ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 07 | July - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

CLINICAL FEATURES, LABORATORY PROFILE, TREATMENT OUTCOMES AND FOLLOW UP OF PATIENTS WITH SERONEGATIVE INFLAMMATORY ARTHRITIS

Rheumatology

Sasha Pereira* Lokmanya Tilak Municipal Medical College and Sion General Hospital, Mumbai
*Corresponding Author

Darshita Gosai Lokmanya Tilak Municipal Medical College and Sion General Hospital, Mumbai

Lalana Kalekar Lokmanya Tilak Municipal Medical College and Sion General Hospital, Mumbai

ABSTRACT

Introduction: Patients with arthritis whose serum does not contain rheumatoid factor are classified as having seronegative arthritis. We, through our study have aimed to study the Clinical Features, Laboratory Profile, Treatment Outcomes and Follow Up of Patients with Seronegative Inflammatory Arthritis. **Material and Methods:** This was a prospective observational study of 50 patients where we compared seronegative patients to a seropositive control and gave a descriptive analysis on the clinical features, laboratory profile and treatment outcome of these patients. **Results:** The prevalence of both seronegative and seropositive rheumatoid arthritis (RA) is more in females as compared to males and maximum in the age group of 40-50 years. Both seropositive and seronegative RA is rare in the extremes of age. `In the Seropositive group RA factor positivity is more prevalent than Anti-CCP positivity. **Conclusion:** The seropositive group had higher disease activity at baseline when compared to the seronegative group. However, response to treatment was more with the seronegative group when compared to the seropositive group at both 3 months and 6 months follow up. Delta DAS response was more in the seronegative group compared to seropositive group with response at 6 months follow up being better compared to 3 months follow-up.

KEYWORDS

INTRODUCTION:

Patients with arthritis whose serum does not contain rheumatoid factor are often classified as having seronegative arthritis. Between 23% to 40% of patients with rheumatoid disorders are seronegative, though recent interest in "hidden rheumatoid factor" has shown that even seronegative patients may have circulating immune complexes [1].Seronegative rheumatoid arthritis appears to have a more benign prognosis than seropositive disease, and the range of clinical symptoms may differ between the variants.

Diagnosis is clinical, based on the presence of joint pain, early morning stiffness (typically >1 hour), swollen, tender joints. If seronegative arthritis is suspected clinically, inflammatory markers such as erythrocyte sedimentary rate, C reactive protein and rheumatoid factor must be checked. Normal or negative results do not exclude inflammatory arthritis or rheumatoid arthritis. Rheumatoid factor is negative in up to a third of patients with rheumatoid arthritis, and in most patients with spondyloarthropathies. Full blood count, urea and electrolytes, liver function tests, and bone biochemistry as a baseline help guide treatment and identify any relevant comorbidities while Imaging techniques such as radiographs of the hands and feet can help identify erosions or typical features of inflammatory arthritis or rheumatoid arthritis, and sacroiliitis in spondyloarthropathies. A Bone scan is indicated on follow up.

A follow-up of patients shows that some become positive for rheumatoid factor while others develop psoriatic arthritis, Reiter's disease, and other non-rheumatoid disorders. Some, however, remain seronegative and do not produce other clearly defined syndromes. The DAS 28 score can be used to measure disease activity and gauge prognosis in arthritis. We, through our study aimed 1) To study clinical and laboratory profile of seronegative inflammatory arthritis patients. 2) To study treatment outcome in seronegative inflammatory arthritis patient 3) To compare clinical, lab profile and treatment outcome of seronegative inflammatory arthritis patients with seropositive controls 4) The use of DAS 28 score in patients with seronegative inflammatory arthritis and look for improvement in DAS 28 score on follow up 5) To study the use of bone scan in seronegative inflammatory arthritis.

MATERIALS AND METHODS

This was a prospective observational study conducted between February 2020 to June 2021. Our sample size consisted of 50 patients with seronegative arthritis from the outpatient and inpatient departments during the study period. The seronegative patients will be compared to a seropositive control group. Our control consisted of 50 patients of the same age, sex who were positive for serological markers such as RA factor, Anti CCP. Patients/ relatives consent was taken before participating in study.

Inclusion Criteria:

Clinical symptoms of arthritis > 6 weeks, Raised acute phase reactants, RA Factor, Anti CCP, HLA B27, ANA negative

Exclusion Criteria:

Patient/ relative not willing for participation. Patients with age less than 18 years.

