

Correlation of Rheumatoid Factor Serotypes and Computed Tomography Findings in Rheumatoid Arthritis Related Interstitial Lung Disease

SAKTHISWARY R¹, RADHIKA S², SYAHRUL SAZLIYANA S¹,
ABDUL WAHAB A³

¹Department of Medicine, ²Department of Radiology, ³Department of Microbiology and Immunology, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia.

ABSTRAK

Manifestasi ekstra artikular rheumatoid arthritis (RA) adalah penyakit paru-paru interstitial (ILD). RA berkaitan ILD (RA-ILD) dikaitkan dengan morbiditi dan mortaliti yang ketara. Objektif utama kajian ini adalah untuk menentukan korelasi antara serotype faktor rheumatoid (RF) dan keterukan RA-ILD berdasarkan penemuan tomografi komputer (CT). Kami telah mendapatkan sejumlah 100 pesakit RA yang diuji untuk IgA RF, IgG RF dan IgM RF dan melalui imbasan CT dada resolusi tinggi. Tujuh puluh dua pesakit mempunyai perubahan ILD pada HRCT dada dan dimasukkan ke dalam kajian ini. Kami mendapati bahawa skor CT bagi "ground glass" menunjukkan korelasi positif yang signifikan dengan tempoh penyakit dan paras IgA manakala skor fibrosis mempunyai hubungan yang signifikan dengan kovariat-kovariat; usia, tempoh penyakit, tahap IgA, tahap IgG dan tahap anti-CCP. Pada analisis multivariat, hanya tahap IgA sahaja yang ketara ($p < 0.05$, pekali beta standard = 0.604) yang dikaitkan dengan skor "ground glass". Bagi skor fibrosis, tahap dan umur IgA adalah prediktor bebas berdasarkan analisis multivariat, dengan skor < 0.05 dan 0.02 , masing-masing. Sebagai kesimpulan, IgA RF adalah satu-satunya serotype yang secara bebas dikaitkan dengan keterukan RA-ILD.

Kata kunci: penyakit paru-paru interstitial, rheumatoid arthritis, serotaip

ABSTRACT

The most common extra-articular manifestation of rheumatoid arthritis (RA) is interstitial lung disease (ILD). RA related ILD (RA-ILD) is associated with significant morbidity and mortality. The main objective of this study was to determine the

Address for correspondence and reprint requests: Associate Professor Dr. Rajalingham Sakthiswary, Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia. Tel: +603-91456099 Email: sakthis5@hotmail.com

correlation between the rheumatoid factor (RF) serotypes and the severity of RA-ILD based on computed tomography (CT) findings. We recruited a total of 100 RA patients who were tested for IgA RF, IgG RF and IgM RF and had high resolution CT chest performed. Seventy-two patients had ILD changes on HRCT of the chest and were included in this study. We found that the the CT scores for ground glass showed significant positive correlation with disease duration and IgA RF levels whereas the fibrosis scores had significant relationship with multiple clinical covariates i.e age, disease duration, IgA RF levels, IgG RF levels and anti-CCP levels. On multivariate analysis, only IgA levels remained significantly ($p < 0.05$, standardized beta coefficient = 0.604) associated with the ground glass scores. Regarding the fibrosis scores, IgA RF levels and age were independent predictors based on multivariate analysis after adjusting for confounders, with p scores of < 0.05 and 0.02 , respectively. In conclusion, the IgA RF was the only serotype which was independently associated with the severity of RA-ILD.

Keywords: interstitial lung disease, rheumatoid arthritis, serotype

INTRODUCTION

Pulmonary involvement in rheumatoid arthritis (RA) is a major contributor to morbidity and mortality (Koduri et al. 2010; Young et al. 2007). Although pulmonary manifestations encompass the main airway, parenchyma, vasculature and pleura, interstitial lung disease (ILD) in particular, is associated with reduced survival (Bongartz et al. 2010). Up to 10% of RA patients suffer from clinically significant ILD while a substantial proportion have abnormal computed tomography (CT) chest findings despite being asymptomatic (Dawson et al. 2001; Fujii et al. 1993).

