

## Determine the Frequency of Extra-Articular Manifestations among Rheumatoid Arthritis Patients

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**Abstract:** Objective: To determine the frequency of extra-articular manifestations among rheumatoid arthritis patients. Subjects and Methods: A total of 110 clinically diagnosed cases of Rheumatoid arthritis (RA) were evaluated in this study. Extraarticular features included renal involvement, Respiratory involvement, pericardial involvement, Sjogren syndrome, rheumatoid nodules, Hematological changes, Felty syndrome, vasculitis were studied. Results: Mean age was 58.3 ±6.9 years. Gender distribution showed female preponderance (Male: Female = 1: 3.2). Results: Extra-articular manifestations of rheumatoid arthritis were diagnosed in 48 (43.6%) patients. Rheumatoid nodules was the most common extra-articular manifestation found in 14 (29.2%) cases followed by hematological manifestation in 12 (25%) cases, carpal tunnel syndrome in 9 (18.8%) cases, respiratory involvement was seen in 7 (14.6%) cases, serositis in 4 (8.3%) cases, eye disease in 3 (6.3%). Conclusion: The prevalence of ExRA during disease course was 43.6%, while rheumatoid nodules was the most common extra-articular manifestation and vasculitides, felty's syndrome, amyloidosis was least common manifestation found in this study. [K.A.Fazlani, B.B.khan, N.K.Sahito. **Determine the Frequency of Extra-Articular Manifestations among Rheumatoid Arthritis Patients.** *N Y Sci J* 2016;9(12):66-69]. ISSN 1554-0200 (print); ISSN 2375-723X (online). <http://www.sciencepub.net/newyork>. 11. doi:[10.7537/marsnys091216.11](https://doi.org/10.7537/marsnys091216.11).

**Keywords:** Rheumatoid arthritis, ExRA, Rheumatoid nodules, Sjogren syndrome.

### 1. Introduction

Rheumatoid arthritis is associated with increased cardiovascular mortality, chronic inflammation may impaired vascular function and lead to and increased of arterial stiffness, Reduce small artery and large artery elasticity and increased systemic vascular resistance and also causes peripheral neuropathy.<sup>1</sup>Lung alteration in Rheumatoid arthritis may be primary or secondary to pharmacological treatment and may involve alveoli, the interstitium, the airway and the pleura. The alterations may significantly impaired lung function and some of them are potentially life threatening.<sup>2</sup> Rheumatoid arthritis a wide spread disease and its Renal Involvement, relatively common, clinically significant because worsen course and mortality of primary disease, kidney injury during Rheumatoid arthritis includes Secondary renal Amyloidosis, nephrotoxic effect of Anti Rheumatic drugs and nephropathies as a Extra articular manifestations.<sup>3</sup>In Rheumatoid arthritis more serious hepatic involvement may also occur which induce vasculitis nodular regenerative hyper plasia and primary biliary Cirrhosis. The eye also represents an important site of involvement and inflammation an important site of involvement and inflammation of the uveal tract is a frequent extra articular feature of rheumatoid arthritis patients.<sup>4</sup> In patients with Rheumatoid arthritis, autoantibodies to glucose phosphate isomerase are associated with the occurrence of extra articular complication

Rheumatoid arthritis (RA) is an autoimmune disease which primarily occur in HLA DR4.<sup>5,6</sup>As the extra articular manifestations are common among the Rheumatoid arthritis patients, this study is design to know the frequency of extra articular manifestations so that these manifestations can be treated in earlier stage and prevent the complications. The objective of the present study was to determine the frequency of extra articular manifestations among Rheumatoid arthritis patients.

### 2. Material & Methods

**Setting:** This study was carried out at Medical Wards and outdoor patients (OPDS).

**Duration:** Duration of study was one year from 20-10-2005 to 19-10-2006.

**Sample size:** Sample size was 110 patients, based on  $P$  (Proportion of extra articular rheumatoid arthritis) = 36.2%<sup>4</sup> = 0.36

$1 - \alpha$  (Confidence level) = 95%

$d$  (Margin of error) = 9%

**Sampling technique:** No probability purposive technique

#### SAMPLE SELECTION

##### Inclusion Criteria

- Clinically diagnosed cases of Rheumatoid arthritis.

##### Exclusion Criteria:

- Rheumatoid arthritis patients which presents with other systemic -disease like, Diabetes mellitus

(D.M), Hepatitis, Ischemic heart disease (I.H.D), Tuberculosis (T.B).

- Non Rheumatoid arthritis.

