at the initial treatment and during the course of disease was taken from the medical record while CRP during the study was examined using RapiTex CRP which is a semiquantitative method for CRP examination.

Erythrocyte sedimentation rate at the initial treatment and during the course of disease was taken from the medical record while during this study ESR test was conducted again.

The degree of joint damage was determined by using modified Larsen score. In this method, radiographs in postero-anterior view of the left and right wrist, hand, and fingers were done. The joints evaluated were those of the wrist, metacarpophalanx (MCP), proximal interphalanx (PIP), and interphalanx I. The film of the radiograph was evaluated by comparing with a standard film.

The degree of damage of each joint was then totaled up. This total value was the Larsen score that ranged from 0 to 110. In this study, what was meant by modification was the modification of the joints being evaluated. In the original method the joint being evaluated was not mentioned. In our modification, the ones being evaluated were of the wrist, MCP, and PIP. The distal interphalangeal joint was not examined because it rarely suffered RA. Reading and evaluation of the radiographic findings were performed by a radiologist specializing in musculoskeletal field in the Department of Radiology at CMGH, Jakarta.

A correlation analysis between age of onset, duration of disease, educational level, ESR, CRP, RF respectively and modified Larsen score was performed. Variables that had a significant correlation with the Larsen score in the bivariate analysis were then analyzed using linear regression with duration of disease as the control variable to determine variables that were significant in determining the Larsen score.

RESULTS

Of the 42 RA outpatients visiting the rheumatology clinic at CMGH Jakarta from October, 1999 until June, 2000, 23 RA patients fulfilling the criteria were recruited. The patients in this study were all women aged between 23 and 59 years with a mean age of 41.9 years, in which 65% of them were less

than 50 years old. In terms of level of education, 4 patients (17.4%) had a level of < or = middle school and 19 (82.6%) had a level of > or = high school. Laboratory findings could be seen in table 2. Twenty three patients had Larsen scores ranging between 0 and 68 with a mean of 21.7, SD 17.3, and 95% CI 14.2-29.3.

Table 2 Data of laboratory findings (N = 23)

Initial ESR, mm/hr, mean (SD) (range)	77.9 (36.1) (14–138)
Intra-study ESR, mm/hr, mean (SD) (range)	69.5 (26.3) (13–103)
Initial CRP, mg/dL, range (SD)	0–768 (237)
Intra-study CRP, mg/dL, range (SD)	0–768 (184)
Initial RF titer, range	0–5120
Positive initial RF, n (%)	10 (43.5)
Negative initial RF, n (%)	13 (56.5)
Intrastudy RF titer, range	0–2560
Positive intrastudy RF, n (%)	11 (48)
Negative intrastudy RF, n (%)	12 (52)

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor.

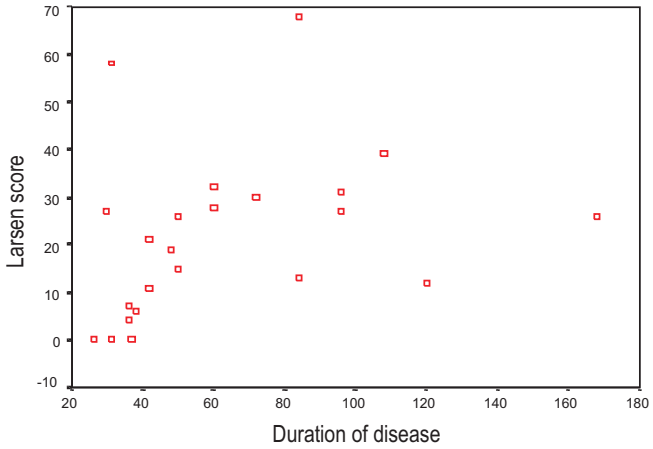
Association between independent variables and Larsen score

Age of onset

The age of onset ranged between 18 and 55 years with a mean of 36.7 years. The majority (78.3%) had age of onset between 21 and 50 years. From the result of bivariate analysis, there was no significant linear correlation between the age of onset and the degree of joint damage according to the modified Larsen score (r = 0.188, p = 0.391).

Duration of disease

The duration of disease of the RA patients ranged between 26 and 168 months with a mean of 62.8 months. From the result of bivariate analysis, it seems that there was no significant linear correlation between the duration of disease and the degree of joint damage according to the modified Larsen score (r = 0.312 and p = 0.148). This was probably caused by one disturbing observation (sample no. 18). If that one observation is ignored/eliminated, there would be a significant linear correlation between the duration of disease and the degree of joint damage according to the modified Larsen score (r = 0.457 and p = 0.032).