RESULTS:

Our study had 100 patients, out of which 50 were seropositive and 50 seronegative patients. Out of the 50 seropositive patients, there were 49 females and 1 male, whereas in 50 seronegative patients 41 were female and 9 were male. In total there were 90% females and 10% males.

The seropositive patients were RA factor or Anti-CCP positive and seronegative patients were RA factor and Anti-CCP negative but with raised acute phase reactants, and clinically fitting into RA. Out of the 50 seropositive patients 38 were RA factor positive, and 12 were RA negative. In total, 62% patients were RA factor negative which included 50% seronegative patients, and 38% were RA factor positive.

Out of the 50 seropositive patients, 24 patients were anti-CCP positive, and 26 patients were anti-CCP negative. Overall, 76% were anti-CCP negative, which included 50% seronegative patients and 24 % were anti-CCP positive.

5% of patients (1 seropositive and 4 seronegative) patients did not fit into the American College of Rheumatology/European League against Rheumatism (ACR/EULAR) criteria of classification for rheumatoid arthritis. Therefore 49 out of 50 seropositive patients and 46 out of 50 seronegative patients could be taken as having definitive Rheumatoid arthritis according to EULAR 2010 criteria with a p value 0.168 using chi square test.

Arthritis was most prominent in the age group between 40 years to 50 years of age which constituted 39% of the study population out of which 23 patients (58.97%) were seropositive and 16 patients (41.02%) were seronegative. This was followed by the age group of 30 years to 40 years of age with 13 patients (54.16%) being seropositive and 11 patients (45.88%) being seronegative.

The seronegative group had more comorbidities compared to the seropositive group. The most common comorbid condition was hypertension with 9 % of the study population (5% seropositive, 4% seronegative) suffering from the same. This was followed by hypothyroidism at 7%, with its prevalence being more in the seronegative group. 6 % of the population suffered from multiple

comorbidities with prevalence of the same being more in the seronegative group. Interstitial lung disease and Diabetes Mellitus were some of the other co-morbid conditions.

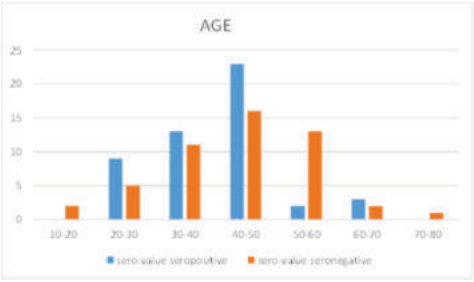

Figure 1: Graph showing distribution of study group according to age.

Table 1: Distribution of study subject according to comorbidities

Comorbidities	Serological Status		Total Percentage (%)
	Seropositive	Seronegative	
None	39	36	75
Hypertension	5	4	9
Interstitial Lung Disease	1	1	2
Diabetes Mellitus	0	1	1
Hypothyroidism	3	4	7
Multiple Co-morbidities	2	4	6
Total	50	50	100

10 patients in seronegative group compared to 4 patients in the seropositive group had early rheumatoid arthritis defined as duration of joint pain lesser than or equal to 3 months.

The mean duration of symptoms was 20 months with a standard deviation of 24.5 months.

In our study, minimum duration of joint pain was 2 months and maximum duration was 10 years, with 100% of patients having morning stiffness. The minimum duration of early morning stiffness was 15 minutes and maximum duration of stiffness was 60 minutes with the mean duration of early morning stiffness being 33 minutes.

In the seropositive group, metacarpophalangeal [MCP] followed by proximal interphalangeal joints [PIP] were commonly affected followed by knee and wrist. In the seronegative group, metacarpophalangeal [MCP] was commonly involved followed by, proximal interphalangeal [PIP], knee, wrist. The least commonly involved joint was the hip. Bone scan in the 3-hour delayed phase was used to look for radiotracer uptake in various joints. Two patients had involvement of the sacroiliac joint.

.

In the seropositive group, 37 patients had a Tender Joint Count[TJC] of 28 which reduced to 22 at 3months, 13 at 6 months.

In the seronegative group, 28 patients had a Tender Joint Count [TJC] of 28 , which decreased to 22 patients at 3 months and 6 patients at 6 months.

In the seropositive group, 0 patients had a Tender Joint Count[TJC] of 0, which remained 0 at 3months and increased to 6 at 6 months.

In the seronegative group, 0 patients had a Tender Joint Count[TJC] of 0 at baseline which increased to 4 at 3 months and 11 at 6 months.