There are various biochemical and serological markers to predict the severity of the joints in RA (Sakthiswary et al. 2016). However, the clinical and laboratory determinants of RA related ILD (RA-ILD) are not well defined owing to the paucity of research data in this

regard. In some patients, ILD preceded the onset of articular manifestations. The underlying pathogenesis is poorly understood. It has been postulated that RA-ILD is linked to the presence of citrullinated proteins (Bongartz et al. 2007). These proteins however, were not specific for RA-ILD, as they were found in the lung tissues of patients with idiopathic pulmonary fibrosis and in the broncho-alveolar lavage of heavy smokers (Makrygiannakis et al. 2008).

RA patients who test positive for rheumatoid factor (RF); which is an autoantibody directed against the Fc portion of immunoglobulin G are more prone to develop ILD. In clinical practice, immunoglobulin M (IgM) RF is used to establish the diagnosis of RA. Studies have pointed out that IgA RF may be a more specific prognostic marker than IgM RF in early RA (Teitsson et al. 1984). However,

results have been conflicting on the relationship between the individual RF serotype and extra-articular manifestations. A recent population based study revealed that RF-positive subjects without clinical evidence of RA had a lower forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) than RF-negative subjects (Hwang et al. 2016). The presence of RF may contribute to the pathogenesis of RA-ILD via the antigen-antibody interactions which interferes with the physiological functions of the targeted proteins.

High titres of RF was associated with more aggressive joint disease. The levels of RF may influence the degree of systemic inflammation and organ-specific damage (Giles et al. 2014). Thus, we sought to explore the correlation between the titres of the individual RF serotypes and the severity of the structural damage in RA-ILD based on CT scan.

MATERIALS AND METHODS

Study Population

We randomly selected 100 patients with RA under our Rheumatology Clinic follow-up, to undergo high resolution computer tomography (HRCT) of the chest in addition to RF serotypes testing. Participants were aged above 18 years, met the 2010 ACR/EULAR RA criteria (van der Helm-van Mil & Huizinga 2012), had RA for more than 6 months, were non-smokers, not pregnant and had no known chronic lung disease or lung malignancy based on their medical

records. This study was approved by the Universiti Kebangsaan Malaysia Medical Centre Institutional Review Board and informed consent was obtained from all study subjects.

Outcome Measures

HRCT protocol and scoring system

HRCT of the chest was performed with 1.5mm thick axial sections at 1cm intervals throughout the thorax. Between 25 to 30 images were obtained for each subject. The images were reviewed independently by 2 Radiologists who were blinded to the patients' identities, clinical and laboratory parameters. Each lobe of the lung was scored based on a scoring system proposed by Kazerooni et al. (Kazerooni et al. 1997). Table 1 shows the scoring scheme of each lobe for both alveolar and interstitial abnormalities. Ground glass opacities represented the alveolar findings whereas honeycombing and septal thickening were the interstitial findings. The ground glass and fibrosis scores were on a scale of 0-5, with higher scores for greater involvement of the lobes. For each subject, the maximum ground glass and fibrosis scores were 25, respectively. The scores from both the radiologists were averaged for the purpose of data analysis.

RF serotypes

The different RF isotypes (IgM, IgA and IgG) were measured by using an indirect solid-phase enzyme-linked immunosorbent assay (ELISA; Orgentec

Table 1: CT scoring system

Score	Features	Involvement of the lobe
Ground Glass Score		
0	No ground glass opacity	0%
1	Presence of ground glass opacity	<5%
2	Presence of ground glass opacity	5-24%
3	Presence of ground glass opacity	25-49%
4	Presence of ground glass opacity	50-75%
5	Presence of ground glass opacity	>75%
Fibrosis Score		
0	No fibrosis	0%
1	Interlobular septal thickening, no discrete honeycombing	Not applicable
2	Presence of honeycombing	<25%
3	Presence of honeycombing	25-49%
4	Presence of honeycombing	50-75%
5	Presence of honeycombing	>75%

Diagnostika, Mainz, Germany) involving the highly purified Fc fragment of human IgG which binds to the relevant autoantibody in the test serum. The quantitative analysis for IgM, IgG and IgA RF were calibrated as reported in the kit manual. The procedure was carried out in triplicate. Due to the lack of international reference values, the IgA and IgG RFs were calibrated in arbitrary units (U/ml). For IgM RF, the assay was calibrated based on the international WHO standards. Hence, the following cutoff values were given in the manufacturer’s instructions; 18 U/ml for IgG RF, 18 IU/ml for IgM RF and 15 U/ml for IgA RF.