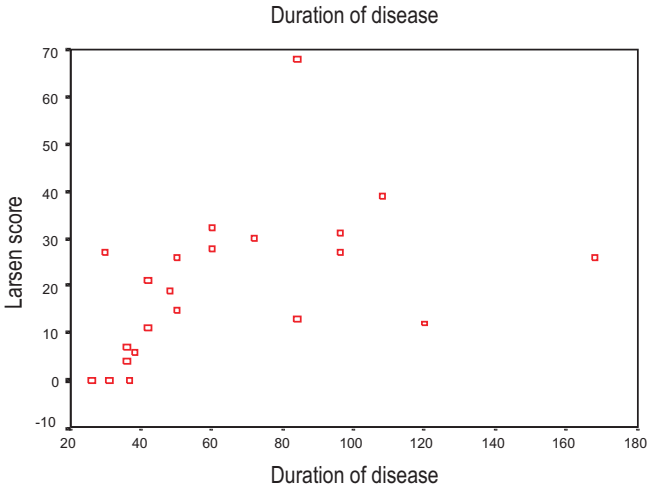


Figure 2 Scattered diagram of the correlation between the duration of disease and Larsen score of all samples (top) and with one extreme observation eliminated (bottom).

Level of education

The majority of patients (83%) had a high school degree or above. In group 1 (< or = middle school), the mean Larsen score was 32.25 ± 20.71 with a median of 30.0 while in group 2 (> or = high school), the Larsen score was 19.53 ± 16.53 with a median of 19.0. The trend of the median Larsen score was lower in those with higher education than in those with lower education although in the Mann-Whitney test, there was no significant difference between the two groups (p = 0.255).

Erythrocyte sedimentation rate

At the initial treatment, there were two patients with normal ESR, one patient without initial ESR data, and the rest with elevated ESR. The initial ESR ranged between 14 and 138 mm/hr with a mean of 77.9 mm/hr. From bivariate analysis, there was no significant correlation between the initial ESR and the Larsen score (r = 0.000…, p = 0.999…).

During the period of this study, we performed ESR tests. Of the 23 patients studied, ESR was between 13 and 103 mm/hr with a mean of 69.7 mm/hr. From bivariate analysis, there was a significant linear correlation between the ESR during the study and the degree of joint damage according to the Larsen score (r = 0.427, p = 0.042).

C- reactive protein

During the initial treatment, 12 patients did not have initial CRP data. There were only 11 patients who had CRP data with scores ranging between 0 and 768 mg/dL with a mean of 192 mg/dL. From bivariate analysis, there was no significant correlation between the CRP at initial treatment and the Larsen score. During the period of study, the CRP values of 23 patients were between 0 and 768 mg/dL with a mean of 178.6 mg/dL. From bivariate analysis, there was a significant correlation between CRP and the degree of joint damage according to the Larsen score (r_s = 0.549, p = 0.007)

Rheumatoid factor

During the initial treatment, RF test was performed on 20 patients using semiquantitative method, 2 patients using quantitative method, and one patient using qualitative method. From the last three patients above, only the positivity of RF was recorded. Positive RF was found in 10 (43.5%) cases with 95% CI 30-70%. The value of Larsen score in the positive initial RF group was 30.5 ± 19.9 while the value of Larsen score in the negative initial RF group was 15.0 ± 12.1.

From the T-test analysis, there was a significant difference in the value of Larsen score between the two groups (p = 0.031). The RF values of the 20 patients whose initial RF were examined semiquantitatively ranged between 0 and 5120. From bivariate analysis, we found that r_s = 0.388 and p = 0.091.

During this study we also evaluated the role of RF changes, that is, the RF during initial treatment and the RF during the period of study. According to one-way analysis of variance (ANOVA), there was a significant difference in the Larsen score between those who always had negative RF and those who had once positive RF (either during the start of treatment or during the period of study) (p_{1-2} = 0.015), and between those who always had negative RF and those who always had positive RF (p_{1-3} = 0.034).

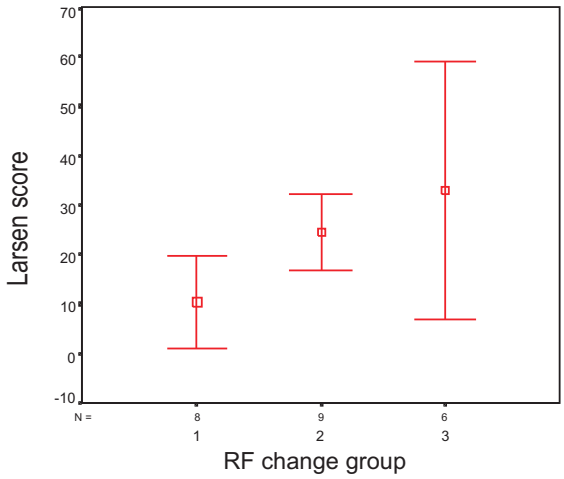


Figure 3 Mean value and 95% CI of the Larsen score of rheumatoid factor (RF) 1, 2, and 3 change group. Larsen score in group 1 = 10.3 ± 11.2, group 2 = 24.4 ± 10.1, group 3 = 33.0 ± 24.9.