Table 2: Distribution of subjects according to Tender Joint Count

TJC	Baseline		3 month		6 months	
	seropositive	seronegative	seropositive	seronegative	seropositive	seronegative
0	0	0	0	4	6	11
2	1	3	2	3	10	4
4	0	1	0	1	0	0
6	0	0	2	0	0	1
8	1	0	0	0	2	0
10	0	0	9	3	2	2
12	2	1	0	1	0	0
14	1	3	1	0	1	0
16	0	1	0	0	0	0
20	1	4	7	18	9	24
22	3	1	2	0	2	0
24	2	4	2	0	2	0
26	2	4	3	4	3	2
28	37	28	22	16	13	6
Total	50	50	50	50	50	50

In the seropositive group, 28 patients had a Swollen Joint Count [SJC] of 0 which increased to 36 at 3 months and 43 at 6 months.

In the seronegative group, 31 patients had a Swollen Joint Count [SJC] of 0 which increased to 43 patients at 3 months and 48 patients at 6 months.

Table 3: Distribution of Swollen Joint Count in patients

SJC	Baseline		3 month		6 month	
	seropositive	seronegative	seropositive	seronegative	seropositive	seronegative
0	28	31	36	43	43	48
1	4	0	2	0	2	0
2	8	9	5	2	2	0
4	3	1	2	0	1	0
6	0	1	0	1	1	1
10	5	2	3	1	0	0
12	1	0	1	0	1	0
20	1	6	1	3	0	1
Total	50	50	50	50	50	50

In the seronegative group, mean ESR at baseline was 38.6, at 3 months was 36.4, and at 6 months was 22.4. In seropositive group mean ESR at baseline was 101.5, at 3 months was 80 and at 6months was 74.

Table 4: Distribution of patients according to ESR

ESR baseline	sero-value		Total
	seropositive	seronegative	Percent(%)
0-20	4	6	10
>20	46	44	90
Total	50	50	100
ESR 3 month	**sero-value**		**Total**
	seropositive	seronegative	Percent(%)
0-20	7	12	19
>20	43	38	81
Total	50	50	100
ESR 6 month	**sero-value**		**Total**
	seropositive	seronegative	Percent(%)
0-20	8	16	24
>20	42	34	76
Total	50	50	100

P value ESR at baseline, 0.5, not significant; p value at 3 months and 6 months 0.06, not significant

In seropositive group, 5 patients had normal CRP and 45 patients had CRP >5. In seronegative group, 16 patients had normal CRP and 34 patients had CRP >5.

Table 5: Distribution of sunjects according to CRP

CRP	sero-value		Total
	seropositive	seronegative	Percent(%)
0-5	5	16	21
>5	45	34	79
Total	50	50	100

P value 0.006, significant

We classified patients as being in remission, having low, moderate, and high disease activity on the based on the Disease Activity Score [DAS-28] activity index.

In the seropositive group, 49 patients had high disease activity at baseline, 1 patient had moderate disease activity at baseline. At 3 months, 12 patients had moderate disease activity and high disease activity group numbers decreased from 49 at baseline to 38. At 6 months 2 patients went into remission, 5 had low disease activity, 18 had moderate disease activity and 28 had high disease activity with p value 0.0004.

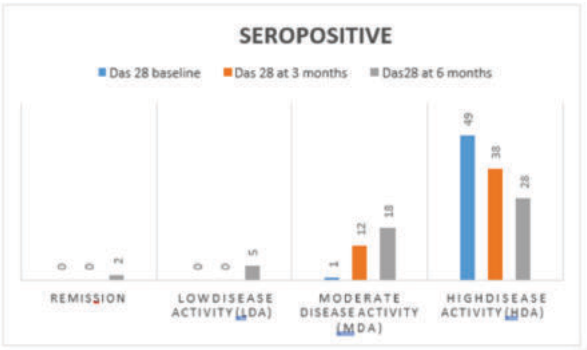

Figure 2: Figure showing Das 28-score distribution in seropositive group.

In the seronegative group, 43 patients had high disease activity at baseline, 7 patients had moderate disease activity at baseline. At 3 months, 12 patients had moderate disease activity and the high disease activity group numbers decreased from 43 at baseline to 34 at 3 months, 1 patient had low disease activity and 3 went into remission. At 6 months 6 patients went into remission, 4 had low disease activity, 19 had moderate disease activity and 21 had high disease activity with p value 0.001.

