

Rheumatoid Factor and Its Association with Disease Severity and Functional Status of Rheumatoid Arthritis Patients

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Abstract

This study aimed to determine the prevalence of positive rheumatoid factor (RF) status, its association with disease severity and functional disability of rheumatoid arthritis (RA) patients. A preliminary, cross sectional study was conducted on 46 RA patients. Blood samples were analysed for erythrocyte sedimentation rate (ESR) and RF levels. Socio-demographic data, disease activity score for 28 joints (DAS28), and modified Health Assessment Questionnaire (mHAQ) score were recorded.

The prevalence of positive rheumatoid factor (RF) in RA patients was 63.0%. The mean \pm SD for DAS28 Score and mHAQ Score were 3.52 ± 1.13 and 0.47 ± 0.61 respectively. Most RA patients (47.8%) had moderate disease severity and mild functional difficulty (89.1%). Pain severity is the only factor which had significant association with functional difficulty ($p < 0.001$). However, no significant association between RF status and disease severity ($p = 0.891$) and between RF status and functional difficulty ($p = 0.269$).

Positive RF status was prevalent in RA patients. Most patients experienced moderate disease severity and mild functional difficulty. Pain severity had significant association with functional difficulty. However, RF status was not significantly associated with disease severity and functional difficulty. RA obviously affects functional ability of RA patients. Thus, early diagnosis and therapeutic intervention is crucial to prevent long term complication and improve the quality of life.

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Introduction

Arthritis Foundation of Malaysia in 2011 reported that rheumatoid arthritis (RA) affects 5 in 1000 adult population in Malaysia ranging from 25 to 50 years old. Evidence from Malaysian Epidemiological Investigation of Rheumatoid arthritis (MyEIRA)¹ conducted by Malaysian Ministry of Health Consensus showed musculoskeletal disorders ranked RA as the third disease mostly common in female which definitely confounding as 53.5% of adult woman in Malaysia participated in the labour force.² National Inflammatory Arthritis Registry reported

that 52% of patients indicated that their unemployment to their disease approving that RA has a socioeconomic impact to the society.³

RA is a chronic autoimmune disease which causes inflammation and progressive destruction of synovial joints cartilage and bones as a result of the pannus tissue formation which leads to severe disability and premature death.⁴ The inflammation and damage of joints caused by RA have no ultimate cure, but it can be controlled by disease modifying anti-rheumatic drugs (DMARD), corticosteroids and/or non-steroidal anti-inflammatory drugs (NSAIDs). RA is treated to limit the progression of the disease and extend the productive life of patients, thus maintain their socioeconomic status in the family. Even though the pathogenesis of RA remains unclear, previous study hypothesized that T cells and B cells produce antibodies to protect from infection or diseases that abnormally attack healthy cells which later causing swelling, tenderness, and restricted joint movements.⁵

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RA was detected with the presence of elevated RF in the blood plasma and synovial fluids which accumulate over time.⁶ RF is an antibody recognizing the Fc or conserved portion of human antibodies.⁷ It presents in 60% to 90% of RA patients with established RA but in less than 50% of patients with early RA.⁸ RA was initially discovered by Erik Waaler by the detection of rheumatoid factors (RF) such as anti-immunoglobulin G (IgG), anti-IgM and anti-IgA.⁹ Positif RF can be found in 80% of RA patients and had been included as an effective tool in diagnosis of rheumatoid arthritis by American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria.¹⁰ However, RF had lower sensitivity (70-75%) and specificity (80-85%) as it may present in other autoimmune diseases, infections and not all RA patients had positive RF.¹¹

RA management was very vital to improve patient's health, prevent functional disability as well as adherence to medication regimens. Investigating disease activity, physical damage that lead to functional disability, global health assessment, pain score, grip strength and fatigue was a complex measure in determining RA severity. Thus, disease activity score of 28 joints (DAS28) was globally used for therapeutic decision-making.¹² Additionally, health assessment in RA patients is assessed to evaluate regarding perceived patients' satisfaction of daily activities with perceived change in the degree of difficulty. Among various types of instrument used in monitoring the functional ability in RA, modified Health Assessment Questionnaire (mHAQ) was simple, short, easy to score, and had been extensively investigated making it useful in studies on prognosis, thus it showed more sensitive when patients treatment modification were done.¹³ This study aimed to investigate the concentration of serum RF in RA patients and its association with severity disease and functional status of the patients.

