

**Clinical Study of Extra-Articular Manifestations of Rheumatoid Arthritis****Saurabh Dikole<sup>1</sup>, Satyajeet Shirale<sup>2</sup> & Prashant Gajbhare<sup>3</sup>**<sup>1</sup>Senior Resident, Department of General Medicine, Government Medical College & Hospital, Chatrapati Sambhajnagar, Maharashtra, India<sup>2</sup>Assistant Professor, Department of General Medicine, Government Medical College & Hospital, Chatrapati Sambhajnagar, Maharashtra, India<sup>3</sup>Associate Professor, Department of General Medicine, Government Medical College & Hospital, Chatrapati Sambhajnagar, Maharashtra, India

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**Abstract:****Background:** Extra-articular manifestations of rheumatoid arthritis (ExRA) occur in about 40% of patients, either in the beginning or during the course of their disease. The presence of ExRA is associated with severe active disease and increased mortality compared to the general population.

So present was carried out to identify the extra-articular manifestations of rheumatoid arthritis and its associated risk factors.

**Material and Methods:** Present study was single-center, prospective Cross-sectional study, conducted in Department of Medicine, MGM Medical College & Hospital Ch. Smabhajnagar, Maharashtra, India during July 2020 to December 2022 were studied. All the diagnosed cases presenting with Rheumatoid arthritis were enrolled in present study. Data analysis was done using Statistical Package for Social Sciences version 20<sup>th</sup>.**Results:** In present study 50 patients diagnosed who had Rheumatoid arthritis after applying exclusion criteria were studied. Majority cases, i.e. 56% cases of age group more than 60 years. 80% affected cases being female, while only 20% affected cases being males. 78% cases that had Positive Rheumatoid Factor had these manifestations. Pulmonary manifestations of Rheumatoid Arthritis were 36.4% had interstitial lung disease, 27.3% had Pleural effusion.**Conclusion:** Present Study concludes that Rheumatoid Arthritis is a serious condition, and extra-articular being a serious complication leading to disability and hampering the daily activity. Thus these patients with extra-articular manifestations should be diagnosed earlier and treated earlier and avoid further complication. Extra-articular manifestations in RA were present in a substantial proportion of patients, which lead to a worse disease outcome. Cardiac, pulmonary, hematological etc systems are affected due to RA factor. They need to be diagnosed early and managed promptly.**Keywords:** Rheumatoid Aarthritis, Antinuclear Antibodies, Articular Manifestation.This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.**Introduction**

Rheumatoid arthritis (RA) is a systemic inflammatory disease, which is associated with a number of extra-articular organ manifestations. Studies of extra-articular RA (ExRA) include cross sectional hospital based [1] and multicentre clinical [2] surveys, series of consecutive patients seen in clinical practice [3] and retrospective surveys of clinic based RA cohorts [4].

Extra-articular manifestations of rheumatoid arthritis (ExRA) occur in about 40% of patients, either in the beginning or during the course of their disease [5]. The presence of ExRA is associated with severe active disease and increased mortality compared to the general population [6]. Suggested predictors of ExRA manifestations include constitu-

tional factors such as male sex and disease associated HLA genes (in particular homozygosity for certain DRB1\*04 subtypes), autoantibodies such as rheumatoid factor and antinuclear antibodies (ANA), and environmental factors such as smoking [7,8]. The strength of these associations is probably variable depending on the exact definition of ExRA used and on the method of patient selection.

Due to the systemic inflammatory process, the incidence of mortality in RA is increased by four-fold compared with the general population [9]. Although few patients die of the disease, or of specific complications such as cervical instability or drug side effects, the major factors that predict mortality are the presence of co-existing heart and lung dis-

ease, malignancy and dementia. Other suggested factors that predict mortality are active disease despite medical treatment and the presence of ExRA [10].

The aim of the current study was to identify the extra-articular manifestations of rheumatoid arthritis and its associated risk factors.

### Materials and Methods

This study was conducted during the period from October 2020 to October 2022 as a prospective observational study in the Department of Medicine at tertiary care hospital.

**Research design:** A prospective observational study was carried out in a tertiary care medical center on the patients diagnosed with rheumatoid arthritis satisfying the inclusion and exclusion criteria. A detailed clinical history was taken after obtaining a written signed informed consent.