Multivariate analysis

As the number of cases (N) = 23 in this study, multivariate analysis was limited to include only two independent variables. It was decided that the duration of disease became the control variable because it is an important factor of joint damage.

Level of initial rheumatoid factor and duration of disease

The result of the linear regression analysis between the initial RF level and the duration of disease, and the degree of joint damage according to Larsen score is seen in table 3.

Table 3 Linear regression analysis between initial rheumatoid factor (RF) level and the duration of disease and Larsen score

Variable	Coefficient B	95% CI-B	t test significance
RF 1	0.0079	0.003–0.01	0.003
Duration of disease	0.215	0.017–0.41	0.035
Constant	2.275	−10.177–14.727	0.705

R^2 = 0.575, regression analysis of variance (ANOVA) test significance = 0.001.

From the result of the above analysis, we can see that 57.5% change in the Larsen score after two years was determined by the duration of disease and the RF level at initial treatment with a level of significance of 0.001. For every 20 fold dilution of RF, the Larsen score changed as much as 0.158.

Positivity of initial rheumatoid factor and the duration of disease

The linear regression analysis between the positivity of RF and the duration of disease, and the degree of joint damage according to Larsen score can be seen in table 4.

Tabel 4 Linear regression analysis between the positivity of initial rheumatoid factor (RF) and the duration of disease and Larsen score

Variable	Coefficient B	95% CI	t test significance
Duration of disease	0.094	−0.114–0.302	0.357
Positive initial RF	13.492	−1.203–28.187	0.070
Constant	9.967	−4.507–24.441	0.166

R^2 = 0.237, regression analysis of variance (ANOVA) test significance = 0.067.

From the result of the analysis above, 23.7% change of the Larsen score was determined by the duration of disease and the positivity of initial RF with a level of significance of 0.067. After 2 years or more, patients with positive initial RF had 13 points higher in the Larsen score for the degree of joint damage than that of patients with a negative initial RF.

Change of positivity of rheumatoid factor and duration of disease

The change of RF positivity is categorized into 3 groups as seen in table 1. For linear regression analysis between the change of RF positivity and the duration of disease, and Larsen score, a dummy variable of RF change was created first as follows:

Delta A = 1 if the RF change was equal to 1
= 0 if the RF change was not equal to 1
Delta B = 1 if the RF change was equal to 3
= 0 if the RF change was not equal to 3

Table 5 Linear regression analysis between the change from initial rheumatoid factor (RF) to RF taken during study and the duration of disease

Variable	Coefficient B	95% CI-B	t test significance
Duration of disease	0.070	−0.140–0.279	0.494
Delta A	−11.181	−28.886–6.524	0.202
Delta B	8.586	−8.378–25.550	0.303
Constant	18.252	−0.935–37.438	0.061

R^2 = 30.4%, regression analysis of variance (ANOVA) test significance = 0.070.

From the outcome of the above analysis, 30.4% change in the Larsen score was determined by the duration of disease and the change of RF positivity with a level of significance of 0.070.

DISCUSSION

The ratio of men to women in RA patients is 1:3. In this study all the cases comprised of women. In reality, there were male RA patients visiting the rheumatology clinic but they did not fulfill the criteria, therefore, they were not included in this study. A 1997 data of the rheumatology clinic at CMGH showed that the ratio of men to women was 1:8. This is different from data mentioned in literatures. This study could not analyze the role of gender on the degree of joint damage according to Larsen score because all of the patients were women.

The role of age of onset as a predictor of joint damage in RA is still controversial. One author stated that the age of onset of over 50 years is associated with a more severe joint damage but another stated that a young age of onset is the one that is associated with a more severe joint damage.[14] However, both authors did not explain why the age of onset affects degree of joint damage. Our study did not find any significant correlation between the age of onset and the degree of joint damage according to Larsen score. This is in line with the results of a study conducted by Peltoma et al that found the course of disease and progression of radiographic abnormality did not differ between patients with the age of onset of less than 55 years and that of over 55 years.[22]

Joint damage in RA mainly occurs in the first two years of onset of disease, afterwards damage still occurs but at a slower rate,[6,7,23] so that it makes sense if the duration of disease also determines joint damage in RA. However, after two years the degree of joint damage slows down and is affected by various factors such as RF, disease activity, and the degree of inflammation so that we must evaluate whether after two years, the duration of disease should be an important predictor of degree of joint damage in RA. In this study, we found that after an average of five years suffering from RA, only three patients (13%) had a Larsen score of 0 while the rest (87%) already had joint damage ranging from mild to severe. A study by Pincus et al also showed the same result on 58 RA patients in which the erosion in the fifth and eighteenth year were 73% and 96.5%, respectively. Our study found no significant correlation between the duration of disease and the degree of joint damage according to Larsen score ($r = 0.312$, $p = 0.148$), but if one particular observation is eliminated/ignored, a significant linear correlation exist between the duration of disease and joint damage according to Larsen score ($r = 0.457$, $p = 0.032$). This occurred because after more than two years of suffering RA, joint damage progress more slowly so that the duration of disease plays a lesser role in predicting the degree of joint damage in RA.

