Impact of Age at Diagnosis on Joint Involvement Patterns in Iraqi Rheumatoid Arthritis Patients

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Running Title: Age at diagnosis in Rheumatoid Arthritis

Abstract: <u>*Objective*</u>*: To assess the pattern of joint involvement in patients with rheumatoid arthritis (RA) diagnosed between the age of 18 - 39 yrs. compared to patients diagnosed at age of 40 - 59 yrs.* <u>*Patients and Methods*</u>*: A total of 200 patients attending the Rheumatology Department in Baghdad Teaching Hospital, Baghdad, Iraq, were enrolled in this cross - sectional study. Patients were diagnosed with RA and classified according to the 2010 ACR/EULAR criteria for RA. Patients were stratified by age at diagnosis into two groups, Group 1 who were 18 - 39 years at RA diagnosis (Young age), (n=100) and Group 2 who were 40 - 59 years at RA diagnosis (Middle age), (n=100). Clinical and ultrasound (US) examinations performed to estimate disease activity score (DSA) and 66/68 joint count assessment.* <u>*Results*</u>*: Median age at RA diagnosis in younger and middle - aged group was 29 yrs. (IQR 18 - 39) and 48 yrs. (IQR (40 - 59), respectively. Positive anti - CCP was found in 79% in younger vs.58% of middle - aged group, p=0.002. US documented arthritis of the hip joints were observed in 20% of the younger group vs.6% in the middle age group (p=0.001. The mean number of swollen joints was 3.6±3.3 in the younger vs.2.4±2.3 for the middle - aged group (p= <0.001). The corresponding mean number of tender joints were 9.1±4.3 in younger vs.7.9±4.5 in the middle - aged group (p=0.05).* <u>*Conclusions*</u>*: Younger adult - onset Iraqi patients suffer more severe RA compared to those diagnosed at higher age. This finding should be taken in consideration in treatment decision and follow - up of patients with RA.*

Keywords: Rheumatoid arthritis, Pattern of joint involvement, young adult onset, Middle age onset

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that impacts the synovial joint and can be associated with socioeconomic burden, premature mortality, and irreversible joint destruction [1]. RA has a worldwide prevalence of about 5 per 1000 adults. The disease affects women 2 to 3 times more often than men [3], its commonly affects patients aged 30–50 years old with a peak incidence in the sixth decade of life [4]. The prevalence of RA among Iraqis was estimated to be 1% of those aged 16 years and older [5]. Although the exact aetiology of RA is yet to be determined, it is believed that RA is a multifactorial disease, with a complex interaction between the host and the environment [6, 7]. The most common presentation is insidious onset (55–65%) of joint pain and swelling, and general symptoms. Less common presentation is an acute onset with pain, joint swelling, stiffness [8]. The chronic joint affection and synovitis may eventually evolved in joint damage and dysfunction [2]. The classical distribution of joint involvement in early disease includes the small joints of the hands and feet as metacarpophalangeal (MCP), proximal interphalangeal joints (PIP), and metatarsophalangeal joints (MTP). In addition, intermediate (wrists, elbows, and ankles) and large (hips, shoulders) joints may become involved. With more advanced and longer duration of disease, RA may also involve other joints, including the temporomandibular joint (TMJ), cricoarytenoid (CAJ) and sternoclavicular joint (SCJ) [9].

Initiation of pharmacotherapy early after the onset of RA induce early remission, reduces the progression of joint damage, and improves long - term outcomes. The European Alliance of Associations for Rheumatology (EULAR) recommends that treatment with a disease - modifying anti - rheumatic drugs (DMARDs) should be initiated as soon as a diagnosis of RA is made because untreated disease does not remit spontaneously (10) Combination therapy with tumour necrosis factor (TNF) and non - TNF biologics with methotrexate (MTX) resulted in improved disease control, Disease Activity Score (DAS) - defined remission, and functional capacity compared with a single treatment of either methotrexate or biologics alone (11). The impact of age at onset on joint manifestations in adult RA was controversial among various previous studies. A study from Colombia (12) revealed that tenderness and limitation of motion scores for most of joints are higher among young age RA patients as compared to older ages. Another Study from Austria (13) reported that ultrasonography showed higher inflammatory changes in older age RA patients in comparison to young age RA patients. A Turkish study (14) found no significant differences in disease activity scores and radiographic scores between young age started RA and older patients.

