



## Frequency of extra-articular manifestations in cohort of Pakistani patients presented with RA at Independent University Hospital Faisalabad.

1. MBBS, FCPS (MED), FCPS (Rheumatology)  
Assistant Professor of Medicine  
Independent University Hospital,  
Faisalabad.
2. MBBS, MRCP (UK)  
Assistant Professor of Medicine  
Independent University Hospital,  
Faisalabad.
3. MBBS, FCPS (Medicine)  
Associate Professor of Medicine  
Independent University Hospital,  
Faisalabad.
4. MBBS, FCPS (MED)  
Professor of Medicine  
Independent University Hospital,  
Faisalabad.
5. MBBS, FCPS (ORTH)  
Associate Professor of Orthopedics  
Independent University Hospital,  
Faisalabad.
6. MBBS  
Medical Officer  
Independent University Hospital,  
Faisalabad.

### Correspondence Address:

Dr. Zafar Ali Zafar  
Assistant Professor of Medicine  
Independent University Hospital,  
Faisalabad  
drzafar353@gmail.com

### Article received on:

22/12/2020

### Accepted for publication:

01/02/2021

Zafar Ali Zafar<sup>1</sup>, Muhammad Absar Alam<sup>2</sup>, Muhammad Sarfraz<sup>3</sup>, Touseef Ahmad<sup>4</sup>, Hafiz Salman Saeed<sup>5</sup>, Aqib Rehman<sup>6</sup>

**ABSTRACT... Objective:** To determine the frequency of extra articular manifestations in Rheumatoid Arthritis patients at independent university hospital Faisalabad. **Study Design:** Cross Sectional study. **Setting:** Rheumatology Division of Internal Medicine Independent University Hospital Faisalabad. **Period:** January 2019 to December 2019. **Material & Methods:** Consecutive Three hundred and twenty-three adult patients of either sex, of age between 20-60 years with baseline RA fulfilling the 2010 criteria of American College of Rheumatology. Extra articular manifestations were assessed. Chi square test was used to compare the frequency of extra articular manifestations among different disease duration, age groups, seropositivity and disease score. A p-value  $\leq 0.05$  was considered statistically significant. **Results:** 323 patients with RA were assessed in this study. Extra articular manifestations were assessed according to clinical presentation. 15.2% (49) patients were found to have lung involvement with predominant interstitial lung disease. Rheumatoid nodules were found in 9.9% (32) patients. 3<sup>rd</sup> most common extra-articular manifestation was sicca syndrome, seen in 3.7% (12) patients followed by neurological 2.2% and cardiac was 1.5%. Other extra-articular manifestations were seen in 2.8% of patients. **Conclusion:** it is very important to assess the extra articular manifestations in rheumatoid arthritis. Early assessment and early intervention can decrease the disease morbidity and mortality.

**Key words:** Rheumatoid Arthritis, Extra Articular Features, Disease Severity.

**Article Citation:** Zafar ZA, Alam MA, Sarfraz M, Ahmad T, Saeed HA, Rehman A. Frequency of extra-articular manifestations in cohort of Pakistani patients presented with RA at Independent University Hospital Faisalabad. Professional Med J 2021; 28(6):819-827. <https://doi.org/10.29309/TPMJ/2021.28.06.6289>

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disorder of unknown etiology, characterized by systemic symptoms that particularly involve the joints and may lead to deformities during the disease.<sup>1</sup> Worldwide it is affecting 0.5-1.0% of the general population. The prevalence is almost same across the globe, regardless of geographic location and race. In year 2005 societal costs of RA, in economic and employment terms have been estimated to 19.3 billion US dollars, while individual Annual treatment costs, 8000 dollars in USA.<sup>2</sup>