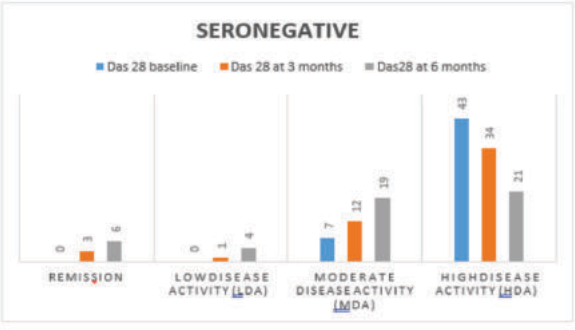

Figure 3: Showing distribution of DAS 28 score in seronegative group

The European League Against Rheumatism (EULAR) classifies good responders as having DAS28 scores of 3.2 or less with reductions in DAS28 of more than 1.2. Patients with DAS28 scores over 3.2 who have reductions in DAS28 scores of more than 1.2 have moderate responses. Patients with reductions in DAS28 of less than 0.6 are considered non-responders. We classified patient response as per the change in their DAS-28 scores [Delta DAS-28] after 3 months and 6 months of therapy when compared to baseline.

In the seropositive group 11 patients had good response, 9 patients had moderate response and 30 patients had no response at 3 months. In seronegative group, 12 patients had good response, 15 had moderate response, and 23 had no response at 3 months. Overall 23 patients had good response, 24 had moderate response, 53 had no response from baseline to 3 months.

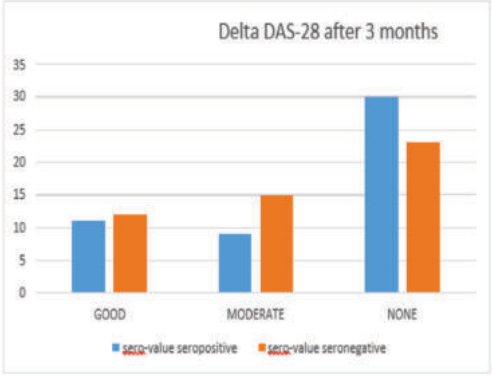

Figure 4: Figure showing Distribution of study subjects according to EULAR response criteria (Delta DAS baseline to 3 months)

After 6 months of therapy, in seropositive group, 28 patients had good response, 15 had moderate response, 7 had no response from baseline to 6 months. In the seronegative group, 29 patients had good response, 16 had moderate response, 5 had no response. Overall, 57 patients had good responses, 31 patients had moderate response, 12 patients had no response.

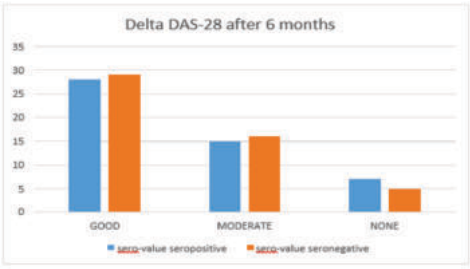

Figure 5: figure showing Distribution of study subjects according to EULAR response criteria (Delta DAS baseline to 6 months)

In our study, 98% received DMARDS, 2% did not receive any treatment. In seropositive group, 46 patients received only methotrexate, whereas 4 patients required 2 DMARDS i.e., methotrexate and leflunomide. In the seronegative group, 2 patients where not started on DMARDS due to low disease activity at baseline, 45 were on methotrexate only, whereas 3 patients required methotrexate and leflunomide.

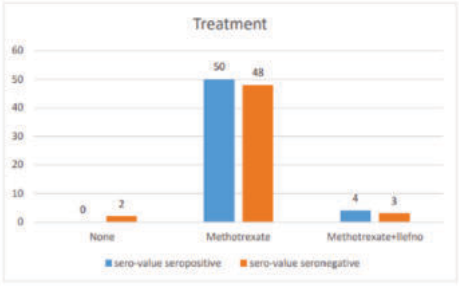

Figure 6: Figure showing treatment given in seropositive and seropositive groups.

We tried co-relating the duration of joint pain with disease activity in both groups, in the seropositive group 11 patients who presented with a joint pain duration of 1 year had high disease activity and 13 patients who presented with a joint pain duration of 2 years had high disease activity at baseline.