No previous studies from Iraq addressed the impact on age at first presentation on disease presentation and outcome. In this study we aimed to shade a light on these controversial issues. In this cross - sectional study we assess the pattern and severity of joint involvement in Iraqi patients diagnosed with RA comparing those with disease onset in two different age groups; young adults (18 - 39 years) vs. middle age (40 - 59 years.) using clinical assessment as well as ultrasound in selected joint group.

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Patients and Methods Study design

This cross - sectional study was conducted at the Rheumatology Unit of Baghdad Teaching Hospital in Medical City, Baghdad, Iraq during January to July 2023.

Sample selection

A total of 200 consecutive adult patients diagnosed with RA with active disease they were newly diagnosed or current patients attending our Rheumatology Unit were enrolled in this study. Patients were classified as Rheumatoid Arthritis according to the 2010 ACR/EULAR classification criteria for RA [15]. Patients were stratified by age at diagnosis into two groups, first group (Young age) included 100 patients who were in the age group 18 - 39 years at diagnosis, and the second group (Middle age) included 100 patients were in the age group 40 - 59 years at diagnosis.

Exclusion criteria

1) Adult patients with previous diagnosis with juvenile idiopathic arthritis.
2) Patients diagnosed as RA at the age of 60 years and over.
3) Patients with connective tissue diseases as systemic lupus erythematosus, Sjögren's syndrome, mixed connective tissue disease, overlap disease, seronegative spondyloarthropathies as psoriatic arthritis.

Ethics

Informed consent was obtained from all the participants. The study was performed according to the declaration of Helsinki. Ethical approval was obtained from the Ethics Committee in Medical Department, College of Medicine, University of Baghdad, Baghdad, Iraq (No.194 in16 - 1 - 2023)

Data collection

Data collection were performed using for this study specifically designed Clinical Research Form (CRF). Clinical and demographic data were obtained through case records interview, questionnaires, and clinical examinations. The following data were collected from each patient: demographics, including age at date of inclusion, age at diagnosis of RA, sex, disease duration (time from date of first diagnosis to date of inclusion and assessment in this study), and smoking status. Height in centimetres and weight in kilograms were assessed and body mass index (BMI) was calculated according to the equation BMI=weight / height 2. Data on treatment of RA were also collected. RA disease activity was assessed using clinical disease activity index (CDAI) and disease activity score 28 joints (DAS28). Functional class was recorded according to the following: class1: able to perform usual activities of daily living like self - care, vocational and avocational activities, class 2: able to do self - care and vocational but limited in avocational activities, class 3: able to do self - care but limited in vocational and avocational activities, and class 4: limited in usual self - care, vocational and avocational activities [16]. Data were also obtained on Health assessment questionnaires disability index using the following definitions: HAQDI: mild to moderate disability score 0 to 1, moderate to severe disability score 1 to 2, severe to very severe disability score 2 to 3 [17]. All patients were examined for tender and swollen joints using 68/66 joints count score, for limited range of motion for 68 joints and examined for the presence of hands or feet deformities, as well as presence or absence of

rheumatoid nodules. In addition, information on duration of morning stiffness in minutes were collected. Laboratory results of Erythrocyte Sedimentation Rate (ESR), C - Reactive Protein (CRP), Rheumatoid Factor (RF) and Anti - Cyclic Citrullinated Peptide Antibodies (Anti - CCP) were recorded. Ultrasonographic examination of hip joints were performed for patients with clinically involved hip joints to confirm the diagnosis of hip arthritis and presence of effusion, synovial tissue thickening‹ and/or bone erosions were reported.