**Study design:** Descriptive Study.

**Data Collection Procedure:** The patients with rheumatoid arthritis were recruited and enrolled in the study. The extraarticular features included renal involvement explained as urinary excretion of protein more than 500 mg protein/24 hours, cellular casts not related to infection, or else histopathology on renal biopsy. Amyloidosis if confirmed by fine needle aspiration or biopsy. Respiratory involvement defines interstitial lung disease, pleritis, scarring and nodule formation in the lungs documented by HRCT scan of the chest. Pericardial involvement as pericarditis, pericardial effusion was reported in the clinical record as related to rheumatoid arthritis. Neurological involvement was included compression neuropathy (e.g. carpal tunnel syndrome) and peripheral neuropathy. Sjogren syndrome explained as dryness of the mucous membrane (xerostomia) and of the eye (xerophthalmia). Rheumatoid nodules were explained nodules with a diameter  $\geq 5$  mm in the extensor surfaces of the upper and lower limb. Hematological findings included leucopenia WBC count  $< 4 \times 10^9/L$ , thrombocytosis platelet count  $> 400 \times 10^9/L$ , anemia either normochromic, hypochromic or megaloblastic. Felty syndrome is explained neutropenia plus splenomegaly documented on ultrasound in the absence of other causes Rheumatoid vasculitis was considered as the presence of acute peripheral neuropathy or mononeuritis multiplex, histological evidence of necrotizing arteritis, or deep cutaneous ulcers and peripheral gangrene while the data collected was saved in the proforma.

**Data Analysis Procedure:** Data was analysis by Statistical Package for Social Sciences 15.0. Frequencies and percentages were calculated for categorical variables. Chi-Square test was used to compare the proportions.

### 3. Results

One hundred and ten diagnosed cases of rheumatoid arthritis were included in this study. Eighty four patients (76.4%) were women while 26 (23.6%) were men with Male to female ratio was 1: 3.2. Out of 110 cases, 72 (65.4%) of cases had age between 51 – 70 years. Rheumatoid nodules was the most common extra-articular manifestation found in 14 (29.2%) cases followed by hematological manifestation in 12 (25%) cases, carpal tunnel syndrome in 9 (18.8%) cases, respiratory involvement was seen in 7 (14.6%) cases, serositis in 4 (8.3%) cases, eye disease in 3 (6.3%) while vasculitides, felty's syndrome, amyloidosis was reported in 1 (2.1%) case each. Table-1 Stratification was done

with respect to gender, age and duration of disease to see the effects of these on outcomes. Proportion of extra-articular manifestation was high in female 41 (48.8%) (P-value = 0.05) and in age between 51 – 70 years, 35 (48.6%) (P-value = 0.02) Table-2 & 3 Proportion of extra-articular manifestation was high in cases with duration of rheumatoid arthritis was  $> 5$  years, 33 (47.1%) but this proportion is statistically insignificant (p-value = 0.5). Table-4.

**Table – 1 Pattern Of Extra Articular Rheumatoid Arthritis Manifestation (N = 110)**

Extra-Articular Manifestations	Number of Cases	Percentages
Rheumatoid nodules	14	29.2%
Hematological	12	25.0%
Carpal tunnel syndrome	9	18.8%
Respiratory Involvement	7	14.6%
Serositis	4	8.3%
Eye disease	3	6.3%
Vasculitides	1	2.1%
Felty's syndrome	1	2.1%
Amyloidosis	1	2.1%

Multiple Response Exist

**Table – 2 Presence Of Extra Articular Rheumatoid Arthritis With Respect To Gender (N = 110)**

Gender	Total	ExRA	Percentage	P-value*
Male	26	7	26.9%	0.05
Female	84	41	48.8%	

ExRA = Extra-articular rheumatoid arthritis \* Chi-Square test

**Table – 3 Presence Of Extra Articular Rheumatoid Arthritis With Respect To Age (N = 110)**

Age (years)	Total	ExRA	Percentage	P-value*
< 30	6	1	16.7%	0.02
31 - 50	32	9	28.3%	
51 - 70	72	38	52.8%	

ExRA = Extra-articular rheumatoid arthritis \* Chi-Square test

**Table – 4 Presence Of Extra Articular Rheumatoid Arthritis With Respect To Duration Of Disease (N = 110)**

Duration (years)	Total	ExRA	Percentage	P-value*
< 1	9	2	22.2%	0.5
1 - 5	31	13	41.9%	
> 5	70	33	47.1%	