Although primarily considered as disease of joints, it can cause variety of extra articular manifestations, like cardiovascular disease, renal failure, interstitial lung disease, rheumatoid nodules, vasculitis, a variety of eye manifestations,

stroke, malignancy and occupational disability. Up to 30-50% of patients with rheumatoid arthritis develop these extra-articular features at some point of the disease, but some rare manifestations like Felty's syndrome, pericarditis are only present in 1-5% of patients in long standing disease.<sup>3</sup>

Extra-articular manifestations occurred in RA patients who are either recently diagnosed or have chronic long-standing illness.<sup>4</sup> Clinical presentations, serological tests, and genetic markers defined the extra-articular manifestations.<sup>5</sup> Different studies showed that RA phenotype is heterogenous and these different disease expressions are probably due to genetic polymorphisms. These different disease expressions and courses are due to the presence of different disease susceptibility alleles that include some patients with mild disease and

some with severe progressive disease with severe joint erosions and extra-articular manifestations.<sup>6</sup>

A study conducted in Karachi showed 53% of RA patients have dyslipidemia.<sup>8</sup> Another study conducted at Karachi showed 27.8% of RA patients developed interstitial lung disease.<sup>9</sup> Another study showed rheumatoid nodules occurred in 30% of RA patients which are painless, variable consistency, are subcutaneous, mostly on olecranon process and proximal ulna, finger joints, sacral prominences, occiput, and Achilles tendon.<sup>10</sup>

Most of the time it is difficult to find the factors that predict extra-articular features in early RA, although these features have very strong association with smokers, more severe joint disease, disease in men, high inflammatory markers, presence of rheumatoid factor and RA HLA-related shared epitope. So early aggressive and targeted therapies with specific RA drugs would have better outcome regarding disease and extra-articular manifestations.<sup>7</sup>

## OBJECTIVES

1. To determine the frequency of extra articular manifestations in Rheumatoid Arthritis patients at Independent University Hospital Faisalabad.
2. To determine the association of extra articular manifestations with disease severity.

## MATERIAL & METHODS

This cross-sectional study was carried out at Rheumatology division of internal medicine independent university hospital Faisalabad, from January 2019 to December 2019. Consecutive Three hundred and twenty-five adult patients with baseline RA fulfilling the 2010 criteria of American College of Rheumatology, visiting the Rheumatology division of internal medicine Independent University Hospital Faisalabad and fulfilling the selection criteria, were selected through Non-Probability Convenient Sampling technique for this study. This study was proved by the Institutional Review Board of the hospital (IUH/IRB/000025).

Inclusion criteria were patients aged between 20 to 60 years of either gender who were diagnosed cases of rheumatoid arthritis. Patients with Seronegative Arthritis, Spondyloarthropathy or diagnosed cases of Osteoarthritis by rheumatologists, also other autoimmune diseases like Systemic Lupus Erythematosus, Systemic Sclerosis, and diagnosed cases of infective or metabolic causes of arthritis were excluded.

A sample size of 323 was estimated by using 95% confidence level, 5% margin of error, with expected frequency of extra-articular manifestations was 30% among RA patients. Patients were explained about the purpose, risk/benefit of the study and informed consent was taken. Demographic data and history including age, gender, hospital registration number, and disease duration and treatment history and primary investigations like Quantitative RA factor, Anti-CCP antibodies, Blood complete with ESR, CRP was noted. All patients were assessed clinically for the number of tender and swollen joints. Tenderness and swelling were assessed by bimanual method, Small and large joint involvement was also noted. All patients were assessed for extra-articular features both clinically and laboratory tests. Rheumatoid nodules were noted clinically according to their site, number and consistency and differentiated clinically from bony swellings and tophi of gouty arthritis. Nodules just around the joints, non-tender, normal temperature and boggy consistency were included as rheumatoid nodule. Patients with eye symptoms including sicca symptoms, scleritis, conjunctivitis were confirmed from eye department for excluding from other etiology. Similarly, patients with respiratory symptoms including cough, shortness of breath, or chest pain were confirmed by high resolution computed tomography scan for pleural or interstitial involvement, which showed pleural effusion or interstitial lung disease. Cardiac involvement was confirmed by echocardiography, showed either pericardial effusion, myocardial involvement or endocardial involvement. Vasculitis was assessed clinically for cutaneous vasculitic rashes, gangrene, or pyoderma gangrenosum. Neurological involvement was seen for mononeuritis multiplex, poly neuropathy,

mononeuropathy or central nervous system involvement as a stroke. These were confirmed by nerve conduction and electromyographic studies and CT scan brain control. Some rare features were noted like Felty's syndrome, which showed neutropenia, and splenomegaly.