Statistical Analysis

Descriptive statistics were employed. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). The differences in the frequency of categorical variables among groups were quantified using X_2 or Fisher's exact test. For continuous and normally distributed variables, data are presented as means (S. D.), and Student's t - test was used for comparison between groups. For continuous and non - normally distributed variables, data are presented as median and interquartile ranges, with the Mann–Whitney U test used for comparison. In all statistical analysis, level of significance (p value) set at ≤ 0.05.

2. Results

The patients

Two - hundred patients (85% females in young age and 89 % female in middle age) were enrolled in this study, with a median age of 39 year for all patients, 32 years for younger group and 51 years for middle - aged group.

Median age at diagnosis of RA in younger and middle - aged group was 29 years (IQR 18 - 39) and 48 years (IQR (40 - 59), respectively, p = 0.001. There was a significant difference in RA disease duration between groups with younger group have longer disease duration (Table 1). Selected clinical and laboratory data are presented in Table 1. The impact of RA expressed by HAQ and functional status was more pronounced in the middle age group (Table 1).

Regarding RA serology, positive anti - CCP was more prevalent among younger patients, however, no differences between groups were observed in other laboratory parameters (Table 1). Sex distribution was equal between the two groups.

Distribution of tender and swollen joints according to study group.

The young age group suffered significantly higher number of tender and swollen joints according to the 28 joint counts compared to the middle age group (Table 2). Similarly, ultrasound documented arthritis were observed in 20% of the younger group compared to 6% in the middle age group (p=0.001, Table 2). The tenderness score in the glenohumeral joints was higher in middle - aged RA patients compared to younger patients (Table 3), the reverse was true for the tenderness score in the wrists, small joints of the hands, hip joints, and small joints of the feet (Table 3). However, no differences were observed in other joints. Overall, younger patients exhibited a higher mean tenderness score in the 68 joint counts compared to middle - aged patients (Table 3). The mean joint swelling score was higher among younger patients

compared to middle - aged patients in the following joints: MCP, PIP joints of the hands, and MTP joints (Table 4). Similarly, the mean joint swollen score at 66 joint counts was higher in the younger group (Table 4).

When limiting the comparison to those with disease duration of less than 10 years, the means of total tender and swollen joints scores were significantly higher among young age compared to middle age group patients. Among RA patients with disease duration of 10 years and longer, the means of total tenderness, swollen joints and limited range of motion scores were significantly higher among young age compared to those of middle age RA patients (p<0.001).

Distribution of limited range of motion measures according to study groups.

The mean motion limitation score of glenohumeral joint was significantly higher among middle age RA patients compared to young RA patients (p=0.03). The mean motion limitation scores of wrists, MCP, PIP, DIP, hip and MTP joints were significantly higher among young age RA patients compared to middle age group (Table 5). The mean motion limitation scores of other joints were not significantly different between RA patients among young age compared to middle age group. The mean total limited range of motion scores of RA patients in young age was significantly higher compared to those of middle age group (p=0.001) as shown in Table (5). Distribution of total 68 joints measures according to study groups among different diseases durations.

3. Discussion

This study is the first in our region to investigate Rheumatoid Arthritis (RA) patients in Iraq, stratifying patients by age into younger and middle - aged groups. We found that younger RA patients have more severe disease presentation compared to their middle - aged counterparts. Significant differences were observed in joint tenderness, joint swelling, and range of joint movement between the two groups. Additionally, younger patients were more likely to test positive for anti - CCP antibodies.

We defined middle - aged individuals as aged 40 - 59 at diagnosis to mitigate the influence of comorbidities associated with older age. Previous research in our region showed that those aged 60 years or older have a higher prevalence of comorbidities such as diabetes mellitus, experience more challenging social circumstances, such as living alone, which may exacerbate symptomatic arthritis [18].