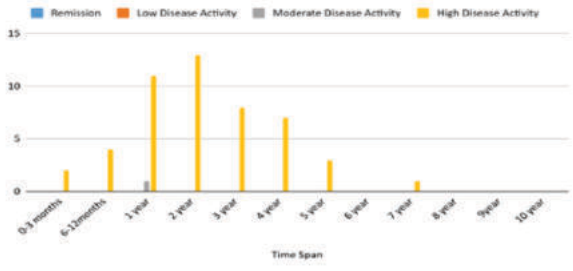

Figure 8: Figure showing co-relation between duration of joint pain and disease activity in seropositive group.

In our study, we tried to correlate duration of joint pain with disease activity. In the seronegative group 12 patients who presented with joint pain duration of 1 year had high disease activity. 10 patients with joint pain duration of 2 years had high disease activity at baseline.

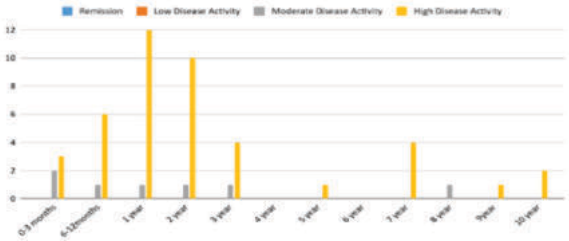

Figure 7: Figure showing co-relation between duration of joint pain and disease activity in seronegative group.

DISCUSSION

Demographics

This study had 50 patients with seropositive rheumatoid arthritis and 50 patients with seronegative inflammatory arthritis. The criteria for seronegative arthritis included clinical inflammatory arthritis with RA factor and anti-CCP negative with raised acute phase reactant (ESR or CRP).

The maximum representation in the study was in the age group 40-50 in both seropositive as well as seronegative groups which shows that both seronegative and seropositive RA is more in middle age group and rare in the extremes of age.

Out of 50 seropositive patients, there were 49 females and 1 male, compared to the 50 seronegative patients out of which 41 were female and 9 were male. Thus, the prevalence of RA was found to be 90% in females and 10% males.

These findings were consistent with the study conducted by Bajraktari IH et al [2] which reported the highest prevalence of RA in the age group of 40-49 years with females accounting for 76.8% of the study population.

The Seronegative group was associated with more comorbidities compared to the seropositive group. The study by J.M. davis[3]found comorbidities in seronegative RA greater than seropositive RA.(68). Hypertension (found in 13%), followed by Autoimmune hypothyroidism anti TPO positive(in 12%), followed by diabetes mellitus(in 5%) were amongst the most common comorbidities.

Clinical Features

100% of patients had morning stiffness. The minimum duration of early morning stiffness was 15 mins and maximum duration of stiffness was 60 mins. The mean duration of early morning stiffness being 33 mins. The most commonly involved joint in both seronegative and seropositive group was found to be metacarpophalangeal [MCP] joints and least commonly involved was the elbow.

Keeping with the ACR-EULAR guidelines for classification of rheumatoid arthritis we included patients with a duration of joint pain of more than or equal to 6 weeks. Amongst them, 10 patients in seronegative group had early RA (duration of joint pain 6 weeks to lesser than or equal to 3 months.)and 4 patients in seropositive group had early RA (duration of joint pain 6 weeks to lesser than or equal to 3 months.)The mean duration of symptoms was 20 months with standard deviation of 24.5 months.

According to a study by K W Chan et al.[4], patients with progressive disease, seropositive arthritis had a shorter median overall lag time to diagnosis, which was determined to be around 36 weeks, with the median diagnosis lag time being 18 weeks. A study by Behzad Heidari [5] claimed early diagnosis and treatment of RA can prevent joint erosions from occurring, reduce the progression of erosive illness, and may even affect treatment outcomes by resulting in remission.

Lab Profile

RA factor positivity was more prevalent than Anti-CCP in the seropositive group. 12 patients had both RA and Anti-CCP positive.

Seropositive RA had higher ESR at baseline compared to seronegative group. However, a significant decrease in ESR was found on follow up in both seropositive and seronegative groups compared to baseline. Similarly seropositive RA had higher CRP compared to the seronegative group. Tender Joint Count [TJC] was more in the seropositive group at baseline compared to the seronegative group. But on follow up at 6 months, the seronegative group had a better response in terms of lower Tender Joint Count [TJC]. On follow up at 6 months, seronegative group had better response in terms of lower Swollen Joint Count [SJC].

The Das-28 score was used to classify patients into high, moderate, low disease activity and remission. Delta DAS response was more in the seronegative group compared to seropositive group with response at 6 months follow up being better compared to 3 months follow up.

