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Original Research Article

STUDY OF COMORBIDITIES AND EXTRA ARTICULAR MANIFESTATIONS IN PATIENTS OF RHEUMATOID ARTHRITIS AND THEIR PREVALENCE WITH SEROPOSITIVITY

Mahin O S[1], Jyotsna Oak[2], Ojas Unavane[3], Vincy Chandran[4]

[1]Assistant Professor, Department of General Medicine, Al Azhar Medical College and Super Specialty Hospital Ezhalloor P O, Thodupuzha, India.
[2]Department of Medicine and Rheumatology, Kokilaben Dhirubhai Ambani Hospital Mumbai, India.
[3]Department of Medicine, Kokilaben Dhirubhai Ambani Hospital, Mumbai, India
[4]Assistant Professor, M Mount Zion. Medical College Adoor, India.

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Corresponding Author:
Dr. Vincy Chandran
Assistant Professor, M Mount Zion. Medical College Adoor, India.
Email: vinci0005@gmail.com

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized by progressive joint destruction, systemic involvement, and multiple comorbidities that significantly affect morbidity, mortality, and quality of life. This study evaluated the prevalence of comorbidities and extra-articular manifestations (EAMs) among patients with RA and their association with seropositivity and disease activity.

Materials and Methods: This observational cross-sectional hospital-based study was conducted among 217 adult patients diagnosed with RA according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria at Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, Mumbai. Demographic details, clinical characteristics, laboratory investigations, Rheumatoid Factor (RF), Anti-Cyclic Citrullinated Peptide (Anti-CCP) antibody status, and Disease Activity Score-28 using ESR (DAS28-ESR) were recorded. Descriptive and inferential statistical analyses were performed, with $p<0.05$ considered statistically significant.

Results: Of the 217 participants, 89.4% were females, with a mean age of 54 years and a mean disease duration of 9.5 years. Overall, 92.1% were seropositive; 89.2% were RF positive and 54.4% were Anti-CCP positive. Vitamin D deficiency was the most prevalent comorbidity (51.2%), followed by hypothyroidism (38.7%), hypertension (35%), diabetes mellitus (18%), vitamin B12 deficiency (18.4%), osteoarthritis (16.1%), coronary artery disease (10.6%), and osteoporosis (10.6%). Anemia was the most common EAM (50.7%), followed by interstitial lung disease (9.2%), secondary Sjögren's syndrome (9.2%), vasculitis (5.1%), and rheumatoid nodules (1.4%). A significant association was observed between EAMs and higher disease activity measured by DAS28-ESR ($p<0.001$).

Conclusion: Vitamin D deficiency and anemia were the most common comorbidity and extra-articular manifestation, respectively, among patients with RA. The presence of EAMs was significantly associated with increased disease activity, highlighting the importance of early screening, comprehensive assessment, and regular monitoring to improve clinical outcomes and quality of life.

Keywords: Rheumatoid arthritis, Comorbidities, Extra-articular manifestations, Rheumatoid factor (RF), Anti-cyclic citrullinated peptide (Anti-CCP) antibodies.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disorder characterized by persistent symmetric polyarthritis, progressive joint destruction, and varying degrees of extra-articular involvement. It is the most common chronic inflammatory arthritis, with a global prevalence of approximately 0.5–1%, affecting women more frequently than men.[1] The disease commonly presents between 25 and 55 years of age and primarily involves the small joints of the hands and feet, although larger joints may also be affected as the disease progresses. Persistent synovial inflammation leads to cartilage destruction, bone erosion, deformities, pain, prolonged morning stiffness, and functional disability if left untreated.[2]

The pathogenesis of RA involves an antibody-mediated immune response resulting in chronic synovitis. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies are important serological markers that aid diagnosis, with anti-CCP demonstrating higher specificity. Disease activity is commonly assessed using the Disease Activity Score-28 with erythrocyte sedimentation rate (DAS28-ESR), while the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria provide a standardized approach for diagnosis.[3]

Beyond joint involvement, RA is associated with several comorbidities that substantially increase morbidity and mortality. Common comorbid conditions include hypertension, diabetes mellitus, hypothyroidism, osteoporosis, vitamin D deficiency, vitamin B12 deficiency, ischemic heart disease, and dyslipidemia. Chronic inflammation, reduced mobility, nutritional deficiencies, and prolonged corticosteroid therapy contribute to the development of these conditions. Cardiovascular disease remains the leading cause of mortality among patients with RA, emphasizing the importance of comprehensive evaluation beyond musculoskeletal manifestations.[4]