Also, few patients showed osteoporosis, confirmed by dual energy X ray absorptiometry showed score  $> -2.5$ . Disease duration with onset of symptoms of inflammation with pain or stiffness or restricted joint motion less than 6 weeks, from 6 weeks to 2 years or more than 2 years was also noted. Treatment history was also noted. Patients taking no treatment or taking DMARDs treatment with methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, or biologics either alone or in combinations was also noted. Also, disease score with either remission, low, moderate, or high was calculated by DAS-28 formula using mobile application of Rheuma helper. It is an electronic formula in which we have put number of tender and swollen joint count along with patient general health score by visual analog scale (VAS) and ESR or CRP. DAS-28 score was calculated as remission, low, moderate or high disease. A score less than 2.6 was remission,  $> 2.6 - 3.2$  was low,  $< 3.2 - 5.1$  was moderate,  $> 5.1$  was high disease activity.

Data was entered and analyzed on computer using IBM SPSS Statistics version 23.0 software program. Data for age, disease duration, were described by using Mean  $\pm$  SD. Data for gender, extra articular manifestations, investigations and treatment history were described by using frequency and percentages. Frequency of extra articular manifestations was described by percentage as per given criteria. Chi square test was used to compare the frequency of extra articular manifestations among different treatments groups, disease duration, age groups and disease score. A p-value  $\leq 0.05$  was considered statistically significant.

## RESULTS

A total of 323 patients with RA were enrolled in this study. Mean age of the patients was  $39.67 \pm 10.6$  years with age range of 20 to 60 years. Out

of 323, 70% (226) patients were of female gender, while only 30% (97) were males.

The age distribution in RA patients was shown in Table-I. A larger number of patients 170(52.6%) were from age group 31-45 years, 71 (22%) patients were from less or equal 30 years of age and only 82 (25,4%) were greater or equal 45 years of age.

Duration of rheumatoid arthritis was also assessed in this study as shown in Table-II. A relative larger number of patients were noted with disease duration of greater than 10 years.

A comparative large number of patients (74%) were noted of having both rheumatoid factor and anti-cyclic citrullinated peptide antibodies positive as shown in Table-III. 16.1% (52) were positive for rheumatoid factor only and 9.9% (34) were positive for anti-cyclic citrullinated peptide antibodies.

All patients were examined for extra-articular manifestations. 64.7% (209) patients were not having any extra-articular manifestations as shown in Table-IV. 15.2% (49) patients were found to have lung involvement with predominant interstitial lung disease. Rheumatoid nodules were found in 9.9% (32) patients. 3<sup>rd</sup> most common extra-articular manifestation was sicca syndrome, seen in 3.7% (12) patients followed by neurological 2.2% and cardiac was 1.5%. Other extra-articular manifestations were seen in 2.8% of patients.

All patients enrolled in the study were also assessed for disease severity. Many patients 48.3% were found to have high disease activity as shown in Table-V. 29.4% were found to have moderate disease activity while 9.9% were of low disease activity. 12.4% were found to have disease in remission according to DAS-28 activity score. Our study has strong correlation of seropositivity with extra articular manifestations, having statistically significant importance (p value:  $< 0.01$ ) as shown in Table-VI. Study was association of disease duration and extra articular features, having statistically significant

importance (p value: <0.05) as shown in Table-VII. A very important finding in our study was association of extra articular manifestations with