Despite higher tender and swollen joint counts in younger patients, there were no differences in disease activity scores (CDAI and DAS28) between young and middle - aged RA patients at study entry. However, the main finding of our study, more severe disease among young patients, was based on using the 66/68 joint score compared to traditional RA disease activity measures of using CDAI and DAS28. Similar findings of no differences in disease activity measures between young and old age group were reported by a study from Japan [19], suggesting consistency across different populations.

Furthermore, we observed a significant association between higher HAQ - DI scores and middle - aged RA patients compared to their younger counterparts. This aligns with findings from other study [20] supporting the validity of HAQ - DI as a tool for monitoring RA disease activity and treatment response in Iraqi patients [21]. Similarly, the current study uncovered that younger Iraqi patients tend to exhibit better functional status, with a higher proportion falling into Class I compared to older patients. Conversely, in Class II patients, predominantly composed of middle - aged individuals, the opposite trend was observed. This divergence is likely due to younger patients being less likely to having other diseases, while middle - aged individuals are more prone to other comorbidities that could impact their functional status.

These findings align with other Asian cohort study [22] which reported better functional status among young age onset RA patients compared to older age onset RA patients. Another study from Iraq [23] reported that active RA impairs work productivity and functional status. These results are consistent with previous studies demonstrated lower mean scores of tender and swollen joint counts among older age RA patients compared to younger counterparts [24].

Furthermore, our study revealed longer RA disease duration in younger RA patients compared to middle - aged patients. This finding echo results from the Canadian Early Arthritis Cohort (CATCH) study [25], which also found longer disease duration among young age onset RA patients compared to older age onset patients. Other studies [26] have shown that RA disease duration indirectly influences the risk of cardiovascular diseases as long - term disease duration increases the risk of cardiovascular events. A recent Iraqi cross - sectional study also found that patients with longer disease duration less responsive to treatment than those with shorter disease duration [27].

Our study found that ultrasound examination confirmed hip joint involvement was more common in the young age group compared to those in the middle age group. This finding aligns with the results of a study from the United Kingdom [28], which demonstrated ultrasound's ability to detect bone erosions in early RA. However, it contrasts with a study from Austria [13] that reported higher inflammatory changes detected by ultrasonography in older age RA patients compared to younger ones, despite no differences being reported in clinical disease activity. This inconsistency might be attributed to differences in imaging selection for diagnosis and techniques used among different studies.

In the current study, we observed that younger RA patients were more likely suffered an anti - CCP positive disease compared to middle - aged group. This finding was supported by previous studies [29] [30].

The study found that middle - aged RA patients experienced more glenohumeral joint tenderness and motion limitations compared to younger patients, indicating a higher prevalence of shoulder involvement in older age RA patients. These findings are supported by a previous study from Egypt [31]. However, younger RA patients had higher tenderness and motion limitation scores in various joints, including wrists, fingers, hips, and feet. This aligns with findings from a study

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in Colombia [12].

Additionally, younger patients had significantly higher swollen joint scores in metacarpophalangeal, finger proximal interphalangeal, and toe joints, consistent with an Egyptian study. [31]. Overall, younger RA patients showed higher total joint tenderness, swelling, and movement limitation scores than middle - aged patients, supported by two other studies [32, 33]. A Turkish study, however, found no significant differences in disease activity between age groups [14], possibly due to differing rheumatoid disease epidemiology and treatment options across countries.

There are several limitations in our study. First, the patients studied may not be representative of other Iraqi patients receiving rheumatology care in smaller units outside referral centres, necessitating caution in drawing firm conclusions. Second, we do not have data on radiologic progression or long - term follow - up. Third, our study did not discuss the impact of modern therapy, including biologics, on the severity and outcome of RA.