Approximately 40% of patients with RA develop extra-articular manifestations (EAMs), particularly those with longstanding disease, high disease activity, smoking history, or seropositivity. Frequently encountered EAMs include anemia, interstitial lung disease, rheumatoid nodules, vasculitis, and secondary Sjögren's syndrome. These manifestations are associated with greater disease severity, poorer functional outcomes, and increased mortality. Early recognition and appropriate management are therefore essential for improving long-term prognosis.[5]

Although RA is widely prevalent in India, data regarding the burden of comorbidities and extra-articular manifestations, particularly their association with serological status and disease activity, remain limited. Understanding these associations is essential for optimizing patient management, reducing complications, and improving quality of life. Therefore, the present study was undertaken to evaluate the prevalence of comorbidities and extra-articular manifestations among patients with rheumatoid arthritis, compare their occurrence in seropositive and seronegative patients, and determine their relationship with disease severity as assessed by the DAS28-ESR score.

MATERIALS AND METHODS

This observational cross-sectional hospital-based study was conducted at the Department of Rheumatology and Department of Internal Medicine, Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, Mumbai. The study included adult patients (≥18 years) of either sex attending the Rheumatology Outpatient Department who fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for rheumatoid arthritis and had a disease duration of more than three months.

The sample size was calculated based on an expected prevalence of 17%,[5] for the selected comorbidities, with a 95% confidence level and 5% allowable error, yielding a minimum required sample of 217 participants.

Patients with other connective tissue disorders, overlap syndromes, advanced disease not fulfilling the ACR/EULAR criteria, disease duration of less than three months, or active infections were excluded from the study.

After obtaining written informed consent, demographic and clinical details were recorded through a structured proforma. A comprehensive clinical examination was performed, and disease activity was assessed using the Disease Activity Score-28 with erythrocyte sedimentation rate (DAS28-ESR), based on tender and swollen joint counts. Laboratory investigations included rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibody, complete blood count, erythrocyte sedimentation rate, C-reactive protein, thyroid profile, vitamin D and vitamin B12 levels, fasting and postprandial blood glucose, antinuclear antibody by immunofluorescence, and urine routine examination. Additional investigations such as electrocardiography, chest radiography, and two-dimensional echocardiography were performed whenever clinically indicated.

As this was a non-interventional observational study, participants were evaluated only once without follow-up. Data were entered into Microsoft Excel and analyzed using appropriate statistical software. Continuous variables were expressed as mean ± standard deviation or median with range, while categorical variables were presented as frequencies

and percentages. Group comparisons were performed using Student's t-test or Wilcoxon signed-rank test for continuous variables and Chi-square or Fisher's exact test for categorical variables. Associations between categorical and continuous variables were assessed using ANOVA or Kruskal–Wallis test, while Pearson's or Spearman's correlation coefficients were used to evaluate correlations. A p-value <0.05 was considered statistically significant.

The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from all participants, and confidentiality was maintained by anonymizing patient data and using coded identifiers throughout the study.

RESULTS

A total of 217 patients fulfilling the 2010 ACR/EULAR criteria for rheumatoid arthritis were included in the study. Females constituted the majority of participants (89.4%), with a mean age of 54.6 ± 13.0 years and a mean disease duration of 9.5 ± 6.4 years.

Table 1: Baseline demographic and clinical characteristics (n=217)

Variable	Value
Female sex	194 (89.4%)
Male sex	23 (10.6%)
Mean age (years)	54.6 ± 13.0
Mean disease duration (years)	9.5 ± 6.4
Mean DAS28-ESR score	3.93 ± 1.6
Mean tender joint count	5.57
Mean swollen joint count	2.98

RA predominantly affected middle-aged females, with a mean disease duration of nearly 10 years.

Table 2: Serological profile and disease activity

Variable	n (%)
RF positive	195 (89.9)
Anti-CCP positive	118 (54.4)
RF+/Anti-CCP+	113 (52.1)
RF+/Anti-CCP−	82 (37.8)
RF−/Anti-CCP+	5 (2.3)
RF−/Anti-CCP−	17 (7.8)
ANA positive	39 (18.0)
Remission	61 (28.1)
Low disease activity	37 (17.1)
Moderate disease activity	52 (24.0)
High disease activity	67 (30.9)

More than 90% of patients were seropositive, and approximately one-third had high disease activity.