Disease severity which was statistically significant (P-value: <0.01) as shown in Table-VIII.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	20-30	71	22.0	22.0	22.0
	31-45	170	52.6	52.6	74.6
	greater than 45	82	25.4	25.4	100.0
	Total	323	100.0	100.0	

**Table-I. Age distribution in RA patients.**

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	<2 year	101	31.3	31.3	31.3
	>2-10 year	104	32.2	32.2	63.5
	>10 year	118	36.5	36.5	100.0
	Total	323	100.0	100.0	

**Table-II. Disease duration in RA patients.**

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Quantitative RA +ve	52	16.1	16.1	16.1
	Anti-CCP +ve	32	9.9	9.9	26.0
	both +ve	239	74.0	74.0	100.0
	Total	323	100.0	100.0	

**Table-III. Investigation.**

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	no	209	64.7	64.7	64.7
	nodules	32	9.9	9.9	74.6
	Lung (ILD)	49	15.2	15.2	89.8
	cardiac	5	1.5	1.5	91.3
	sicca syndromes	12	3.7	3.7	95.0
	neurological	7	2.2	2.2	97.2
	others	9	2.8	2.8	100.0
	Total	323	100.0	100.0	

**Table-IV. Extra Articular Feature.**

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	remission	40	12.4	12.4	12.4
	low disease	32	9.9	9.9	22.3
	moderate	95	29.4	29.4	51.7
	severe	156	48.3	48.3	100.0
	Total	323	100.0	100.0	

**Table-V. Disease Score.**

Extra Articular Feature		Investigation			Total	
		Quantitative RA +ve	Anti-CCP +ve	Both +ve		
no	Count	43	25	141	209	
	% within Extra Articular feature	20.6%	12.0%	67.5%	100.0%	
nodules	Count	0	2	30	32	
	% within Extra Articular feature	0.0%	6.3%	93.8%	100.0%	
lung(ILD)	Count	2	5	42	49	
	% within Extra Articular feature	4.1%	10.2%	85.7%	100.0%	
cardiac	Count	0	0	5	5	
	% within Extra Articular feature	0.0%	0.0%	100.0%	100.0%	
Sicca syndrome	Count	0	0	12	12	
	% within Extra Articular feature	0.0%	0.0%	100.0%	100.0%	
neurological	Count	7	0	0	7	
	% within Extra Articular feature	100.0%	0.0%	0.0%	100.0%	
others	Count	0	0	9	9	
	% within Extra Articular feature	0.0%	0.0%	100.0%	100.0%	
Total		Count	52	32	239	323
		% within Extra Articular feature	16.1%	9.9%	74.0%	100.0%

**Table-VI. Cross tabulation seropositivity with extra articular features. Crosstab.**

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	62.895 <sup>a</sup>	12	.000
Likelihood Ratio	65.209	12	.000
Linear-by-Linear Association	2.027	1	.155
N of Valid Cases	323		

**Chi-Square Tests**

Extra Articular Feature		Duration			Total
		<2 year	>2-10 year	>10 year	
no	Count	96	79	34	209
	% within Extra Articular feature	45.9%	37.8%	16.3%	100.0%
nodules	Count	0	2	30	32
	% within Extra Articular feature	0.0%	6.3%	93.8%	100.0%
Lung (ILD)	Count	5	2	42	49
	% within Extra Articular feature	10.2%	4.1%	85.7%	100.0%
cardiac	Count	0	0	5	5
	% within Extra Articular feature	0.0%	0.0%	100.0%	100.0%
Sicca syndrome	Count	0	12	0	12
	% within Extra Articular feature	0.0%	100.0%	0.0%	100.0%
neurological	Count	0	0	7	7
	% within Extra Articular feature	0.0%	0.0%	100.0%	100.0%
others	Count	0	9	0	9
	% within Extra Articular feature	0.0%	100.0%	0.0%	100.0%
Total	Count	101	104	118	323
	% within Extra Articular feature	31.3%	32.2%	36.5%	100.0%