Materials and methods

This cross-sectional study was conducted at Rheumatology Clinic, Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan from September 2019 until January 2020. A total of 46 RA patients aged 18 years old and above were

included. Pregnant woman, lactating mother, smokers, patients with autoimmune diseases such as systemic lupus erythematosus (SLE); chronic liver disease, renal diseases, haematological malignancies, uncontrolled chronic illnesses such as diabetes mellitus, hypertension, cardiovascular diseases, and patients with infectious diseases such as tuberculosis and AIDS were excluded. The established diagnosis of RA was made by the attending physician based on the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 classification criteria.¹⁰ Convenience sampling method was used for patients' recruitment. Written informed consent was obtained from all patients. Socio-demographic data including age, sex, race, marital status, education level, employment status, co-morbidities and disease duration were obtained using data collection form and medical records. This study protocol was approved by Universiti Sains Malaysia Human Research and Ethics Committee (USM/JEPeM/16030138).

RF level and ESR measurement

A standard venepuncture procedure was employed to collect 5 millilitres of blood from antecubital vein of each participant for RF and ESR analysis. The blood samples were centrifuged and stored in refrigerator at -80°C until assayed. The RF level was analysed according to manufacturer's instruction using the RF Direct Latex Test (VEDALAB, Cerise, France). RF level of more than 8 IU/mL is considered positive. ESR (mm/hr) was measured using the Westergren method.

RA disease activity

Disease activity of RA patients was assessed by using the Disease Activity Score-28 (DAS28). The DAS28 is a composite score derived from the following 4 measurements: 1) number of swollen joints out of 28 joints of the shoulder, elbow, wrist, hand and knee, 2) number of tender joints out of the 28 joints of the shoulder, elbow, wrist, hand and knee, 3) ESR, and 4) global assessment of health, indicated by marking on a 10cm line of the Visual Analogue Scale (VAS) to represent their perception of their current pain intensity between "no pain" at the left terminus and "worst pain" at the right terminus. The distance (mm) from the left terminus indicates pain intensity from a range from 0 to 100. A higher score indicates greater pain

intensity and worse global health. An online DAS28 calculator (<http://www.4s-dawn.com/DAS28/>) was used to compute and produce the overall DAS28 score. Disease severity was classified according to the European League against Rheumatism (EULAR) response criteria as follows: ≤ 3.2 =low disease activity; >3.2 and ≤ 5.1 =moderate disease activity and >5.1 =high disease activity. A DAS28 value of ≤ 2.6 implies remission.¹⁴

Functional status

Functional status of the participants was measured using the modified Health Assessment Questionnaire (mHAQ). The self-administered mHAQ comprises of 8 items to evaluate patient difficulty with the following activities of daily living over the course for the past week: 1) dressing, 2) getting in and out of bed, 3) lifting cup or glass to mouth, 4) walking on flat ground, 5) body washing and drying, 6) bending and picking up clothing from floor, 7) turning faucets on and off, and 8) getting in and out of car. The ability to perform the activities are rated on a 4-point Likert scale where 0=without any difficulty, 1=with some difficulty, 2=with much difficulty, and 3=unable to do. The score of all items are added and divided by 8 to generate the mHAQ score, ranging from 0 to 3. Higher scores indicate worse function and greater disability. Additionally, the score can be interpreted as follows: ≤ 1.3 =mild, >1.3 and ≤ 1.8 =moderate and >1.8 =severe.¹⁵

Statistical analysis

All data were analysed using IBM SPSS version 24.0 software. Numerical data were reported as mean and standard deviation (SD) or median and interquartile range (IQR). The categorical data were described in frequency and percentage (%). Mann-Whitney U test was used to determine the association between RF status and disease severity, as well as RF status and functional status of the participants. Factors associated with functional status were analysed using simple and multiple linear regression.

Results

Socio-demographic characteristics of participants

Table 1 shows socio-demographic characteristics of the participants. Most of them aged between 30 to 59 years with the mean age of 54.14 (SD 12.77) years. Majority of them were female (80.4%), Malay (89.1%) and married

(87.0%). The highest education level for most participants was upper secondary school (37.0%) and majority of them were unemployed (58.7%).

