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ORIGINAL ARTICLE

Clinico-demographic differences and severity of rheumatoid arthritis.

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ABSTRACT… Objective: To find out the differences in disease severity of Rheumatoid Arthritis (RA) depending on clinic-demographic variables and determine association between clinic-demographic variables and disease severity of RA. **Study Design:** Cross-sectional Analytical study. **Setting:** Department of Medicine & Allied at CMA Hospital, Azra Naheed Medical College, Superior University Lahore. **Period:** August 2021 to April 2022. **Material & Methods:** After IRB approval 266 patients, aged 21 to 80 years, of both sexes, diagnosed with RA were enrolled. DAS-28 score was employed to assess disease severity. Demographic information and medical records of the patients were assessed and recorded. SPSS version 21 was used for data analysis. **Results:** Among the 133 patients with active disease, 113 (85.0%) were females and 20 (15.0%) male having mean age 40.0±12.8 years. Mean duration of disease in years was 8.3±6.2 and mean DAS-28 score was 5.5±0.9. RA Factor was positive in 96 (72.2%) and Anti-CCP antibody was seen in 78 (58.8%). Mean Hemoglobin level was 11.7±1.1 g/dl and anemia was found in 47 (35.5%) patients. Mean TLC and platelet count were 8.8±2.2 $\times 10^9$/L and 375.9±83.5 $\times 10^9$/L respectively. Among the 133 patients with LDA/remission, 106 (79.7%) were females and 27 (20.3%) male having mean age 44.5±15.5 years. Mean duration of disease in years was 8.5±7.6 and Mean DAS-28 score was 2.5±0.5. RA Factor was positive in 106 (79.7%) and Anti-CCP antibody was seen in 94 (70.7%). Mean Hemoglobin level was 12.6±1.8 g/dl and anemia was found in 29 (21.8%) patients. Mean TLC and platelet count were 9.5±3.5 $\times 10^9$/L and 333.7±109.1 $\times 10^9$/L respectively. **Conclusion:** Anti-CCP antibody positive patients with anemja and having disease for more than 3 years are more likely to have active rheumatoid arthritis whereas there was no significant difference with regards to age, sex and RA Factor status.

Key words: DAS-28 Score, Disease Severity, Rheumatoid Arthritis.

INTRODUCTION

Occurring in almost 1% population globally, Rheumatoid arthritis (RA) being one of the commonly seen inflammatory arthritis.[1] RA, essentially a joint disease, can have extra-articular features and abnormal immune responses. The pathogenesis of RA is not understood completely and is related to complex interactions of gene-environment which abrupt immune tolerance accelerating systemic and articular and systemic inflammation.[2] There are numerous safe and effective DMARDs available that help to reduce inflammation and help achieve remission or low disease activity in Rheumatoid Arthritis.[3] Treat-to-target principles highlight the necessity of achieving low disease activity or remission to prevent complications and disability.[4] Maintaining a continuous state of stable low disease activity or remission, however, is not achieved in all patients in spite of stringent therapy.[5,6] Various studies report moderate or high disease activity is not uncommonly seen among RA patients despite compliance to therapy.[7,8,9] Rheumatoid Arthritis is a chronic debilitating disease which amounts to a crucial portion of disability and disease burden causing significant financial strain in Pakistan where majority of population lives under the poverty line and healthcare resources are near exhaustion. In particular, it is not known whether ethnic, demographic and clinical differences affect disease severity of Rheumatoid Arthritis. No evidence has been generated yet regarding this in the Pakistani population.

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The rationale of present study was to find out the differences in disease severity of Rheumatoid Arthritis (RA) depending on clinic-demographic variables and determine association between clinic-demographic variables and disease severity of RA so that appropriate management may be given to the patients to reduce morbidity, disability and mortality.

