ORIGINAL RESEARCH PAPER
Volume - 14 | Issue - 04 | April - 2025 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

FEVER MANIFESTATIONS IN AUTOIMMUNE RHEUMATIC DISORDERS: A COMPREHENSIVE REVIEW

Rheumatology

Dr R N Tejaswini — Dr NB Resident Department Of Rheumatology And Clinical Immunology, ESIC Medical College And Hospital, Sanath Nagar, Hyderabad, Telangana, India

Dr Vijaya Prasanna Parimi — Senior Consultant Department Of Rheumatology And Clinical Immunology, ESIC Medical College And Hospital, Sanath Nagar, Hyderabad, Telangana, India

Dr S Bhavana — Dr NB Resident Department Of Rheumatology And Clinical Immunology, ESIC Medical College And Hospital, Sanath Nagar, Hyderabad, Telangana, India

Dr G Narsimulu — Professor Department Of Rheumatology And Clinical Immunology, ESIC Medical College And Hospital, Sanath Nagar, Hyderabad, Telangana, India

ABSTRACT

Objective: The objective of this prospective study is to assess the clinical presentation and underlying causes of fever in patients with autoimmune rheumatic diseases (AIRDs). To assess the utility of biomarkers such as C-reactive protein (CRP), Procalcitonin, NLR (Neutrophil Lymphocyte Ratio) in differentiating fever secondary to disease flare and infection among Systemic lupus erythematous(SLE) patients. **Methods:** This prospective cohort study was conducted at a Rheumatology department in a tertiary care center in South India, spanning from April 2022 to December 2022. The study encompassed patients admitted with fever to the Department. Comprehensive data, including demographics, fever etiology, and disease activity indices were collected and analyzed. **Results:** 92 patients exhibited signs of fever during the study period. Among these, 31 cases were of Rheumatoid arthritis (RA), 26 cases of SLE and 35 cases were of other AIRD categories. Infection was the most prevalent cause of fever (48.9%), while 45.6% were attributed to flare-ups of underlying AIRDs. Additionally, infections mimicking AIRDs constituted 4.3% and 1.08% were drug-related fever. In SLE patients, elevated CRP levels were significantly associated with infections ($p<0.006$) and a heightened NLR was observed in those with disease flare ($p<0.001$). **Conclusions:** Fever commonly manifests in AIRDs, with infections and disease flare as the key etiological factors. The findings underscore the impact of disease activity and poor adherence to treatment on the increased incidence of infections. The study emphasizes the necessity for comprehensive evaluation upon the onset of fever in different AIRDs, as discerning the underlying causes guides appropriate management strategies.

KEYWORDS

Fever, Autoimmune Rheumatic Diseases, Infections, Disease Flare, C - reactive protein, Neutrophil-lymphocyte Ratio.

INTRODUCTION

Fever within autoimmune rheumatic diseases often serves as an indicator of disease activity or potential complications, covering a broad spectrum of conditions like Rheumatoid arthritis, Systemic lupus erythematosus (SLE), Systemic sclerosis, and Sjogren's syndrome. The interpretation of fever's significance hinges on the specific disease context. Various reasons underlie fever occurrences in these conditions, potentially signalling increased inflammation, disease exacerbation, heightened activity, or susceptibility to infections due to immune system irregularities and immunosuppressive treatments. Fever may also arise as a side effect of certain medications or indicate disease-related complications like vasculitis or organ involvement, necessitating vigilant monitoring and potential changes in treatment strategies.

Patients experiencing fever alongside autoimmune rheumatic diseases require comprehensive evaluation by healthcare providers. This involves detailed clinical examinations, lab tests, and potentially imaging studies to pinpoint the underlying cause. Factors such as the individual's specific autoimmune condition, treatment history, recent medication adjustments, and symptomatology play crucial roles in this evaluation. Tailoring treatment depends on identifying the exact cause of the fever, whether it involves adjustments to ongoing disease management or addressing complications identified through the evaluation process.