Other measures

Demographics, past medical and RA disease history were gathered by interviewing the subjects and going through the medical records. The

cumulative dose of methotrexate (MTX) was calculated for all subjects given the association between MTX and ILD (Barrera et al. 1994; Cottin et al. 1996). Twenty-eight joints were examined for swelling and tenderness by a single rheumatologist and RA disease activity was calculated using the Disease Activity Score for 28 joints with erythrocyte sedimentation rate (DAS28-ESR) (Inoue et al. 2007). The Stanford Health Assessment Questionnaire (HAQ) (Maska et al. 2011) was used to determine the functional capacity. Radiographs of the hands and feet were scored using the modified Sharp score (MSS) (Pincus et al. 1997) by a single experienced radiologist who was blinded to the study data. Serum samples from all subjects were obtained for the testing of anti-citrulinated cyclic peptide (CCP) using a commercial kit.

Table 2: Demographic and clinical characteristics of the subjects

		All patients (n = 72)
Age (years)**		53.51 ± 9.24
Gender (%)	Male	10 (13.90)
	Female	62 (86.10)
Race (%)	Malay	39 (54.20)
	Chinese	20 (27.80)
	Indian	13 (18.10)
Duration of Illness (years)**		8.49 ± 5.10
Rheumatoid factor Positive(%)		
Ig M (%)		61 (84.72)
Ig A (%)		61 (84.72)
Ig G (%)		60 (83.33)
Median Ig M titre (U/ml)*		46.08 (0-300)
Median Ig A titre (U/ml)*		18.11 (0-300)
Median Ig G titre (U/ml)*		65.20 (0-299.25)
Anti CCP positive (%)		69 (95.8)
Median Anti CCP titre* (U/ml)		300 (0-300)
ESR (mm/hr)**		63.24 ± 18.49
CRP (mg/dL) **		1.26 ± 0.86
DAS 28**		3.82 ± 1.43
Total MSS*		25.00 (0-189)
HAQ DI*		0.56 (0-2.50)
On methotrexate therapy		48 (66.66)
Median methotrexate dose(mg/week)*		12.5 (0-20.00)
Cumulative methotrexate dose(mg)		1665.50 ± 735.00

ESR: erythrocyte sedimentation rate; CRP: C reactive protein; DAS 28: 28 joint based Disease Activity Score; JSN: joint space narrowing; MSS: Modified Sharp Score; HAQ-DI: Health Assessment Questionnaire Disability Index

Data presented as either counts (percentages), mean ± standard deviation** or median (range)*

Statistical Analysis

All data were analysed using Statistical Package for Social Sciences (SPSS) version 21.0. The continuous variables were tested for normality using Kolmogorov Smirnov test. Data with normal distribution were expressed as mean standard deviation (SD) whereas the data which were skewed

or with no particular distribution, were presented as median range. The relationship between two continuous variables were determined using bivariate correlation analysis. Multivariable linear regression was used to model the association of CT ground glass and fibrosis scores with the panel of RF serotypes and the other clinical covariates while adjusting for

confounders. A p value of less than 0.05 was considered to be significant.

RESULTS

Subject Characteristics

Out of the 100 patients, only 72 had ILD changes on HRCT of the chest and were finally included in this study and the statistical analysis. Subject characteristics were summarised in Table 2. The mean age was 53.5 years with 62% females. The median disease duration was 8.5 years, and the majority were anti-CCP antibody positive. The frequency of RF positivity was comparable across the 3 serotypes (83.33-84.72%). The mean RA disease activity was moderate. All subjects in this study had radiographic joint erosions. However, the mean HAQ DI was less than 1; which indicated no significant functional disability.

As MTX is the anchor drug in the treatment of RA, more than half of the subjects were on this form of therapy either as monotherapy or in

combination with other DMARDs (disease modifying anti-rheumatic drugs). The above subjects were on oral MTX. Apart from MTX, the other conventional synthetic DMARDs used in this study included leflunomide, sulfasalazine and hydroxychloroquine. Fourteen of the subjects were on advanced therapies i.e. tumour necrosis factor inhibitors, interleukin 6 receptor inhibitor or janus kinase inhibitors.