MATERIAL & METHODS

The present cross-sectional observational study was carried in Out-Patient Department of Medicine & Allied at CMA Hospital, Azra Naheed Medical College, Superior University Lahore from August 2021 to April 2022. The objective of this study was to find out the differences in disease severity of Rheumatoid Arthritis (RA) depending on clinic-demographic variables and determine association between clinic-demographic variables and disease severity of RA. The 2010 ACR Diagnostic Criteria (Table-I) was used to define RA and to determine disease severity DAS-28 score (Table-II) was employed. After approval from IRB of CMA Hospital Lahore, 266 patients aged 21 to 80 years of both sex with RA as per operational definition were enrolled using non-probability consecutive sampling technique with 133 patients with active disease and 133 patients with LDA/remission. Patients currently on steroids and biologic DMARDS; patients with history of steroid or biologic DMARDs use in last 12 weeks; patients having chronic diseases including diabetes mellitus, hypertension, ischemic heart disease, chronic kidney failure, chronic lung disease, hematologic diseases and malignancy; and patients with pregnancy or breast feeding were excluded.

After informed consent, basic demographic information e.g. age, sex, socioeconomic status, duration of disease, educational status, along with medical history was taken from each participant and recorded. DAS-28 score of each patient was assessed and noted. Active disease was labelled as patients having DAS-28 score >3.2 and low disease activity/remission were patients with DAS-28 score <3.2. Standard treatment as per hospital protocol was given to all patients. SPSS 21 was employed to enter and analyze data. Numerical variables were represented by mean and standard deviation. For qualitative variables, percentage and frequency were generated. Confounders and effect modifiers were controlled via stratification, with $p \leq 0.05$ significant, Chi Square test applied.

RESULTS

Of the 266 patients included in our study, 219 (82.3%) were females and 47 (17.7%) male having mean age 42.6$\pm$14.3 years. One hundred and twenty-three (46.2%) patients were younger than 40 years old, 108 (40.6%) were aged 41-60 years and 35 (16.2%) were older than 61 years. Mean duration of disease in years was 8.4$\pm$6.9 with 193 (72.6%) patients having duration of disease greater than 3 years. Mean ESR was 32.6$\pm$23.8 mm/hr. Mean VAS score, tender joint count, swollen joint count and DAS-28 score were 3.9$\pm$2.8, 4.2$\pm$4.1, 2.4$\pm$2.7 and 4.0$\pm$1.6 respectively. RA Factor was positive in 202 (75.9%) and Anti-CCP antibody was seen in 172 (64.7%). Mean Hemoglobin level was 12.2$\pm$1.5 g/dl and anemia was found in 76 (28.6%) patients. Mean TLC and platelet count were 9.1$\pm$2.9 $\times 10^9$/L and 354.8$\pm$99.2 $\times 10^9$/L respectively.

Among the 133 patients with active disease, 113 (85.0%) were females and 20 (15.0%) male having mean age 40.0$\pm$12.8 years. Sixty-seven (50.4%) patients were younger than 40 years old, 52 (39.1%) were aged 41-60 years and 14 (10. 5%) were older than 60 years. Mean duration of disease in years was 8.3$\pm$6.2 with 105 (78.9%) patients having duration of disease greater than 3 years. Mean ESR was 49.9$\pm$22.6 mm/hr. Mean VAS score, tender joint count, swollen joint count and DAS-28 score were 6.4$\pm$1.5, 7.2$\pm$3.8, 4.5$\pm$2.3 and 5.5$\pm$0.9 respectively. RA Factor was positive in 96 (72.2%) and Anti-CCP antibody was seen in 78 (58.8%). Mean Hemoglobin level was 11.7$\pm$1.1 g/dl and anemia was found in 47 (35.5%) patients. Mean TLC and platelet count were 8.8$\pm$2.2 $\times 10^9$/L and 375.9$\pm$83.5 $\times 10^9$/L respectively.

Among the 133 patients with LDA/remission, 106 (79.7%) were females and 27 (20.3%) male having mean age 44.5$\pm$15.5 years. Fifty-six

(42.1%) patients were younger than 40 years old, 56 (42.1%) were aged 41-60 years and 21 (15.8%) were older than 60 years. Mean duration of disease in years was 8.5±7.6 with 88 (66.2%) patients having duration of disease greater than 3 years. Mean ESR was 15.3±4.8 mm/hr. Mean VAS score, tender joint count, swollen joint count and DAS-28 score were 1.4±1.2, 1.2±1.0, 0.3±0.8 and 2.5±0.5 respectively. RA Factor was positive in 106 (79.7%) and Anti-CCP antibody was seen in 94 (70.7%). Mean Hemoglobin level was 12.6±1.8 g/dl and anemia was found in 29 (21.8%) patients. Mean TLC and platelet count were 9.5±3.5 $\times 10^9$/L and 333.7±109.1 $\times 10^9$/L respectively.