**Table-VII. Cross tabulation disease duration and extra articular features:**

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	201.772 <sup>a</sup>	12	.000
Likelihood Ratio	218.089	12	.000
Linear-by-Linear Association	39.829	1	.000
N of Valid Cases	323		

**Chi-Square Tests**

			Disease Score				Total
			Remission	Low Disease	Moderate	Severe	
Extra Articular feature	no	Count	40	32	52	85	209
		% within Extra Articular feature	19.1%	15.3%	24.9%	40.7%	100.0%
	nodules	Count	0	0	32	0	32
		% within Extra Articular feature	0.0%	0.0%	100.0%	0.0%	100.0%
	lung(ILD)	Count	0	0	0	49	49
		% within Extra Articular feature	0.0%	0.0%	0.0%	100.0%	100.0%
	cardiac	Count	0	0	0	5	5
		% within Extra Articular feature	0.0%	0.0%	0.0%	100.0%	100.0%
	Sicca syndrome	Count	0	0	0	12	12
		% within Extra Articular feature	0.0%	0.0%	0.0%	100.0%	100.0%
	neurological	Count	0	0	7	0	7
		% within Extra Articular feature	0.0%	0.0%	100.0%	0.0%	100.0%
	others	Count	0	0	4	5	9
		% within Extra Articular feature	0.0%	0.0%	44.4%	55.6%	100.0%
Total	Count	40	32	95	156	323	
	% within Extra Articular feature	12.4%	9.9%	29.4%	48.3%	100.0%	

Table-VIII. Disease severity: Crosstab.

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	184.887 <sup>a</sup>	18	.000
Likelihood Ratio	212.291	18	.000
Linear-by-Linear Association	30.538	1	.000
N of Valid Cases	323		

**Chi-Square Tests**

## DISCUSSION

Rheumatoid arthritis is a chronic, autoimmune inflammatory disease, predominantly affecting the synovial joints and as the disease progresses it leads to multiple deformities. It also affects the extra-articular organs as well leading to organ failure and increasing morbidity and mortality.<sup>11,12</sup> In our study most of patients are females which are comparable to a study conducted in India,<sup>13</sup> which accounts almost more than 70%. Mean age of patients in my study was 39 years and most of patients belong to age group of 31-45 years, which was also comparable to other studies.<sup>13,14</sup> Our study has strong correlation of seropositivity with extra articular manifestations, having statistically significant importance (p value: <0.01). Shankar S et al.<sup>15</sup> and others found that up to 80% of patients were seropositive rheumatoid arthritis in their studies during assessment of extra

articular manifestations. This small difference in seropositive might be due to inclusion criteria as we only enrolled patients with seropositive either rheumatoid factor or anti cyclic citrullinated peptide antibodies.<sup>13,15,16</sup> So most of studies have clearly demonstrated the positive correlation of presence of rheumatoid factor and extra articular manifestations.<sup>17</sup>

In our study about 35% of patients were found to have extra articular manifestations either in single or multiple forms. A large study conducted on US population clearly showed decreasing trend of extra articular manifestations.<sup>18</sup> This reduction in extra articular manifestations might be due to early assessment and targeted therapy especially with methotrexate and biologics. A recent study conducted in India showed almost 63.3% of patients have extra articular manifestations.<sup>14</sup> This



high incidence of extra articular manifestations may be due to study design and selection criteria. They even included clinical manifestations of disease as extra articular forms like early morning stiffness and anemia of all forms. A study conducted in Kingdom of Saudi Arabia<sup>19</sup> showed 70% while a study in north America showed the 40% of extra articular manifestations<sup>20</sup>, results of which are close to our study. A large study conducted in Spain in 2003 showed the prevalence of extra articular manifestation was about 36% which is like our study.<sup>21</sup>