Correlation between RF Serotypes and CT Scores of the Chest

The correlation between the clinical variables and the CT scores are listed in Table 3. The CT scores for ground glass showed significant positive correlation with disease duration and IgA RF levels. Based on the Pearson’s r value, the strength of the relationship was weak for disease duration but moderate for IgA RF levels. The CT scores for fibrosis, on the hand, demonstrated significant correlation with multiple clinical covariates i.e age, disease duration, IgA

Table 3: Correlation of CT scores with clinical covariates and antibodies

Parameters	Ground glass		Fibrosis	
	r*	p value	r*	p value
Age	0.229	0.053	0.334	0.004
Disease duration	0.235	0.047	0.240	0.042
Total MSS	0.058	0.628	0.224	0.145
Cumulative Methotrexate dose	0.039	0.748	0.098	0.413
Ig A	0.608	<0.05	0.576	<0.05
Ig M	0.053	0.660	0.019	0.873
Ig G	0.183	0.124	0.241	0.041
Anti CCP	0.117	0.328	0.319	0.006

MSS: Modified Sharp Score; CCP: citrullinated cyclic peptide; r*: Pearson correlation

RF levels, IgG RF levels and anti-CCP levels. The strength of the relationship between the fibrosis scores and each of the above mentioned factors was weak except for IgA RF levels which was moderate. On multivariate analysis, only IgA RF levels remained significantly ($p < 0.05$, standardized beta coefficient = 0.604) associated with the ground glass scores. As for the fibrosis scores, IgA RF levels and age were independent predictors based on multivariate analysis after adjusting for confounders, with p scores of < 0.05 and 0.02, respectively. The IgA RF was the only serotype which showed significant association with both the ground glass and fibrosis scores in adjusted and unadjusted analyses.

DISCUSSION

This was one of the few studies which investigated the association between CT findings in RA related ILD and the RF serotypes. We found that IgA RF levels had a significant relationship with the severity of ILD in RA. Higher IgA RF levels were associated with higher ground glass and fibrosis scores. The severity of the lung involvement did not parallel the extent of the radiographic joint damage based on the total MSS. This finding suggests that the pathogenesis of ILD in RA in terms of cytokine signalling, citrullination of proteins and antigen-antibody interactions may differ from the joints. Although RA is a systemic inflammatory disease, there maybe a disparity between the lungs and joints with regard to the rate of progression. The lung involvement in

RA has the tendency to progress with time based on our study results which demonstrated a significant correlation between disease duration and the CT scores for ground glass and fibrosis. This finding, however was insignificant on adjusted analyses.

In the last decade, there were several reports (Sakthiswary et al. 2014; Teitsson et al. 1984) on the association between IgA RF and severe manifestations of RA. IgA RF is more specific for RA than IgM and IgG RFs as it is the least frequently found serotype in asymptomatic individuals (Silman et al. 1991). Although the precise role of IgA RF in the pathogenesis of RA remains unclear, IgA RFs form immune complexes (Aho et al. 1995) that are believed to activate an alternative complement pathway with a sequential release of cytokines. This leads to tissue damage which contributes to a vicious cycle of more autoantibodies production through a positive feedback loop mechanism. Our findings were consistent with the results of the study published by Jonsson et al. (Jonsson et al. 1995). Jonsson et al. reported that IgA RF had stronger association with extra-articular manifestations in RA compared to IgM and IgG serotypes. Up to 80% of RA patients who tested positive for IgA RF had one or more extra-articular manifestations in the above mentioned study.

Apart from IgA RF, we found that higher circulating levels of IgG RF and anti CCP autoantibodies correlated with more severe lung fibrosis. Seropositivity in RA has a well established link with the presence of extra-articular manifestations.

However, the relationship between the quantitative measurements of the autoantibodies and the severity of the RA-related ILD lacks convincing evidence. In terms of prognosis, Solomon et al. (Solomon et al. 2016) disclosed that IgM RF and not anti CCP was a predictor of mortality in RA-related ILD. However, the finding was based on univariate analyses.

The fibrosis scores were more correlated with the levels of autoantibodies i.e. IgA RF, IgG RF and anti-CCP compared to the ground glass scores. This can be partially explained by the fact that ground glass pattern on CT imaging is nonspecific. Ground glass opacification encompasses filling of the alveolar spaces and thickening of the interstitium or alveolar walls (Lynch 1996). The predominant pattern of RA-related ILD is usual interstitial pneumonia which is characterised by honeycombing (Kelly et al. 2014) which was measured by the fibrosis scores.