Comparisons of quantitative and qualitative variables with regards to disease severity of Rheumatoid Arthritis are shown in Table-III and Table-IV respectively. On stratification, a statistically significant association of disease severity was seen with duration of disease (p-value: 0.019), Anti-CCP antibody positivity (p-value: 0.040), and anemia (p-value: 0.015). However, other variables did not demonstrate an association with disease severity: age (p-value: 0.282), sex (p-value: 0.260), and RA factor (p-value: 0.151).

DISCUSSION

Rheumatoid arthritis (RA), a frequently seen inflammatory arthritis, is primarily a joint disease however abnormalities in systemic immune reactions lead to a variety of extra-articular features.[1] Being a chronic autoimmune disease, RA is heralded with penetration of inflammation cells such as neutrophils, macrophages and dendritic cells in the synovium, leading to continuous demolition of joints, cartilage and bone and therefore marked disability, morbidity and reduced quality of life.[10] No single variable is present to assess disease severity in RA.[11] Disease severity in RA is generally evaluated by the DAS-28 score at baseline and follow up, which is calculated by the swollen joint count, tender joint count, patient global assessment on VAS and ESR.[12] Cut points of DAS-28 score are used to identify patients in remissions along with severe, moderate and low disease activity as mentioned in Table-II. Using the DAS-28 score, we divided the participants in to active disease group (DAS-28 score >3.2) and LDA/remission group (DAS-28 score <3.2).

2010 ACR Diagnostic Criteria For Rheumatoid Arthritis	
Clinical Parameters	**Score**
A. Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
More than 10 joints (at least 1 small joint)	5
B. Serology	
Negative RA Factor and negative Anti-CCP Antibody	0
Low-positive RA Factor or low-positive Anti-CCP Antibody	2
High-positive RA Factor or high-positive Anti-CCP Antibody	3
C. Acute-phase reactants	
Normal CRP and normal ESR	0
High CRP or high ESR	1
D. Duration of symptoms	
Less than 6 weeks	0
More than 6 weeks	1
Interpretation: Add score of categories A–D. A score of 6 or more is diagnostic for Rheumatoid Arthritis.	

Table-I. 2010 ACR diagnostic criteria for rheumatoid arthritis

DAS-28 Score to assess disease severity in Rheumatoid Arthritis
Scoring items: Tender joint count: 0-28 joints Swollen joint count: 0-28 joints ESR: in mm/h Patient global assessment (VAS): 0-10
Interpretation: Remission: <2.6 Low Disease Activity: 2.7 to 3.2 Moderate Disease Activity: 3.3 to 5.1 High Disease Activity : More than 5.1

Table-II. DAS-28 Score to assess disease severity in rheumatoid arthritis

Clinical Parameters	Group Assigned According to Disease Activity	
	Active Disease	LDA/ Remission
Mean age (years)	40.0±12.8	44.5±15.5
Mean Duration of disease (years)	8.3±6.2	8.5±7.6
Mean ESR (mm/hr)	49.9±22.6	15.3±4.8
Mean VAS score	6.4±1.5	1.4±1.2
Mean Tender joint count	7.2±3.8	1.2±1.0
Mean Swollen joint count	4.5±2.3	0.3±0.8
Mean DAS-28 score	5.5±0.9	2.5±0.5
Mean Hemoglobin (g/dl)	11.7±1.1	12.6±1.8
Mean TLC ($\times 10^9$/L)	8.8±2.2	9.5±3.5
Mean Platelet Count ($\times 10^9$/L)	375.9±83.5	333.7±109.1