Characteristics	Mean (SD)	Frequency (%)
Age (Years)	54.14 (12.77)	
<30		2 (4.3)
30-59		28 (60.9)
≥ 60		16 (34.8)
Sex		
Female		37 (80.4)
Male		9 (19.6)
Ethnicity		
Malay		41 (89.1)
Chinese		2 (4.3)
Indian		1 (2.2)
Others		2 (4.3)
Marital status		
Single		6 (13.0)
Married		40 (87.0)
Educational Level		
Primary school		8 (17.4)
Lower secondary school		7 (15.2)
Upper secondary school		17 (37.0)
Post-secondary school		6 (13.0)
Tertiary		8 (17.4)
Employment status		
Employed		19 (41.3)
Unemployed		27 (58.7)

Table 1. Socio-demographic characteristics of participants (n=46).

Clinical characteristics of participants

Most patients (93.5%) were treated with DMARDs, NSAIDs or corticosteroids (Table 2). The mean disease duration was 4.74 (SD 4.86) years and most of them had positive RF status (78.3%), moderate disease severity (47.8%) and mild functional difficulty (89.1%).

Mean scores for mHAQ items

The mean mHAQ score was 0.47 (SD 0.61), indicating mild functional difficulty. The mean scores for mHAQ items are shown in Table 3. Bending down to pick up clothing from the floor had the highest mean score, followed by getting in and out of bed, and getting in and out of bus, car, train or airplane.

Clinical characteristics	Frequency (%)	Mean (SD)
Medication		
Yes	43 (93.5)	
No	3 (6.5)	
Presence of comorbidity		
Yes	20 (43.5)	
No	26 (56.5)	
Disease duration (year)		
<5	29 (63.0)	4.74 (4.86)
5-10	12 (26.1)	
>10	5 (10.9)	
Rheumatoid factor		
Positive	36 (78.3)	
Negative	10 (21.7)	
Pain severity (VAS score)		
		3.63 (2.07)
ESR (mm/hr)		
		43.57 (31.72)
Disease severity (DAS28 score)		
		3.52 (1.13)
Remission (≤ 2.6)	11 (23.9)	
Low ($2.6 < \text{score} \leq 3.2$)	9 (19.6)	
Moderate ($3.2 < \text{score} \leq 5.1$)	22 (47.8)	
High (> 5.1)	4 (8.7)	
Functional difficulty (mHAQ score)		
		0.47 (0.61)
Mild (≤ 1.3)	41 (89.1)	
Moderate ($1.3 < \text{score} \leq 1.8$)	2 (4.3)	
Severe (> 1.8)	3 (6.5)	

Table 2. Clinical characteristics of participants (n=46).

For the past week, are you able to...	Mean (SD)
Dress yourself, including tying shoelaces and doing buttons?	0.37 (0.74)
Get in and out of bed?	0.57 (0.75)
Lift a full cup or glass to your mouth?	0.37 (0.71)
Walk outdoors on flat ground?	0.41 (0.69)
Wash and dry your entire body?	0.46 (0.78)
Bend down to pick up clothing from the floor?	0.65 (0.87)
Turn regular faucets on and off?	0.46 (0.75)
Get in and out of bus, car, train or airplane?	0.48 (0.75)

Table 3. Mean scores for mHAQ items (n=46).

Variable	Median (IQR)		Z statistics	p value
	RF positive	RF negative		
DAS28 score	0.25 (0.72)	0.25 (0.97)	-0.137	0.891
mHAQ score	3.40 (1.60)	3.87 (1.98)	-1.106	0.269

Table 4. Association between RF status and disease severity and level of functional difficulty of participants (n=46).

Association between RF status, disease severity and functional difficulty

The association between RF status, disease severity and level of functional difficulty are shown in Table 4. No significant association was found between RF status and disease severity ($p=0.891$), as well as between

RF status and level of functional difficulty ($p=0.269$).

Factors associated with level of functional difficulty

Table 5 shows the results of simple linear regression analysis of factors associated with participants' functional status. At univariable level, pain severity (VAS score) was the only factor significantly associated with functional status (mHAQ score) (crude regression coefficient, $b=0.179$, 95% CI=0.11-0.25). Age, sex, marital status, employment status, RA duration, intake of medication, presence of comorbidity, RF status, diseases severity, and ESR level not influence the functional difficulty of patients. Additionally, pain severity remained the only factor significantly associated with functional status of participants at multivariable level (adjusted regression coefficient, $b=0.179$, 95% CI=0.11-0.25). The positive linear relationship indicates that if the VAS score increases by 1 unit, the mean mHAQ score of the participants increases by 0.179 unit, meaning that the more severe the pain, the higher the level of functional difficulty. The model explains 37% of variation of mHAQ score in this study ($R^2= 0.37$).