However, our study also has strengths. Patients underwent a thorough clinical and ultrasound assessment by the same team, improving the validity of the results. Furthermore, we assessed many joints affected by RA using the 68/66 joint score, which is not commonly used to assess disease activity. We used this scoring to shed light on other joints that are commonly involved in RA and can be severely affected, impacting daily activities. Additionally, these joints can be affected differently according to the age of patients at RA diagnosis, showing differences from other commonly used scores. We found these differences in our study and recommend further studies to confirm this.

In conclusion, our study demonstrated differences in the severity of RA between patients in different age groups, with younger adult - onset Iraqi RA patients being more severely affected by their disease compared to patients with disease onset at a middle age. This finding should be taken into consideration in the management of RA in Iraq.

Conflict of interest: Authors declare no conflict of interest.

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Table 1: Distribution of RA disease characteristics according to study groups

Variable	Study groups				P. value
	Young age		Middle age		
	No.	100%	No.	100%	
Disease duration					<0.001
<10 years	34	34.0	69	69.0	
≥10 years	66	66.0	31	31.0	
CDAI score					0.19
Remission	1	1.0	0	-	
Low disease	9	9.0	13	13.0	
Moderate disease	52	52.0	61	61.0	
High disease	38	38.0	26	26.0	
DAS28 score					0.88
Remission	3	3.0	2	2.0	
Low disease	4	4.0	4	4.0	
Moderate disease	58	58.0	63	63.0	
High disease	35	35.0	31	31.0	
HAQDI score					0.007
Mild to moderate	40	40.0	23	23.0	
Moderate to	50	50.0	54	54.0	
Severe to very	10	10.0	23	23.0	
Functional status					0.03
Class I	68	68.0	54	54.0	
Class II	26	26.0	43	43.0	
Class III	6	6.0	3	3.0	
ESR					0.8

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Mean±SD	41.3±24.2		40.8±28.6		
		CRP			0.8
Mean±SD (mg/L)	8.9±16		9.3±16.7		
Rheumatoid factor					
Negative	27	27.0	36	36.4	0.15
Positive	73	73.0	63	63.6	
Anti ccp					
Negative	21	21.4	42	42.4	0.002
Positive	77	78.6	57	57.6	

CDAI=Clinical Disease Activity Index (remission=<2, 8, low disease activity >2, 8and=<10, moderate disease activity >10and =<22, high disease activity >22) DAS - 28=Disease Activity Score - 28 (remission<2, 6 - low>2, 6and=<3, 2, moderate >3, 2and=<5, 1_high>5, 1), HAQDI=Health Assessment Questionnaire - Disability Index, ESR=Erythrocyte Sedimentation rate, CRP=C - reactive Protein, RF=Rheumatoid factor, Anti ccp=Anti cyclic citrullinated peptide.

Table 2: Distribution of activity scores according to study groups.

Variable Study Groups				P
TJC28 score				0.05
Mean±SD	9.1±4.3		7.9±4.5	
SJC28 score				<0.001
Mean±SD	3.6±3.3		2.4±2.3	
Patient assessment score				0.2
Mean±SD	5±1.6		5.2±1.3	
Physician assessment score				0.1
Mean±SD	4±1.5		4±1.3	
Hip joint ultrasound				
No.				
No hip	74	74.0	94	94.0	0.001
Hip joint	20	20.0	6	6.0	
Replaced	3	3.0	0	-	
Need but	3	3.0	0	-	

TJC28=Tender Joint Count - 28, SJC28=Swollen Joint Count - 28.

Table 3: Distribution of tender joints measures according to study groups.