**Study population:** All the diagnosed cases presenting with Rheumatoid arthritis who admitted in wards, emergency department & attending OPD of department of medicine at tertiary care hospital.

**Sampling technique & sample size:** For the present study the samples were those cases of Rheumatoid arthritis that got admitted during the study period and got treatment for the same at tertiary care hospital. Total 50 samples were selected by non-probability convenient sampling method was used to select patients at tertiary care hospital and who met the designed set of criteria.

#### Inclusion criteria:

- Patients above the age of 18 years
- Patients diagnosed with rheumatoid arthritis
- Patients giving written signed informed consent.

#### Exclusion criteria:

- Patients less than the age of 18 years
- Those patients who did not gave consent for the study.

**Baseline screening process and recording:** A detailed clinical history was obtained in each case, which included the age and sex of the patients, relevant history, presenting symptoms and diagnosis. Routine blood investigation- complete blood count, liver function test, renal function test, sr. electrolyte urine routine microscopy (microalbuminuria), BSL etc.

The serum rheumatoid factor, radiographic imaging were studied in detail. The data collected included demographic features, clinical findings, including duration of the disease at the time of the study (classified as 5 to 10 years, and >10 years), disease activity (based on the number of tender/swollen joints or the disease activity score obtained from

the 28-joint count), 20 treatment, the presence of articular and extra-articular manifestations of RA, a positive family history of RA and associated comorbidities, laboratory parameters (complete blood count, rheumatoid factor [RF] and antinuclear antibody [ANA]), and radiological changes (characteristics of lesions on chest radiographs and the typical radiological features of involved joints).

Extra-articular features included renal involvement defined as urinary excretion of more than 500 mg protein/24 hours, cellular casts not attributable to infection, or abnormal histology on renal biopsy.

Amyloidosis was considered if confirmed by biopsy or fine needle aspiration. Respiratory involvement was defined as pleuritis or interstitial lung disease, scarring and the formation of nodules in the lungs documented by a high-resolution CT scan of the chest.

Pericardial involvement was considered if pericarditis and/or pericardial effusion was documented in the clinical record as related to RA. Nervous system involvement was considered compression neuropathy (e.g. carpal tunnel syndrome) and peripheral neuropathy. Sjogren syndrome was defined by dryness of the eyes (xerophthalmia) and mucous membrane (xerostomia).

Rheumatoid nodules were defined as subcutaneous nodules with a diameter  $\geq 5$  mm in the extensor surfaces of the extremities and fingers. Haematological changes included leukopenia (WBC count  $400 \times 10^9 /L$ ), anaemia (normochromic, hypochromic or megaloblastic). Felty syndrome was considered present if there were neutropenia plus splenomegaly documented by ultrasound in the absence of other causes in the RA patient.

Rheumatoid vasculitis was defined as the presence of mononeuritis multiplex or acute peripheral neuropathy, peripheral gangrene, histological evidence of necrotizing arteritis, or deep cutaneous ulcers. Ischemic heart disease, lung disease, infection and malignancy were considered co-morbid illnesses. Gender, duration of the disease, RF, ANA and smoking (either active or had stopped within the last 5 years) were evaluated as risk factors for the development of ExRA. We examined the effect of age, gender, RF and the presence of co-morbid illness on the mortality rate in patients with ExRA.

**Data analysis:** Data analysis was done using Statistical Package for Social Sciences (SPSS software, version 20). Mean and standard deviation were calculated for quantitative data and proportions for categorical variables. Proportions were compared by the chi-square test. Results were considered significant if the P value was less than .05.

**Observations and Results:** The study was undertaken to find out extra-articular manifestations of Rheumatoid arthritis. Total 50 patients diagnosed

to had Rheumatoid arthritis after applying exclusion criteria were studied during 2020 to 2022 in

medicine department of tertiary care centre.

**Table 1: Distribution of Demographic profile of patients**

		No. of patients	Percentage
Age-Group	12 to 30	07	14.0
	30 to 60	15	30.0
	>60	28	56.0
Gender	Male	10	20.0
	Female	40	80.0

In our study, the demographic data consisted of majority cases, i.e. 56% cases of age group more than 60 years. Around 30% cases were in between the age group of 30 to 60 years while the least amount of patients i.e. 14% were in between the age of 12 to 30 years. Majority, i.e. 40 cases were female while only 10 cases were male. This demographic data suggests almost 80% affected cases being female, while only 20% affected cases being males.