Fever significantly impacts the well-being and, in severe cases, the survival of individuals with Autoimmune Rheumatic Diseases (AIRDs). However, diagnosing its cause presents challenges due to factors like low-grade fever common in AIRDs, complications from medications like NSAIDs and corticosteroids, and fever mirroring infectious disease symptoms. Research indicates that about 22% of fever cases with unknown origins link to underlying inflammatory causes, particularly prevalent in conditions like adult-onset Still's disease (AOSD) and large vessel vasculitis.(1) Ongoing studies aim to categorize fever origins, identify common infections in rheumatological disorders, evaluate disease activity indices, and explore biomarkers to distinguish fever from disease flare, especially in Systemic Lupus Erythematosus (SLE) patients.

MATERIALS AND METHODS:

Conducted between April 2022 and December 2022, this prospective cohort study took place in the rheumatology department of a tertiary care center in South India. Patients admitted with fever to the department were considered for inclusion.

Collected data includes patient demographics, particulars to determine the origins of fever, disease activity indices of various AIRDs, and laboratory parameters such as C-reactive protein (CRP), Procalcitonin, ESR (Erythrocyte sedimentation ratio) and neutrophil-lymphocyte ratio (NLR) to evaluate their effectiveness in distinguishing between fever and disease flare in SLE patients.

Following data analysis, patients were classified based on their specific rheumatic diseases. The study included patients with persistent documented evidence of fever (temperature >99.9F, orally or axillary) for more than 24 hours, while those with only a single record of fever or incomplete data were excluded from the study.

RESULTS:

Demographic Data:

Table I: AIRDs Among Patients With Fever

AIRDs PATIENTS WITH FEVER	PERCENTAGE
RA	31(33.69%)
SLE	26(28.26%)
RA/SLE OVERLAP	3(3.26%)
OTHER CTD	9(9.78%)
SPA	8(8.69%)
VASCULITIS	5(5.43%)
SOJIA	3(3.26%)
JIA	2(2.17%)
RHEUMATOLOGICAL MANIFESTATIONS OF INFECTIOUS DISEASES	5(5.43%)

Among 92 admitted patients, Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) were predominant, comprising 33.69% and 28.26%, respectively. RA/SLE overlap constituted 3.26%, while other Connective Tissue Diseases (CTDs) represented 9.78%, showcasing diverse rheumatic conditions. Spondyloarthritis (SPA) accounted for 8.69%, Vasculitis for 5.43%, and Systemic-Onset

Juvenile Idiopathic Arthritis (SOJIA) and Juvenile Idiopathic Arthritis (JIA) jointly represented 5.4%. Rheumatological Manifestations of Infectious Diseases contributed 5.43%, emphasizing infectious impact on rheumatic symptoms.

Table I offers a thorough breakdown of Autoimmune Rheumatic Disease (AIRD) patients admitted to the Rheumatology department from April to December 2022, highlighting fever cases. This breakdown offers valuable insights into AIRD prevalence, aiding tailored management strategies for specific subtypes amidst fever admissions.

Etiology Of Fever In Rheumatoid Arthritis Patients:

Table II: Etiology Of Fever In Rheumatoid Arthritis Patients

RA etiology	Frequency	Percentage
INFECTION	22	70.97
RESPIRATORY TRACT INFECTIONS(TOTAL) 1.COVID19 INFECTION 2.URTI/PHARYNGITIS 3.LRTI	 13 1 8 4	 41.94 3.23 25.81 12.90
UTI (E.coli> Klebsiella)	4	12.90
GE	3	9.68
KNEE BURSITIS	1	3.23
RT KNEE SEPTIC ARTHRITIS	1	3.23
DISEASE FLARE	9	29.03
Grand Total	**31**	**100**

In Rheumatoid Arthritis (RA) patients, infections were the primary cause of fever, making up 70.97% of cases. Most were respiratory tract infections (41.94%), including one COVID-19 case and four confirmed lower respiratory infections. Urinary tract infections (UTIs) contributed 12.90%, primarily caused by Escherichia coli and Klebsiella. Viral infections, like upper respiratory and gastroenteritis, accounted for the rest. Patients with moderate to severe disease activity showed mild fever, which eased with optimized Disease-Modifying Antirheumatic Drugs (DMARDs).