We acknowledge the limitations of our study. Autoantibodies levels tend to fluctuate with time and treatment in RA. The ideal way of testing would be the average values of a few measurements of each autoantibody for every subject. Besides, pulmonary function testing was not performed as part of this study. The relationship between RF serotypes and pulmonary function test parameters would have provided a more comprehensive assessment of the clinical utility of the aforementioned autoantibodies.

CONCLUSION

In conclusion, the IgA RF was the only serotype which was independently associated with the severity of RA-ILD. High level of IgA RF should prompt clinicians to investigate for ILD and treat accordingly.

REFERENCES

- Aho, K., Palosuo, T., Heliövaara, M. 1995. Predictive significance of rheumatoid factor. *J Rheumatol* 22(11): 2186-7.
- Barrera, P., Van Ede, A., Laan, R.F., Van Riel, P.L., Boerbooms, A.M., Van De Putte, L.B. 1994. Methotrexate-related pulmonary complications in patients with rheumatoid arthritis: cluster of five cases in a period of three months. *Ann Rheum Dis* 53(7): 479-80.
- Bongartz, T., Cantaert, T., Atkins, S.R., Harle, P., Myers, J.L., Turesson, C., Ryu, J.H., Baeten, D., Matteson, E.L. 2007. Citrullination in extra-articular manifestations of rheumatoid arthritis. *Rheumatology* 46(1): 70-5.
- Bongartz, T., Nannini, C., Medina-Velasquez, Y. F., Achenbach, S.J., Crowson, C.S., Ryu, J.H., Vassallo, R., Gabriel, S.E., Matteson, E.L. 2010. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. *Arthritis Rheum* 62(6): 1583-91.
- Cottin, V., Tebib, J., Massonnet, B., Souquet, P. J., Bernard, J.P. 1996. Pulmonary function in patients receiving long-term low-dose methotrexate. *Chest* 109(4): 933-8.
- Dawson, J.K., Fewins, H.E., Desmond, J., Lynch, M. P., Graham, D.R. 2001. Fibrosing alveolitis in patients with rheumatoid arthritis as assessed by high resolution computed tomography, chest radiography, and pulmonary function tests. *Thorax* 56(8): 622-7.
- Fujii, M., Adachi, S., Shimizu, T., Hirota, S., Sako, M., Kono, M. 1993. Interstitial lung disease in rheumatoid arthritis: assessment with high-resolution computed tomography. *J Thorac Imaging* 8(1): 54-62.
- Giles, J.T., Danoff, S.K., Sokolove, J., Wagner, C.A., Winchester, R., Pappas, D.A., Siegelman, S., Connors, G., Robinson, W.H., Bathon, J.M. 2014. Association of fine specificity and repertoire expansion of anticitrullinated peptide antibodies with rheumatoid arthritis associated interstitial lung disease. *Ann Rheum Dis* 73(8): 1487-94.
- Hwang, J., Song, J.U., Ahn, J.K. 2016. Decline of pulmonary function is associated with the presence of rheumatoid factor in Korean health