**Table 2: Distribution of RA factor of patients**

		No. of patients [n=50]	Percentage
RA factor	Positive	39	78.0
	Negative	11	22.0
Duration of disease (year )	<5	16	32.0
	5 to 10	09	18.0
	>10	25	50.0

Total 50 cases, 39 cases had Positive Rheumatoid Factor, while only 11 cases had Negative Rheumatoid Factor. This data suggested that about 78% cases that had Positive Rheumatoid Factor had these manifestations, whereas only 22% cases with these manifestations had Negative Rheumatoid Factor. 25 cases had the disease for more than 10 years, 16 cases had disease since less than 5 years, and whereas only 9 cases had the disease had this disease for 5 to 10 years.

**Table 3: Associated co morbid condition**

Co morbidity	No. of patients [n=50]	Percentage
Hypertension	24	48.0
Diabetes mellitus	18	36.0
Coronary artery disease	13	26.0
Tuberculosis	06	12.0
Cerebral vascular accident	02	4.0
Malignancy	01	2.0

In our study, we observed multiple associated co morbidities associated with the cases. Majority, i.e. 48% cases had associated Hypertension. Next was Diabetes mellitus which was 36% association. 26% cases had associated Coronary artery disease. 12% had Tuberculosis. Around 4% had Cerebral vascular accident. While only 2% had associated malignancy.

**Table 4: Extra articular manifestation**

Manifestations		No. of patients [n=50]	Percentage
Extra articular manifestation	Hematological	30	60.0
	Pulmonary	22	44.0
	Dermatological	14	28.0
	Ophthalmological	10	20.0
	Cardiac	08	16.0
	Others	02	4.0
Hematological Manifestation [n=30]	Iron deficiency anaemia	14	46.7
	Megaloblastic anaemia	08	26.7
	Thrombocytosis	04	13.3
	Leukopenia	02	6.7
	Eosinophilia	02	6.7
Pulmonary Manifestation [n=22]	Interstitial lung disease	08	36.4
	Pleural effusion	06	27.3
	Fibrosis	04	18.1
	Respiratory failure	02	9.1

	Pneumonia	02	9.1
Dermatological Manifestation [n=14]	Leg ulcer	06	42.8
	Nodule	04	28.6
	Raynauds phenomenon	02	14.3
	Vasculitis	02	14.3
Ophthalmological Manifestation [n=10]	Dry eye	04	40.0
	Scleritis	02	20.0
	Episcleritis	02	20.0
	Retinal vasculities	01	10.0
	Keratoconjunctivitis sicca	01	10.0
Cardiac manifestation [n=08]	Pericardial effusion	04	50.0
	Cardiac failure	02	25.0
	Amyloidosis	01	12.5
	Pulmonary hypertension	01	12.5
Other manifestation [n=2]	Peripheral Neuropathy	01	50.0
	Felty syndrome	01	50.0

Majority, i.e. 60% of our study population had Hematological manifestations. About 44% cases had associated pulmonary manifestations. 28% cases had Dermatological manifestations. 20% cases had associated Ophthalmological manifestations. 16% cases had associated Cardiac manifestations. While only 4% cases had other manifestations.

Among Hematological manifestations, we observed majority cases, i.e. 46.7% cases had Iron deficiency anaemia, 26.7% cases had Megaloblastic anaemia, 13.3% cases had Thrombocytopenia, 6.7% cases had Leukopenia while 6.7% cases had Eosinophilia. Most common among them was Interstitial lung disease, while was observed to be almost 36.4%.

This was followed by second most common being Pleural effusion, which was 27.3% Pulmonary Fibrosis was seen to be occurring in 18.1% cases. Respiratory failure was seen in 9.1% cases along with Pneumonia which made upto 9.1% of cases. Interstitial lung disease observed to be most common manifestation of Rheumatoid Arthritis, fol-

lowed by Pleural effusion. Least common were Respiratory failure and Pneumonia, intermediate being Fibrosis. The most common was Leg ulcer, which composed of almost 42.8%. Nodules were seen in 28.6% cases associated with Rheumatoid arthritis. Raynauds Phenomenon was seen in almost 14.3% cases, similar association seem with Vasculitis. Among dermatological manifestations seen in Rheumatoid Arthritis, most common was Leg ulcer, followed by Nodules.