In our study interstitial lung disease was found in 15.2% of study population. Dahani A et al<sup>9</sup> done study in 2020 in Pakistan found that 27.8% patient with rheumatoid arthritis had interstitial lung disease. 10% of interstitial lung disease was found in a study conducted in KSA<sup>19</sup>, while Carmona L et al<sup>21</sup> showed only 3.7% of interstitial lung disease in their study conducted in Spain. This difference might be due to the sample size, selection criteria, and the method of investigations. Symptomatic patients with only X ray chest findings show <12% of disease features while even asymptomatic patients with high resolution CT chest showed 30-80% of lung involvement in rheumatoid arthritis patients.<sup>22</sup> Regarding different presentations of lung diseases in rheumatoid patients Balbir-Gurman et al<sup>23</sup>, showed that most of the middle-aged men with rheumatoid arthritis have pleural effusion as most common lung disease especially in seropositive patients.

9.9% of patients in our study were found to have rheumatoid nodules at different level of presentations. Kumar B et al<sup>14</sup> showed 16.6% of patients have rheumatoid nodules in their patients. Many authors found that the prevalence of rheumatoid nodules was 20-30% in white peoples while in some countries it was 2-5% especially outside Europe.<sup>24</sup> This variation in prevalence might be due to geographic and ethnic difference. Also, there might be reason that most of time nodules are underestimated and are missed during clinical examination especially if they are at rarer sites.

Presence of secondary sicca symptoms might be

an important complicating factor in rheumatoid arthritis patients and may lead to increased morbidity and sometimes mortality as well. Our data showed that 3.7% of patients presented with secondary sicca symptoms. While 6.6% of keratoconjunctivitis sicca symptoms were noted by Kumar B<sup>14</sup> et al. Spanish study<sup>21</sup> in 2003 showed 16% of Sjogren's syndrome in RA while a large data base study in US showed about 30% of prevalence of sicca syndrome in RA. This variation in sicca symptoms might be due to sample size, selection criteria used, difference in study population, physician verses patient interactions and most important disease duration and disease activity of sample size. It was noted clearly that patients with high disease activity and longer duration of disease, seropositivity, and females have higher incidence of sicca symptoms.<sup>25,26</sup>

Peripheral neuropathy mostly presenting as mononeuritis multiples or mono or poly neuropathy and central nervous system presenting as stroke has significant impact on quality of life in rheumatoid arthritis patients. Our data showed 2.2% of patients complicated with neurological symptoms. Aneja et al.<sup>27</sup> found that 24.2% of patients had sensory loss whereas 9.09% had motor symptoms. This difference might be because we selected patients only with definite clinical symptoms, both motor and sensory. Other reason could be that most studies purely assessing neurological presentation as extra articular feature in RA patients so specific test like nerve conduction studies done in every patient.

A very important finding in our study was association of extra articular manifestations with disease duration which was statistically significant (P-value: <0.01). Our finding was like many other studies that showed increasing duration has strong association with extra articular manifestations.<sup>14,28,29</sup> Very rarely noted findings in our study was felty syndrome <1%, osteoporosis. No single case was noted for amyloidosis. All reason for decreasing trend of these rare presentations might be due early intervention with DMARDs especially methotrexate or other biologics.

Findings noted in our study may differ from studies conducted in other parts of World. Most of time this variation is due difference in human leukocyte antigen which pathophysiological antigen of rheumatoid arthritis. It varies between Caucasians and other populations like HLA DR4, HLA DR1 in Caucasians, HLA DR10 in KSA.<sup>30</sup>

Our study was not without limitations. It was cross sectional study, so results cannot be generalized due to small sample size, and we are unable to analyze the association of extra articular presentations with rheumatoid arthritis. Also, histopathological assessment was not done in most of extra articular manifestations due to lack of biopsy specimen. So due to all these factors, there is need of more research of prospective design on a large scale of population to assess adequate disease presentations and to recognize the proper time of development of extra articular manifestations and to determine the factors associated with development of extra articular manifestations. So timely intervention with specific therapy can herald the disease severity and decreasing the morbidity and mortality related to extra articular features of rheumatoid arthritis.