C-reactive protein is one of the inflammatory markers that is most responsive towards a change in inflammatory condition. Combe reported that the CRP level in severe RA is significantly higher than that in mild RA.[2] Leuwen et al reported that initial CRP level was significantly associated with progression of joint damage after three years.[14] Our study found no significant correlation between initial CRP level and the degree of joint damage according to Larsen score. Our study only found 11 patients who had their initial CRP level written in the medical record and factors affecting the result of CRP tests at initial treatment could not be controlled so that they could have affected the outcome of the study. Joint damage is really the end result of a whole process especially through inflammatory process that occurred in the joints of RA patients so that the ones that are correlated to the joint damage should be the cumulative inflammatory markers (CRP, ESR) evaluated at certain intervals and calculated using area under curve (AUC). This is supported by a study conducted by Leuwen et al that found a significant correlation between CRP AUC and the progression of 3-year joint damage.[14]

In our study, CRP level during the period of study showed a significant correlation with Larsen score ($r_s = 0.549$, $p = 0.007$). This outcome is in line with the outcome of a study conducted by Matsuda Y,[24] that found CRP level after 6 months of treatment was a predictor of the progression of joint damage in early RA. This could occur because CRP level after 2 years displayed the CRP level after patients receive either nonsteroidal anti-inflammatory drugs or disease-modifying antirheumatic drugs (DMARDs) treatment, but if after 2 years of treatment the CRP level was still elevated, it showed that the patient had severe RA that was not responsive to treatment so that it could be assumed that during the 2 years or more of illness, CRP level was also high. This assumption is not entirely true because the course of RA disease often fluctuates: in one period it would be in remission and in another it would be recurrent.

From the data above, we could learn that RA patients who still had elevated CRP levels after adequate treatment would probably experience a more severe joint damage in the future so that patients in this category need to be treated more aggressively with DMARDs.

Our study showed that the correlation between ESR and joint damage had almost the same result as that of CRP test but with a lower level of significance ($r = 0.427$, $p = 0.043$). Some studies showed the same results with CRP.[2,24]

Rheumatoid factor is an autoantibody against Fc IgG. This autoantibody mainly consists of IgM, but other immunoglobulins (G, A, D, and E) are also found. The role of RF in the pathogenesis of RA includes its capability to form an immune complex and activate complement.

The positive RF at initial treatment in this study was found in 43.5% of cases with 95% CI = 30–70%. This outcome is almost the same as that found in other countries in which positive RF was found in 60-90% of cases. Our study found a significant difference in Larsen scores between patients with positive initial RF and those with negative initial RF ($p = 0.031$). This study also found a correlation between initial RF level and Larsen score with a lower level of significance ($r_s = 0.388$, $p = 0.091$). This is also in line with the result of studies conducted by Mottonen,[9] Paimela,[12] and van Zeben.[25] The change from initial RF value to RF value taken during the study also showed a correlation with the degree of joint damage in which the difference in Larsen score was significant enough between patients whose RF were always negative, once been

positive, and always positive. Linear regression test found that initial RF level was a significant predictor in determining joint damage after 2 years in which for every 20 IU/mL change in RF would be followed by a 0.158 change in Larsen score after 2 years with a level of significance of 0.003. This could be stated by the following equation:

$$Y \text{ (Larsen score)} = 2.275 + 0.215 \text{ duration of disease} + 0.0079 \text{ RF level}$$

The outcome of the linear regression test for positivity of initial RF and the duration of disease showed a lower level of significance. This was possibly caused by small number of samples. The outcome of this study was in line with the statement made by Hazes JM who stated that at that time (October 2000) the IgM rheumatoid factor was the only strong predictor of joint damage.[26]

Based on this study, we could learn from the result that RA patients with positive RF, especially those with high levels of RF, should immediately be treated aggressively to reduce the possibility of joint damage in the future.

CONCLUSIONS

In this study we found out that positive RF and higher level of RF at the beginning of treatment were the significant predictive factors for joint damage after two-year duration of disease in female RA patients. C-reactive protein and ESR after two-year treatment were linearly correlated with Larsen score in RA patients. After two years, the duration of disease was still the important factor of joint damage in RA patients.

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