ExRA = Extra-articular rheumatoid arthritis \* Chi-Square test

#### 4. Discussions

This study is related with the study conducted by Symmons et al.<sup>141</sup> Mean (SD) duration of disease was  $10.5 \pm 3.1$  years (Min – Max = 4 months – 15 years), (63.6%) patients had > 5 years' disease duration. A cohort study with a 46-year follow-up carried out in Minnesota, USA reported mean duration of disease was 12.2 years (range, 0–64 years).<sup>7</sup> In this study, a family history of rheumatoid arthritis was reported in (19.1%) cases. A study from Saudi Arabia reported only 1.3% patients had positive family history of RA.<sup>143</sup> Proportion of Extra-articular manifestations in rheumatoid arthritis cases was 43.6%. This is similar to North American populations (40%).<sup>8</sup> A cohort study of a 46-year follow-up period carried out in USA, Minnesota, which report a 30-year cumulative incidence of 46%,<sup>8</sup> and to another found in a retrospective study carried out in Turkey, which assessed 526 medical cases in 2006 and reported a 38.4% frequency of ExRA.<sup>9</sup> A study from Brazil reported 45.8% cases of rheumatoid arthritis had extra-articular rheumatoid arthritis.<sup>10</sup> A study were taken over 788 rheumatoid patients in which extra articular rheumatoid arthritis was present in 285 (36.2%).<sup>4</sup> The overall frequency of Extra-articular manifestations in rheumatoid arthritis in Itali was 40.9%.<sup>15</sup> It differs, however, from other publications. A retrospective study was carried out in the state of São Paulo has found a 23.3% prevalence of ExRA in three years,<sup>11</sup> and a one-year follow-up carried out in France in 82 centers has reported an ExRA prevalence of 8.4%.<sup>12</sup> In British population (68%)<sup>73</sup> while 76% in Canada<sup>11,12</sup> and 66.4% in UK.<sup>13</sup> A study from Saudi Arabia studied 140 diagnosed cases of RA reported that 98 of 140 (70%) had features of ExRA.<sup>13</sup> Such differences are due to the heterogeneity of the classifications used by each author. In this study, rheumatoid nodules was the most common extra-articular manifestation found in (29.2%) cases followed by hematological manifestation in (25%) cases, carpal tunnel syndrome in (18.8%) cases, respiratory involvement was seen in (14.6%) cases, serositis in (8.3%) cases, eye disease was found in (6.3%) while vasculitides, felty's syndrome, amyloidosis was reported in (2.1%) case each. These results confirm the results of Salvarani et al.<sup>14</sup> In Italy rheumatoid nodules were reported in 16.7% cases, 53% in Canada,<sup>15</sup> and 51.4% in UK. The prevalence of rheumatoid nodules was as low as 1% in Nigeria<sup>15</sup> and 5.6% in Greece.<sup>14</sup> A study were taken over 788 rheumatoid patients in which nodules was present in (24.5%), atlantloaxial subluxation (12.1%), carpal tunnel syndrome (10.7%), interstitial lung disease (3.7%), serositis( 2.5%), eye disease (2.5%), vasculitis (1.3%), felty's syndrome (0.3%).<sup>4</sup> A Brazilian study

reported rheumatoid nodules in 21% of the patients studied,<sup>12</sup> while 29% in São Paulo<sup>146</sup> and by Turesson et al.<sup>16</sup> (34%). Rheumatoid nodules correlate with the appearance of ExRA and with a poor prognosis of RA in general.<sup>13</sup> In a Brazilian study pulmonary manifestations were found (54.2%),<sup>12</sup> A study carried out in São Paulo has reported a 15% frequency.<sup>16</sup> Pulmonary manifestations are believed to appear within the first five years after the diagnosis of rheumatoid arthritis. Even though pulmonary infections pulmonary toxicity or both to drugs are frequent complications, pulmonary disease linked with RA is more common. Even though cardiovascular diseases are more responsible for most deaths related to RA, pulmonary complications are also common and directly responsible for 10%–20% of the deaths directly attributed to RA.<sup>17</sup> In Brazilian study amyloidosis was found in 12.5% of the patients.<sup>142</sup> Al-Ghamdi et al.<sup>13</sup> and Turesson et al. have reported 6% and 0.7%, respectively, in their studies, while Çalgüneri et al.<sup>7</sup> 1.1% of the patients. That ExRA is rarely considered and usually develops in patients with long-term RA, worsening their prognosis.<sup>15</sup> At the rheumatology service of the HUEC, these manifestations are screened in patients with disease for more than five years, with the use of abdominal fat biopsy and hematoxylineosin (HE) staining, regardless of the presence of clinical features. Vasculitides, such as Raynaud's phenomenon and ulcers, had been reported by Moura et al 10% of the patients,<sup>14</sup> Turesson et al.<sup>9</sup> (3.6%) and Çalgüneri et al.<sup>7</sup> (1.3%). Rheumatoid vasculitis typically affects small and medium vessels that are associated with high rate of early mortality with approximately 40% of the patients dying in five years. It has also significant morbidity as because of organ damage caused by vasculitis and consequent to treatment. In Brazilian study approximately 4% of the sample had hematological features during the course of illness. Anemia due to chronic disease was the most common finding, in accordance with data in the literature (60% of hematological manifestations) in our group.<sup>18,19</sup> Al-Ghamdi et al.<sup>14</sup> have reported 8.2%.