## CONCLUSION

Above discussion has an urge to understand the significance of extra articular manifestations of RA. Extra articular manifestations are present in significant number of patients which are often missed during clinical examination. Disease severity, long disease duration and seropositivity has a strong association with extra articular manifestations. So early assessment of extra articular feature and early intervention can prevent the disease morbidity and mortality.

Copyright© 01 Feb, 2021.






## REFERENCES

1. Kojima M, Kojima T, Ishiguro N, Oguchi T, Oba M, Tsuchiya H, Sugiura F. et al. **Psychosocial factors, disease status, and quality of life in patients with rheumatoid arthritis.** J Psychosom Res. 2009; 67(5):425–431.
2. Firestein GS, Budd RC, Gabriel SE, **McInnes IB editors in Kelly's textbook of rheumatology.** 9<sup>th</sup> ed. Philadelphia: WB Saunders; 2013:1059-1108.
3. Lagrutta M, Alle G, Parodi RL, Greca AA. **Severe Extra-articular manifestations of rheumatoid arthritis in absence of concomitant articular activity following longstanding spontaneous remission.** Reumatol Clin. 2016; 12:223–225.
4. Turesson C, Jacobsson L, Bergstrom U. **Extra-articular rheumatoid arthritis: Prevalence and mortality.** Rheumatology (Oxford) 1999; 38:668–674.
5. Turesson C, Jacobsson LT. **Epidemiology of extra-articular manifestations in rheumatoid arthritis.** Scand J Rheumatol. 2004; 33:65–72.
6. Grant SF, Thorleifsson G, Frigge ML, Thorsteinsson J, Gunnlaugsdottir B, Geirsson AJ, Gudmundsson M, Vikingsson A, Erlendsson K, Valsson J, et al. **The inheritance of rheumatoid arthritis in Iceland.** Arthritis Rheum. 2001; 44:2247–2254.
7. Adam Y, Gouri K. **Extra-articular manifestations and complications of rheumatoid arthritis.** Clin Rheumatol; 2007 Oct; 21(5):907-27.
8. Erum U, Ahsan T, Khowaja D. **Lipid abnormalities in patients with rheumatoid arthritis.** Pak J Med Sci. 2017 Jan-Feb; 33(1): 227–230.
9. Dahani A, Arain S R, Riaz A, Khan F,1 and Jabeen R. **Prevalence and pattern of pulmonary manifestation in patients with connective tissue disorder.** Cureus. 2020 Apr; 12(4): e7618.
10. Ziff M. **The rheumatoid nodule.** Arthritis. Rheum. 1990; 33(6):761–7.
11. Turesson C, Jacobsson J, Bergström U. **Extra-articular rheumatoid arthritis: Prevalence and mortality.** Rheumatol. 1999 Jul; 38(7):668–74.
12. Gabriel SE, Crowson CS, Kremers HM, Doran MF, Turesson C, O'Fallon WM, Matteson EL. **Survival in rheumatoid arthritis: A population-based analysis of trends over 40 years.** Arthritis Rheum. 2003 Jan; 48(1):54–8.
13. Intriago M, Maldonado G, Cardenas J, Ríos C. **Clinical characteristics in patients with rheumatoid arthritis: Differences between genders.** Scientific World Journal. 2019; 2019:8103812.
14. Kumar B, Das MP, Misra AK. **A cross-sectional study of association of serostatus and extra-articular manifestations in patients with rheumatoid arthritis in a teaching hospital.** J Family Med Prim Care. 2020 Jun; 9(6): 2789–2793.