Table-III. Comparison of quantitative parameters and disease activity

Clinical Para-meters	Group Assigned According to Disease Activity		P-Value
	Active Disease	LDA/ Remission	
Age Groups:			0.282 (non-significant)
<40 years	67 (54.5%)	56 (45.5%)	
40-60 years	52 (48.2%)	56 (51.8%)	
>60 years	14 (40.0%)	21 (60.0%)	
Sex:			0.260 (non-significant)
Female	113 (51.5%)	106 (48.5%)	
Male	20 (42.5%)	27 (57.5%)	
Duration of disease:			0.019 (significant)
<3 years	28 (38.3%)	45 (61.7%)	
>3 years	105 (54.4%)	88 (45.6%)	
RA Factor status:			0.151 (non-significant)
Positive	96 (47.5%)	106 (52.5%)	
Negative	37 (57.8%)	27 (42.2%)	
Anti-CCP Antibody status:			0.040 (significant)
Positive	78 (45.3%)	94 (54.7%)	
Negative	55 (58.5%)	39 (41.5%)	
Anemia:			0.015 (significant)
Present	47 (61.8%)	29 (38.2%)	
Absent	86 (45.2%)	104 (54.8%)	

Table-IV. Comparison of qualitative parameters and disease severity

In our study age (p-value: 0.282), sex (p-value: 0.260), and RA factor (p-value: 0.151) did not have any statistical association with disease severity of Rheumatoid Arthritis. One hundred and five (54.4%) with duration of disease greater than 3 years had active disease as compared with 28 (38.3%) with duration of disease less than 3 years having a p-value of 0.019, significant. With regards to Anti-CCP antibody status, active disease was seen in 78 (45.3%) patients with Anti-CCP antibody positivity and 55 (58.5%) with negative Anti-CCP antibodies (p-value: 0.040, significant). Forty-seven (61.8%) anemic patients had active disease while 86 (45.2%) patients without anemia had active disease having a statistically significant association with p-value: 0.015. Current management guidelines recommend conventional synthetic DMARDs (methotrexate, leflunomide, sulfasalazine etc) as first-line for all patients.[13] In case of failure to achieve remission or low disease activity, TNF inhibitors (adalimumab, etanercept, certolizumab etc) are second-line therapy.[13] In case of failure to a TNF inhibitor, switching to a different TNF inhibitor may be tried. Non-TNFi biologic DMARDs (Rituximab, tofacitinib, tocilizumab etc) are treatment options when there is failure to a second TNF inhibitor therapy.[14] This algorithm of treatment, however, does not address the characteristics which might affect probability of achieving remission in spite of therapy escalation. It may be possible to predict patient response to different therapies based on clinical and demographic differences including that the previous history of disease activity fluctuation so that decisions regarding therapy escalation may be tailored accordingly.

Our study has some limitations as well that need to be considered. This was single center study with relatively small sample size and included the patients taking outpatient care only. For establishing the exact association of clinical and demographic variables with disease severity of RA, cohort or case-control studies are a better option but require more resources and time. Utilizing the results of present study as baseline information, further studies should be planned to generate further evidence regarding this. In conclusion, the present study demonstrates that Anti-CCP antibody positive patients with anemia and having disease for more than 3 years are more likely to have active rheumatoid arthritis

whereas there was no significant difference with regards to age, sex and RA Factor status.

CONCLUSION

Anti-CCP antibody positive patients with anemia and having disease for more than 3 years are more likely to have active rheumatoid arthritis whereas there was no significant difference with regards to age, sex and RA Factor status. However further studies should be planned to generate further evidence regarding clinical and demographic differences with regards to disease severity in Rheumatoid Arthritis so that appropriate management may be done to reduce disease morbidity and disability.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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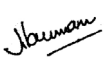
1	Nauman Ismat Butt	Conception and design, Analysis and interpretation of the data, Drafting of the article.	
2	Fahmina Ashfaq	Collection and assembly of data, Analysis and interpretation of the data, Critical revision and review.	
3	Osama Habib	Conception and design, Analysis and interpretation of the data, Drafting of the article.	
4	Aniqa Anser Tufail Khan Kakar	Literature review, Collection and assembly of data, Drafting of the article.	
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