#### Conclusion

The prevalence of ExRA during disease course was 43.6%, while rheumatoid nodules was the most common extra-articular manifestation found in (29.2%) cases and vasculitides, felty's syndrome, amyloidosis was least common manifestation found in (2.1%) case each.

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### References

1. Magro CM, Crowson AN. The spectrum of cutaneous lesions in Rheumatoid arthritis: a clinical and pathological study of 43 patients. *J cutan pathol.* 2003;30:1-10.
2. Walker NJ, Zurier RB. Liver abnormalities in Rheumatis disease. *Clin Liver Dis.* 2002;6: 933-46.
3. Kalugina Y, Petruzzelli GJ, Wojcik EM. Fine needle aspiration of Rheumatoid nodule: a case report with review of diagnostic feature and Difficulties. *Diagn Cytopathol.* 2003;28: 322-4.
4. Carmona L, Gonzalez Alvaro I, Balsa A, Angel Belmonate M, Tena X, Sanmarti R. Rheumatoid arthritis in Spain: occurrence of extra articular manifestations and estimates of disease severity. *Ann rheum Dis.* 2003;62:897-900.
5. Qayyum a, Abid Mehmood, Nazir Ahmed. The articular involvement in rheumatoid arthritis a prospective study. *Biomedica* 2004;20:85-9.
6. Klocke R, Cockcroft JR, Taylor GJ, Hall IR, Blake DR. Arterial stiffness and central blood pressure, as determine by pulse wave analysis, in rheumatoid arthritis. *Ann Rheum Dis.* 2003;62:414-8.
7. Symmons DPM, Barrett EM, Bankhead CR, Scott DGI, Silman AJ. The incidence of rheumatoid arthritis in United Kingdom: results from the Norfolk Arthritis Register. *Br J Rheumatol* 1994; 33: 735-9.
8. Moura MC, Zakszewski PT, Silva MB, Skare TL. Epidemiological profile of patients with extra-articular manifestations of rheumatoid arthritis from the city of Curitiba, south of Brazil. *Rev Bras Reumatol.* 2012;52:679-94.
9. Al-Ghamdi A, Attar SM. Extra-articular manifestations of rheumatoid arthritis: a hospital-based study. *Ann Saudi Med* 2009;29:189-93.
10. Turesson C, McClelland RL, Christianson T, Matteson E. Clustering of extraarticular manifestations in patients with rheumatoid arthritis. *J Rheumatol.* 2008;35:179-80.
11. Cimmino MA, Salvarani C, Macchioni P, Montecucco C, Fossaluzza V, Mascia MT et al. Extra-articular manifestations in 587 Italian patients with rheumatoid arthritis. *Rheumatol Int.* 2000; 19:213-7.
12. Louzada-Junior P, Souza BDB, Toledo RA, Ciconelli RM. Análise descritiva das características demográficas e clínicas de pacientes com artrite reumatoide no estado de São Paulo. *Rev Bras Reumatol* 2007; 47:84-90.
13. Sany J, Bourgeois P, Saraux A, Durieux S, Lafuma A, Daurès JP et al. Characteristics of patients with rheumatoid arthritis in France: a study of 1109 patients managed by hospital based rheumatologists. *Ann Rheum Dis* 2004; 63:1235-40.
14. Gordon DA, Stein JL, Broder I. The extra-articular features of rheumatoid arthritis. A systematic analysis of 127 cases. *Am J Med.* 1973; 54:445-52?
15. Drosos AA, Lanchbury JS, Panayi GS, Moutsopoulos HM. Rheumatoid arthritis in Greek and British patients. A comparative clinical, radiologic, and serologic study. *Arthritis Rheum.* 1992; 35:745-8.
16. Salvarani C, Macchioni P, Mantovani W, Rossi F, Veneziani M, Boiardi L, Lodi L, Portioli I. Extraarticular manifestations of rheumatoid arthritis and HLA antigens in northern Italy. *J Rheumatol.* 1992;19:242-6.
17. Adebajo AO, Reid DM. The pattern of rheumatoid arthritis in West Africa and comparison with a cohort of British patients. *Q J Med.* 1991;80:633-40.
18. Brown KK. Rheumatoid lung disease. *Proc Am Thorac Soc* 2007; 4:443-8.
19. Montenegro R, Rocha A. Manifestações extra-articulares da artrite reumatoide. *Temas de Reumatologia Clínica* 2009; 10:74-83.

12/13/2016