Most common ophthalmological manifestations of Rheumatoid Arthritis was 40% dry eye, 20% scleritis, 20% episcleritis, 10% retinal vasculities, and 10% had Keratoconjunctivitis sicca.

Most common cardiac manifestations of Rheumatoid Arthritis were 50% pericardial effusion, 25% had cardiac failure, 12.5% had amyloidosis, 12.5% had pulmonary hypertension. Most common other manifestations of Rheumatoid Arthritis were 50% peripheral neuropathy and 50% had felty syndrome.

**Table 5: Association between Demographic Profile and Extra-Articular Manifestations of Rheumatoid Arthritis**

Demographic Profile		Extra-Articular Manifestations of Rheumatoid Arthritis		P-value
		Positive (n= 39)	Negative (n= 11)	
Age in years	12 to 30	06	01	P=0.80 NS
	30 to 60	12	03	
	>60	21	07	
Gender	Male	07	03	P=0.24 NS
	Female	32	08	
Duration of disease	<5	11	05	P=0.50 NS
	5 to 10	07	04	
	>10	21	02	
Co morbidity	Hypertension	21	05	P=0.30 NS
	DM	16	02	P=0.08 NS
	Coronary artery disease	10	03	P=0.40 NS
	Tuberculosis	03	03	P=0.03 S
	Cerebral	02	00	P=0.22 NS

	vascular accident			
	Malignancy	01	99	P=0.29 NS

There was significant association between Extra-Articular Manifestations of Rheumatoid Arthritis and tuberculosis ( $p=0.03$ ), rest other factors didn't show any statistical significance in Age in years, Gender, Duration of disease, Hypertension, DM, Coronary artery disease, Cerebral Vascular accident and Malignancy.

### Discussion

In present study, the demographic data consisted of majority cases, i.e. 56% cases of age group more than 60 years. Around 30% cases were in between the age group of 30 to 60 years while the least amount of patients i.e. 14% were in between the age of 12 to 30 years. Mean age was 54.2+16.8 years. This typical distribution is in correlation with the fact that extra articular manifestations are more common in the older age groups having rheumatoid arthritis. The deformities are progressive in nature and maximum cases are seen after the age of 60 years as the disease progresses with age. In our study, we had observed total 50 cases, of which 28 cases were above the age of 60 years, 15 cases were in between the age of 30 to 60 years followed by 7 cases between 12 to 30 years of age. Study by Kalappan M et al [11] showed that mean age was 52.61+ 14.45 years. In study done by Turesson C et al [12] showed that mean age was 58.1 years. Al-Ghamdi A et al [13] showed that mean age was 47.2 years.

In our study, we observed 50 cases of which majority, i.e. 40 cases were female while only 10 cases were male. This demographic data suggests almost 80% affected cases being female, while only 20% affected cases being males. This data suggests probably a female predilection towards extra articular manifestation in rheumatoid arthritis, whereas males are somewhat protected from these manifestations. Study by Kalappan M et al [11] showed that majority were females. Male : female was 16: 84. Other study done by Marc C Hochberg et al [14] 84% patients were female and 16% were males. In the study done by Turesson C et al [12], the ratio of male to female patients was 1:2.71. The sex ratio in this study is comparable to the same in the current study. Al-Ghamdi A et al [13] showed that 75% were females. Our study, of total 50 cases, 39 cases had Positive Rheumatoid Factor, while only 11 cases had Negative Rheumatoid Factor. This data suggested that about 78% cases who had Positive Rheumatoid Factor had these manifestations, whereas only 22% cases with these manifestations had Negative Rheumatoid Factor. Hence, a Positive Rheumatoid Factor had a stroger association or possibility of developing extra articular manifestations of rheumatoid arthritis. Study by

Kalappan M et al [11] showed that 72% had positive results. In study done by Turesson C et al [12] 80% of RA patients were sero-positive for RA factor and 20% were seronegative.