Table 3: Prevalence of comorbidities

Comorbidity	n (%)
Vitamin D deficiency	111 (51.2)
Hypothyroidism	84 (38.7)
Hypertension	76 (35.0)
Vitamin B12 deficiency	40 (18.4)
Diabetes mellitus	39 (18.0)
Osteoarthritis	35 (16.1)
Coronary artery disease	23 (10.6)
Osteoporosis	23 (10.6)

Vitamin D deficiency was the commonest comorbidity, followed by hypothyroidism and hypertension.

Table 4: Distribution of number of comorbidities

Number of comorbidities	n (%)
None	34 (15.7)
One	54 (24.9)
Two	55 (25.3)
Three	41 (18.9)
≥4	33 (15.2)

Nearly 60% of patients had two or more comorbidities.

Table 5: Factors associated with number of comorbidities

Variable	p-value
Age	<0.001
Disease duration	<0.001
ANA positivity	0.035
Serological status	0.722

Increasing age, longer disease duration, and ANA positivity were significantly associated with a higher number of comorbidities, whereas RF/Anti-CCP status showed no significant association.

Table 6: Prevalence of extra-articular manifestations (EAMs)

Extra-articular manifestation	n (%)
Anemia	110 (50.7)
Interstitial lung disease	20 (9.2)
Secondary Sjögren syndrome	20 (9.2)
Vasculitis	11 (5.1)
Rheumatoid nodules	3 (1.4)

Anemia was the most frequent extra-articular manifestation.

Table 7: Distribution of extra-articular manifestations

Number of EAMs	n (%)
None	85 (39.2)
One	102 (47.0)
Two or more	30 (13.8)

Approximately 61% of patients had at least one extra-articular manifestation.

Table 8: Factors associated with extra-articular manifestations

Variable	p-value
Age	0.012
Disease duration	<0.001
ANA positivity	<0.001
Anti-CCP positivity	0.005
RF positivity	0.516

Extra-articular manifestations were significantly associated with increasing age, longer disease duration, ANA positivity, and Anti-CCP positivity.

Table 9: Association between disease activity and comorbidities

Variable	Significant association
Vitamin B12 deficiency	Yes (p=0.038)
Diabetes mellitus	No
Hypertension	No
Hypothyroidism	No
Coronary artery disease	No
Vitamin D deficiency	No
Osteoporosis	No
Osteoarthritis	No

Among all comorbidities, only vitamin B12 deficiency demonstrated a significant association with disease activity.

Table 10: Association between disease activity and extra-articular manifestations

Variable	p-value
Anemia	0.010
Interstitial lung disease	0.020
Secondary Sjögren syndrome	<0.001
Vasculitis	0.088
Rheumatoid nodules	0.078
Number of EAMs	<0.001

Disease activity increased significantly with the presence and number of extra-articular manifestations. Patients with anemia, interstitial lung disease, and secondary Sjögren syndrome were more likely to have high disease activity.

DISCUSSION

This cross-sectional study evaluated the prevalence of comorbidities and extra-articular manifestations (EAMs) among patients with rheumatoid arthritis (RA) and their association with serological status and disease activity. The study demonstrated that vitamin D deficiency was the most common comorbidity, while anemia was the most frequent extra-articular manifestation. Increasing age, longer disease duration, and ANA positivity were significantly associated with a greater burden of comorbidities, whereas EAMs were significantly associated with age, disease duration, anti-CCP positivity, ANA positivity, and higher disease activity.

The study population predominantly consisted of females (89.4%), with a mean age of 54.6 years and a mean disease duration of 9.5 years. These findings are consistent with large international cohorts such as the COMORA and QUEST-RA studies, as well as Indian registries, which have consistently reported a female predominance and middle-aged presentation of RA.[6,7,8] The observed increase in comorbidities among older patients and those with longer disease duration also agrees with previous studies, highlighting the cumulative effect of chronic inflammation and prolonged treatment exposure.