Mean tenderness score of joints	Study groups		P
	Young Mean±SD	Middle age Mean±SD	
TMPJ	0.81±0.9	0.77±0.9	0.7
SCJ	0.31±0.7	0.46±0.8	0.15
ACJ	0.55±0.8	0.78±0.9	0.07
GHJ	0.6±0.8	1±0.9	0.002
Elbow	1.2±0.9	1.1±0.8	0.48
Wrist	1.67±0.68	1.36±0.87	0.006
MCPJ	2.7±2.1	2.1±2.2	0.04
PIPJ	1.68±1.8	0.87±1.5	0.001
DIPJ	0.8±1.5	0.23±0.85	0.001
Hip	0.51±0.83	0.24±0.63	0.01
Knee	0.8±0.9	0.97±0.97	0.2
Ankle	1.2±0.9	1±0.96	0.07
Tarsus/mid	1.2±0.9	0.65±0.9	<0.001
MTPJ	3±2.1	1.1±1.9	<0.001
Toe	1.8±2	0.45±1.2	<0.001
Mean total joint tenderness	18.6±8.3	12.4±7	<0.001

TMPJ=Temporomandibular Joint, SCJ=Sternoclavicular Joint, ACJ=Acromioclavicular Joint, GHJ=Glenohumoral Joint, MCPJ=MetacarpoPharngeal Joint, PIPJ=Finger Proximal Interphalangeal Joint, DIPJ= Finger Distal Interphalangeal Joint, MTPJ=Metatarsophalangeal Joint.

Table 4: Distribution of swollen joint measures according to study group.

Mean Swollen score of joints	Study groups		P
	Young age	Middle age	
MPJ	0.17±0.47	0.12±0.4	0.4
SCJ	0.03±0.17	0.03±0.17	1.0
ACJ	0.04±0.2	0.04±0.19	1.0
GHJ	0.09±0.4	0.08±0.3	0.8
Elbow J	0.32±0.6	0.27±0.5	0.5
Wrist J	0.78±0.8	0.64±0.8	0.2
MCPJ	1.17±1.4	0.56±1	0.001
PIPJ	0.7±1.2	0.28±0.7	0.004
DIPJ	0.01±1	0.0±0.0	0.3
Knee J	0.42±0.6	0.49±0.7	0.4
Ankle J	0.61.2±0.8	0.61±0.8	1.0
MTPJ	1.15±1.3	0.48±0.9	<0.001
Toe J	0.51±1	0.25±0.7	0.04
Mean total swollen joints	6.1±4.7	4±3	<0.001

TMPJ=Temporomandibular Joint, SCJ=Sternoclavicular Joint, ACJ=Acromioclavicular Joint, GHJ=Glenohumoral Joint, MCPJ=Metacarpal Pharngeal Joint, PIPJ=Finger Proximal Interphalangeal Joint, DIPJ= Finger Distal Interphalangeal Joint, MTPJ=Metatarsophalangeal Joint. All values are given in mean±SD

Table 5: Distribution of limited range of motion measures according to study group

Limited range of motion	Young age Mean±SD	Middle age Mean±SD	p
TMPJ	0.48±0.7	0.49±0.8	0.7
ACJ	0.44±0.7	0.55±0.8	0.3
GHJ	0.42±0.7	0.76±0.9	0.03
Elbow J	1.1±0.9	0.93±0.92	0.2
Wrist J	1.4±0.8	1.0±0.9	0.004
MCPJ	1.44±1.42	0.92±1.3	0.009
PIPJ	0.59±1.1	0.19±0.7	0.003
DIPJ	0.16±0.6	0.0±0.0	0.001
Hip J	0.42±0.7	0.15±0.4	0.002
Knee J	0.46±0.7	0.53±0.7	0.5
Ankle J	0.97±0.9	0.84±0.9	0.3
MTPJ	0.81±1.2	0.33±0.8	0.001
Toe	0.18±0.6	0.15±0.6	0.7
Mean total limited motion	8.6±4.8	6.5±3.4	<0.001

TMPJ=Temporomandibular Joint, SCJ=Sternoclavicular Joint, ACJ=Acromioclavicular Joint, GHJ=Glenohumoral Joint, MCPJ=Metacarpal Pharngeal Joint, PIPJ=Finger Proximal Interphalangeal Joint, DIPJ= Finger Distal Interphalangeal Joint, MTPJ=Metatarsophalangeals Joint.