Variable	Simple Linear Regression		
	b	(95% CI)	p value
Age (year)	0.006	(-0.01, 0.02)	0.422
Sex			
Male*			
Female	0.253	(-0.20, 0.71)	0.268
Marital status			
Single*			
Married	0.034	(-0.51, 0.58)	0.899
Employment status			
No*			
Yes	-0.023	(-0.39, 0.35)	0.902
Comorbidity			
No*			
Yes	0.257	(-0.10, 0.62)	0.158
Medication			
No*			
Yes	0.054	(-0.69, 0.79)	0.883
Pain severity (VAS score)#	0.179	(0.11, 0.25)	<0.001
Rheumatoid Factor status			
Negative*			
Positive	-0.122	(-0.56, 0.32)	0.582
Disease activity score (DAS28)	0.105	(-0.06, 0.27)	0.194
ESR (mm/h)	0.004	(-0.00, 0.01)	0.123
Disease duration (year)	0.000	(-0.04, 0.04)	0.981

Table 5. Factors associated with level of functional difficulty of participants (n=46).

b=crude regression coefficient

*Reference category

#Multiple linear regression analysis showed that pain severity was the only factor associated with participants' level of functional difficulty (Adjusted regression coefficient=0.179, 95% CI=0.11-0.25)

Discussion

In this present study, the mean age of RA patients was 54.14 years. This result is almost similar to study by Sulaiman et al¹⁶ with the mean age of 52.9 years. Majority of patients were female (80.4%), indicating RA is mainly occur in middle age women consistent with female preponderance as demonstrated in previous local studies in Malaysia.^{17, 18} Most patients were from Malay ethnic group, followed by Chinese and others. This reflects the demographic pattern of Malaysian population in which Malay is the main ethnic group followed by Chinese and other races.¹⁷

Most patients were treated with anti-rheumatic drugs. This may influence the disease severity as well as functional disability. This study shows most RA patients had moderate disease activity and mild functional difficulty. Disease score or activity is one of the factors associated with functional difficulty. Oken et al¹⁹ reported the main factors associated with functional disability were disease activity score as reflected in a high score of the DAS-28 ($r=0.68$, $p<0.001$) and disease duration ($r=0.23$, $p<0.05$). In 2002, Molenaar et al²⁰ reported their RA patients in remission showed minimal functional disability and radiographic joint damage.

We found no significant association between RF status and disease severity ($p=0.891$). Similar findings were observed in previous studies.^{21,22} On the contrary, earlier studies^{23,24} reported higher RF titre had significant association with higher disease severity with erosive joints. Conversely, Potter et al²⁵ found that negative RF patients had higher disease activity improvement compared to positive RF status.

This present study shows there is no significant association between RF status and functional difficulty ($p=269$). In 2010, Miriovsky et al²³ reported higher titre of RF among RA patients has significant association with lower functional ability, poorer clinical outcomes and less probability to achieve remission. In addition, Wanruchada et al²⁶ reported RF positive patients were found to had significantly higher

radiographic erosion, lower potential of achieving remission and impaired functional status despite receiving more aggressive treatment with anti-rheumatic drugs. Furthermore, Boyd et al²⁷ claimed that positive RF showed stronger correlation with health assessment questionnaire and DAS28 score.

Pain score was a dominant determinant of functional disability in our patients and has significant association with functional disability. This was in agreement with previous studies.^{28, 29} Although the improvement of joint pain indicates effective treatment, majority of patients still have significant amounts of pain despite therapy. Sokka et al³⁰ reported functional disability of their patients correlated at higher levels with pain scores compared to radiographic scores in small joints.

Disability was one of the most important outcome measures in RA whether improvement after introduction of antirheumatic drugs or effect of RA disease to patient's quality of life. In addition, it also involved complex measures in determining the definite way to predict disability.²⁷

Conclusions

Positive RF was prevalent in RA patients. Most patients had moderate disease activity with mild functional difficulty. Pain score influences the functional disability of RA patients. No significant association between RF status and disease activity as well as functional difficulty in our patients. However, both DAS28 and mHAQ Scores are important tools to assess disease severity and functional disability in RA in monitoring disease progression, assessing the efficacy and side effects of anti-rheumatic drugs. Early diagnosis and early therapeutic intervention improves the clinical outcomes and reduces the accrual of joint damage and disability. Future study with larger sample size is crucial to obtain more convincing findings.

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Declaration of Interest

The authors report no conflict of interest.

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