Seropositive RA constituted over 90% of the study population, with 89.9% positivity for rheumatoid factor and 54.4% positivity for anti-CCP antibodies. These findings are comparable with previous Indian studies, although RF positivity was higher than that reported in several international cohorts.[6,7] Anti-CCP positivity was similar to that observed in other published studies and reinforces its role as an important diagnostic and prognostic marker.

Vitamin D deficiency (51.2%) was the most prevalent comorbidity observed, consistent with previous reports demonstrating a high prevalence of hypovitaminosis D among patients with RA. Chronic inflammation, reduced sunlight exposure, and limited physical activity may contribute to this deficiency. Hypothyroidism (38.7%) and hypertension (35%) were the next most frequent comorbidities. While the prevalence of hypertension was comparable with several international studies, hypothyroidism was relatively higher than that reported in many Western populations but similar to findings from Indian studies, suggesting regional differences and emphasizing the importance of routine thyroid screening in RA.[9,10]

Diabetes mellitus, vitamin B12 deficiency, osteoarthritis, coronary artery disease, and osteoporosis were also commonly encountered. Cardiovascular disease remains one of the leading causes of mortality in RA, although the prevalence of coronary artery disease in the present study was comparable with previous reports. Osteoporosis occurred less frequently than in several published studies, possibly reflecting earlier diagnosis, adequate vitamin D and calcium supplementation, and judicious corticosteroid use.

Approximately 84% of patients had at least one comorbidity, demonstrating the substantial burden of multimorbidity in RA. The number of comorbidities increased significantly with age and disease duration but was not associated with RF or anti-CCP serological status. Among the individual comorbidities, only vitamin B12 deficiency showed a significant association with disease activity, whereas the overall number of comorbidities did not correlate with DAS28-ESR scores.

Extra-articular manifestations were identified in 60.8% of patients, a prevalence comparable with several published studies. Anemia was the commonest manifestation (50.7%), followed by interstitial lung disease and secondary Sjögren syndrome (9.2% each), vasculitis (5.1%), and rheumatoid nodules (1.4%). The predominance of anemia agrees with previous Indian and international studies and reflects the combined effects of chronic inflammation, nutritional deficiencies, impaired erythropoiesis, and drug-related adverse effects.[11,12]

Interstitial lung disease remains one of the most clinically significant extra-articular manifestations because of its association with poor prognosis. The prevalence observed in the present study was comparable to reports from other Asian populations.[13,14]

Unlike comorbidities, extra-articular manifestations demonstrated significant associations with age, disease duration, anti-CCP positivity, ANA positivity, and disease activity. Although RF-positive patients showed a higher frequency of EAMs, the association was not statistically significant. These findings support previous evidence suggesting that anti-CCP positivity is a better predictor of severe systemic disease than rheumatoid factor alone.

Overall, the findings emphasize that RA should be regarded as a systemic disease rather than an isolated inflammatory arthritis. Early identification of comorbidities and extra-articular manifestations, particularly among patients with prolonged disease duration, advanced age, and anti-CCP positivity, may facilitate timely intervention and improve long-term clinical outcomes. Routine screening for vitamin D deficiency, thyroid dysfunction, cardiovascular risk factors, anemia, and pulmonary involvement should therefore be incorporated into the comprehensive management of patients with rheumatoid arthritis.

CONCLUSION

Rheumatoid arthritis is a chronic autoimmune disorder often associated with comorbidities and extra articular manifestations. Comorbidities include diabetes mellitus, hypertension, coronary artery

disease, hypothyroidism, vitamin D deficiency, Vitamin B12 deficiency, osteoporosis and osteoarthritis; among which Vitamin D deficiency is the most prevalent. Extra articular manifestations include anemia, interstitial lung disease, vasculitis, Sjogrens syndrome and rheumatoid nodule among them, anemia is the most prevalent extra articular manifestation. The presence of comorbidities and extra articular manifestations can be associated with the age, duration of disease, disease process and modalities of treatment. Long term use of steroids and NSAIDs plays a role in developing these associated conditions. The EAMs and comorbidities are more in seropositive patients compared to seronegative RA. Presence of extra articular manifestations increases the severity of disease in rheumatoid arthritis patients. Presence of comorbidities and extra articular manifestations in a patient of rheumatoid arthritis affects the line of treatment and course of the disease. Early screening and identification of such condition will improve the outcome and the overall wellbeing of the patients. RA patients with EAM should be treated and monitored regularly in order to reduce the mortality rate.

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