- screening subjects without clinically apparent lung disease: a cross-sectional study. *Med* 95(19): e3668.
- Inoue, E., Yamanaka, H., Hara, M., Tomatsu, T., Kamatani, N. 2007. Comparison of Disease Activity Score (DAS)28-erythrocyte sedimentation rate and DAS28-C-reactive protein threshold values. *Ann Rheum Dis* 66(3): 407-9.
- Jonsson, T., Arinbjarnarson, S., Thorsteinsson, J., Steinsson, K., Geirsson, A.J., Jonsson, H., Valdimarsson, H. 1995. Raised IgA rheumatoid factor (RF) but not IgM RF or IgG RF is associated with extra-articular manifestations in rheumatoid arthritis. *Scand J Rheumatol* 24(6): 372-5.
- Kazerooni, E.A., Martinez, F.J., Flint, A., Jamadar, D. A., Gross, B.H., Spizarny, D.L., Cascade, P.N., Whyte, R.I., Lynch, J.P., 3rd, Toews, G. 1997. Thin-section CT obtained at 10-mm increments versus limited three-level thin-section CT for idiopathic pulmonary fibrosis: correlation with pathologic scoring. *AJR Am J Roentgenol* 169(4): 977-83.
- Kelly, C.A., Saravanan, V., Nisar, M., Arthanari, S., Woodhead, F.A., Price-Forbes, A.N., Dawson, J., Sathi, N., Ahmad, Y., Koduri, G., Young, A., British Rheumatoid Interstitial Lung, N. 2014. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics-a large multicentre UK study. *Rheumatology* 53(9): 1676-82.
- Koduri, G., Norton, S., Young, A., Cox, N., Davies, P., Devlin, J., Dixey, J., Gough, A., Prouse, P., Winfield, J., Williams, P. 2010. Interstitial lung disease has a poor prognosis in rheumatoid arthritis: results from an inception cohort. *Rheumatology* 49(8): 1483-9.
- Lynch, D. A. 1996. Ground glass attenuation on CT in patients with idiopathic pulmonary fibrosis. *Chest* 110(2): 312-3.
- Makrygiannakis, D., Hermansson, M., Ulfgren, A. K., Nicholas, A.P., Zendman, A.J., Eklund, A., Grunewald, J., Skold, C.M., Klareskog, L., Catrina, A.I. 2008. Smoking increases peptidylarginine deiminase 2 enzyme expression in human lungs and increases citrullination in BAL cells. *Ann Rheum Dis* 67(10): 1488-92.
- Maska, L., Anderson, J., Michaud, K. 2011. Measures of functional status and quality of life in rheumatoid arthritis: Health Assessment Questionnaire Disability Index (HAQ), Modified Health Assessment Questionnaire (MHAQ), Multidimensional Health Assessment Questionnaire (MDHAQ), Health Assessment Questionnaire II (HAQ-II), Improved Health Assessment Questionnaire (Improved HAQ), and Rheumatoid Arthritis Quality of Life (RAQoL). *Arthritis Care Res* 63(Suppl 11): S4-13.
- Pincus, T., Larsen, A., Brooks, R.H., Kaye, J., Nance, E.P., Callahan, L.F. 1997. Comparison of 3 quantitative measures of hand radiographs in patients with rheumatoid arthritis: Steinbrocker stage, Kaye modified Sharp score, and Larsen score. *J Rheumatol* 24(11): 2106-12.
- Sakthiswary, R., Omimah, K., Endom, I., Shaharir, S., Sridharan, R. 2016. Serum matrix metalloproteinase-3 predicts radiographic joint damage and functional disability in rheumatoid arthritis. *Med & Health* 11(2): 209-17.
- Sakthiswary, R., Shaharir, S.S., Mohd Said, M.S., Asrul, A.W., Shahril, N.S. 2014. IgA rheumatoid factor as a serological predictor of poor response to tumour necrosis factor alpha inhibitors in rheumatoid arthritis. *Int J Rheum Dis* 17(8): 872-7.
- Silman, A.J., Ollier, B., Mageed, R.A. 1991. Rheumatoid factor detection in the unaffected first degree relatives in families with multicase rheumatoid arthritis. *J Rheumatol* 18(4): 512-5.
- Solomon, J.J., Chung, J.H., Cosgrove, G.P., Demoruelle, M.K., Fernandez-Perez, E.R., Fischer, A., Frankel, S.K., Hobbs, S.B., Huie, T.J., Ketzer, J., Mannina, A., Olson, A.L., Russell, G., Tsuchiya, Y., Yunt, Z.X., Zelarney, P.T., Brown, K.K., Swigris, J.J. 2016. Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. *Eur Respir J* 47(2): 588-96.
- Teitsson, I., Withrington, R.H., Seifert, M.H., Valdimarsson, H. 1984. Prospective study of early rheumatoid arthritis. I. Prognostic value of IgA rheumatoid factor. *Ann Rheum Dis* 43(5): 673-8.
- van der Helm-van Mil, A.H., Huizinga, T.W. 2012. The 2010 ACR/EULAR criteria for rheumatoid arthritis: do they affect the classification or diagnosis of rheumatoid arthritis? *Ann Rheum Dis* 71(10): 1596-8.
- Young, A., Koduri, G., Batley, M., Kulinskaya, E., Gough, A., Norton, S., Dixey, J. 2007. Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. *Rheumatology* 46(2): 350-7.

Received: 12 Jul 2019

Accepted: 27 Aug 2019