In our study, were observed 50 cases, among them 25 cases had the disease for more than 10 years, 16 cases had disease since less than 5 years, whereas only 9 cases had the disease had this disease for 5 to 10 years. And mean duration was 9.56 years. This data suggests that almost 50% cases developed extra articular manifestations after the duration being more than 10 years. Study by Kalappan M et al [11] showed that mean duration was 5.8+ 5 years. Other study done by Marc C Hochberg et al [11] average duration of RA was 5.85 years. In the study done by Turesson et al., the mean duration of disease was found to be 11.8years. This is comparable to the present study. Al-Ghamdi A et al [13] showed that mean duration was 10 years. Majority had disease for more than 10 years.

In our study, we observed multiple associated co morbidities associated with the cases. Majority, i.e. 48% cases had associated Hypertension. Next was Diabetes mellitus which was 36% association. 26% cases had associated Coronary artery disease. 12% had Tuberculosis. Around 4% had Cerebral vascular accident. While only 2% had associated malignancy. Al-Ghamdi A et al [13] showed that 6% had Tb, 5% had hypertension, DM 4%, 3% had malignancy, 2% had CVA.

We observed various extra articular manifestations in our study. Majority, i.e. 60% of our study population had Hematological manifestations. About 44% cases had associated pulmonary manifestations. 28% cases had Dermatological manifestations. 20% cases had associated Ophthalmological manifestations. 16% cases had associated Cardiac manifestations. While only 4% cases had other manifestations. Study by Kalappan M et al [11] showed that, 27% of patients had extra articular manifestations. The most common was pulmonary manifestation among them interstitial lung disease is seen in 11% of patients. 4% had neurological manifestation, 5% had hematological and 10% had others and study by Bharadwaj et al [15] showed that 25.7% had extra articular manifestation. Al-Ghamdi A et al [13] showed that 70% had extra articular manifestation.

Among Hematological manifestations, we observed majority cases, i.e. 46.7% cases had Iron deficiency anaemia, 26.7% cases had Megaloblastic anaemia, 13.3% cases had Thrombocytopenia, 6.7% cases had Leukopenia while 6.7% cases had Eosinophilia. Iron deficiency anaemia was seen to be most

common Hematological manifestation of Rheumatoid Arthritis, followed by next most common being Megaloblastic anaemia, while least common being Leukopenia and Eosinophilia.

Study by Kalappan M et al [11] showed that, 55 had anaemia. Anaemia (61%) which was the common extra articular manifestations seen in study by Bharadwaj et al [15]. Al-Ghamdi A et al [13] showed that 60% had anaemia.

Most common other manifestations of Rheumatoid Arthritis were 50% peripheral neuropathy and 50% had felty syndrome. Study by Kalappan M et al [11] showed that, 10% had nodule and 1% had vasculitis. Study was Chen X et al [16] showed that 0.39% had neuropathy. In the study done by Turesson et al [12] peripheral neuropathy is seen in 2.1% of cases. Al-Ghamdi A et al [13] showed that 1% had pericardial effusion and 1% had Felty syndrome.

Study shows association for tuberculosis ( $p=0.03$ ), rest other factors didn't show any statistical significance. In study done by Turesson C et al [12] showed that association between smoking and ExRA was independent of RF, indicating that other mechanisms may play a part.

Suggested pathogenic factors in ExRA include complement binding and activating circulating immune complexes, clonally expanded CD4+ CD28 (null) T cells and generalised endothelial activation.

It is unknown to what extent these mechanisms are directly or indirectly influenced by smoking. Environmental factors such as smoking are likely to interact with the individual genetic background in shaping disease outcome.

### Conclusion

Present Study concludes that Rheumatoid Arthritis is a serious condition, and extra-articular being a serious complication leading to disability and hampering the daily activity.

Thus these patients with extra-articular manifestations should be diagnosed earlier and treated earlier and avoid further complication. Extra-articular manifestations in RA were present in a substantial proportion of patients, which lead to a worse disease outcome. Cardiac, pulmonary, hematological etc systems are affected due to RA factor. They need to be diagnosed early and managed promptly.

**Limitation:** A major limitation of the study is single-centre study with a small sample size of 50 patients which may not be representative of the entire rural population of the state.

In view of the socio-economic and cultural diversity of rural Maharashtra. Prospective study with no control group so generalization of findings is diffi-

cult. We did not collect follow-up data after hospital discharge.

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