15. Shankar S, Grover R, Handa R. **Role of anti-cyclic citrullinated peptide antibodies in erosive disease in patients with rheumatoid arthritis.** Indian J Med Res. 2006; 124:589–96. [PubMed] [Google Scholar].
16. Sahatciu-Meka V, Rexhepi S, Manxhuka-Kerliu S, Rexhepi M. **Extra-articular manifestations of seronegative and seropositive rheumatoid arthritis.** Bosn J Basic Med Sci. 2010; 10:26–31.
17. Jonsson T, Arinbjarnarson S, Thorsteinsson J, et al. **Raised IgA rheumatoid factor (RF) but not IgM RF or IgG RF is associated with extra-articular manifestations in rheumatoid arthritis.** Scand. J. Rheumatol. 1995; 24(6):372–375.
18. Bartels CM, Bell CL, Shinki K, Ann Rosenthal A, and Bridges AJ. **Changing trends in serious extra-articular manifestations of rheumatoid arthritis among United State veterans over 20 years.** Rheumatology (Oxford). 2010 Sep; 49(9): 1670–1675.
19. Al-Ghamdi A, Attar SM. **Extra-articular manifestations of rheumatoid arthritis: A hospital-based study.** Ann Saudi Med. 2009 May-Jun; 29(3): 189–193.
20. Hochberg MC, Johnston SS, John AK. **The incidence and prevalence of extra-articular and systemic manifestations in a cohort of newly diagnosed patients with rheumatoid arthritis between 1999 and 2006.** Curr Med Res Opin. 2008 Feb; 24(2):469–80.
21. Carmona L, González-Alvaro I, Balsa A, Angel Belmonte M, Tena X, Sanmartí R. **Rheumatoid arthritis in Spain: Occurrence of extra-articular manifestations and estimates of disease severity.** Ann. Rheum. Dis. 2003; 62:897–900.
22. Gochuico BR, Avila NA, Chow CK, et al. **Progressive preclinical interstitial lung disease in rheumatoid arthritis.** Arch Intern Med. 2008; 168:159–66.
23. Balbir-Gurman A, Yigla M, Nahir AM, Braun-Moscovici Y. **Rheumatoid pleural effusion.** Semin. Arthritis. Rheum. 2006; 35(6):368–378.
24. Mangat G. **A comparative study of rheumatoid arthritis in Malaysian and British hospital.** Br. J. Rheum. (suppl) 1988:70–71.
25. Harrold LR, Shan Y, Rebello S, Kramer N, Connolly SE, Alemao E, Kelly S, et al. **Prevalence of Sjögren's syndrome associated with rheumatoid arthritis in the USA: An observational study from the Corrona registry.** Clin Rheumatol. 2020; 39(6): 1899–1905.
26. Santosh K, Dhir V, Singh S, Sood A, Gupta A, Sharma A, Sharma S. **Prevalence of secondary Sjogren's syndrome in Indian patients with rheumatoid arthritis: A single-center study.** Int J Rheum Dis. 2017; 20:870–874.
27. Aneja R, Singh MB, Shankar S, Dhir V, Grover R, Gupta R, et al. **Prevalence of peripheral neuropathy in patients with newly diagnosed rheumatoid arthritis.** Indian J Rheumatol. 2007; 2:47–50.
28. Marcucci E, Bartoloni E, Alunno A, Leone MC, Cafaro G, Luccioli F, et al. **Extra-articular rheumatoid arthritis.** Reumatismo. 2018; 70:212–24.
29. Bharadwaj A, Haroon N. **Interstitial lung disease and neuropathy as predominant extra-articular manifestation in patients with rheumatoid arthritis.** Med Sci Monit. 2005; 11:CR498–502.
30. Al-Arfaj AS. **Characteristics of rheumatoid arthritis relative to HLA-DR in Saudi Arabia.** Saudi Med J. 2001 Jul; 22(7):595–8.

### AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Zafar Ali Zafar	Primary author, Data collection, Analysis, Introduction, Discussion writing.	
2	M. Absar Alam	Data collection.	
3	Muhammad Sarfraz	Review paper.	
4	Touseef Ahmad	Proof reading.	
5	Hafiz Salman Saeed	Data collection.	
6	Aqib Rehman	Data collection.	