According to the study by Choi et al. [6], in the population with high disease activity, the Delta DAS-28 at 1 year was higher in seronegative arthritis patients than in seropositive arthritis patients, with radiologic outcomes at baseline and at 1- or 2-year follow-up being similar between the 2 groups.

They concluded that seronegative arthritis patients manifested more active disease at baseline, but showed a better response to treatment compared with seropositive patients. This contrasts with our study wherein patients with seropositive RA were found to have more aggressive disease at baseline even though the response to therapy was more in the seronegative group.

Treatment:

In our study group 2 patients in seronegative group had low DAS activity and were not initiated on DMARDS and were treated symptomatically. 98% of patients required DMARDS. In seropositive group, 46 patients received only methotrexate, whereas 4 patients required 2 DMARDS i.e. methotrexate and leflunomide. In the seronegative group, 45 were on methotrexate only, whereas 3 patients required methotrexate and leflunomide. Thus the total number of DMARS used were almost similar in both groups. HCQs and Sulfasalazine was used in all patients in our study. The decision to add leflunomide in addition to methotrexate was made for patients who had either high disease activity at baseline, or the patients who did not respond to methotrexate alone on 3 months follow up.

CONCLUSION

In our study, the prevalence of both seronegative and seropositive RA is more in females compared to males.The prevalence of RA was found to be maximum in the age group of 40-50 years. Both seropositive and seronegative RA is rare in the extremes of age. In the Seropositive group RA factor positivity is more prevalent than Anti-CCP positivity. Comorbid conditions were more common in patients of seronegative as compared to seropositive rheumatoid arthritis. The most common comorbidity associated with both groups was Hypertension, followed by autoimmune hypoth yroidism. Most involved joint in both seronegative and seropositive group is metacarpophalangeal [MCP] followed by proximal interphalangeal joints [PIP] followed by knee and least commonly involved is the hip.

All patients in our study had early morning stiffness with a mean duration of 33 minutes The seropositive group had higher disease activity at baseline when compared to the seronegative group. However, response to treatment was more with the seronegative group when compared to the seropositive group at both 3 months and 6 months follow up. Delta DAS response was more in the seronegative group compared to seropositive group with response at 6 months follow up being better compared to 3 months follow up. There was no difference in total number of DMARDs used in our study in seronegative and seropositive group.

Limitations

1. We carried out a single center institutional study; multi-center study on the parameters influencing clinical features, lab profile and treatment of seronegative rheumatoid arthritis is required to confirm or refute the findings of this study.
2. The sample size is small (n=100).
3. The follow-up duration in our study included baseline, 3 months, 6 months. Longer follow-up duration is required to analyze complete response to treatment.

REFERENCES:

1. Dai, Hui & Gao, Xiao-Ming. (2011). Elevated levels of serum antibodies against alpha-1, 6-glucan in patients with systemic lupus erythematosus or rheumatoid arthritis. Protein & cell. 2. 739-44. 10.1007/s13238-011-1095-1.
2. Bajraktari IH, Teuta BÇ, Vjollca SM, Bajraktari H, Saiti V, Krasniqi B, Muslimi F. Demographic features of patients with rheumatoid arthritis in kosovo. Med Arch. 2014 Dec;68(6):407-10. doi: 10.5455/medarh.2014.68.407-410. Epub 2014 Dec 16. PMID: 25649180; PMCID: PMC4314179.
3. Davis JM 3rd. Rheumatoid Arthritis: A Severe Disease That Preventive Approaches Would Greatly Benefit. *Clin Ther*. 2019;41(7):1240-1245. doi:10. 1016/j. clinthera. 2019.04.026
4. Chan KW, Felson DT, Yood RA, Walker AM. The lag time between onset of symptoms and diagnosis of rheumatoid arthritis. *Arthritis Rheum*. 1994;37(6):814-820. doi:10.1002/art.1780370606
5. 2. Heidari B. Rheumatoid Arthritis: Early diagnosis and treatment outcomes. Caspian J Intern Med. 2011 Winter;2(1):161-70. PMID: 24024009; PMCID: PMC3766928.
6. Choi S, Lee KH. Clinical management of seronegative and seropositive rheumatoid arthritis: A comparative study. PLoS One. 2018 Apr 6;13(4):e0195550. doi: 10. 1371/ journal.pone.0195550. Erratum in: PLoS One. 2018 Jun 18;13(6):e0199468. PMID: 29624625; PMCID: PMC5889180.