Table II visually breaks down these fever causes in RA patients. This data emphasizes the significant impact of infections, especially respiratory and UTIs, on fever in RA. Highlighting COVID-19 among respiratory infections stresses monitoring during the pandemic. Identifying pathogens like Escherichia coli and Klebsiella underscores the need for targeted strategies in managing these challenges in RA patients.

Etiology Of Fever In Systemic Lupus Erythematosus Patients

Table III: Etiology Of Fever In Systemic Lupus Erythematosus Patients

SLE Etiology	Frequency	Percentage
DISEASE FLARE	17	65.38
UTI	4	15.38
ACUTE G.E	2	7.7
DENGUE	1	3.85
LT ELBOW SYNOVITIS	1	3.85
RESPIRATORY TRACT INFECTION	1	3.85
Grand Total	**26**	100

In Systemic Lupus Erythematosus (SLE) patients, fever mostly stemmed from underlying disease flare (65.38%), with 47% linked to poor treatment compliance due to various reasons like economic constraints. Infections, notably UTIs, accounted for 15.38% of fever cases, followed by gastroenteritis, respiratory infections, and other causes. One patient with SLE and Rheumatoid Arthritis (RA) overlap experienced fever due to an infusion reaction to Rituximab. Figure 3 visually breaks down these fever causes in SLE patients. The data highlights disease flares' significant impact on fever, stressing the need for effective management strategies and monitoring. Poor treatment compliance among those with flares underscores the necessity of patient education and support for better adherence. UTIs' prominence signals the need for targeted preventive measures in managing infections in SLE patients.

Additionally, the infusion reaction with Rituximab calls for vigilant monitoring and prompt management of adverse drug reactions in SLE and overlapping rheumatic conditions.

Association With Disease Activity:

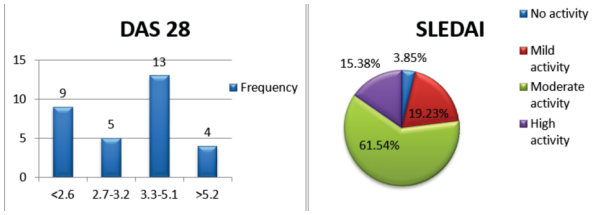

Figure 1: Disease activity (DAS28) in patients with RA and SLEDAI 2K in patients with SLE

In Rheumatoid Arthritis (RA) patients with fever, nine were in remission, thirteen showed moderate disease activity, and four had high disease activity based on the Disease Activity Score 28 (DAS28). Those with inadequate disease control had more infections, highlighting the link between disease activity and infection susceptibility in RA.

For Systemic Lupus Erythematosus (SLE) patients, one with fever was in remission, attributed to a urinary tract infection. Five had mild disease activity, while the majority (twenty patients, 77%) showed moderate to high disease activity based on the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Figure 4 visually represents these disease activity levels in RA and SLE patients with fever, emphasizing the connection between disease activity and infections in these cases.

Laboratory Parameters In Sle Patients

Parameter	SLE – Disease Flare	SLE - Infection	P value
ESR	40.77±20.74	44.6±26.45	0.37
CRP	1.2±2.48	8.66±0	0.006
Pro Calcitonin	0.566±0.40	1.71±2.1	0.00004*
NLR(Neutrophil, Lymphocyte ratio)	2.78±1.12	1.54±0.68	0.001
SLEDAI	9.14±3.03	6.22±2.28	0.02

*F statistic P value

Table IV: Laboratory parameters in SLE patients

In Systemic Lupus Erythematosus (SLE) patients, comparing those with infections to those experiencing disease flare, the erythrocyte sedimentation rate (ESR) showed higher levels in infection cases, though not significantly different (p=0.37). Conversely, C-reactive protein (CRP) and procalcitonin levels were notably elevated in infection cases ($p<0.006$ and $p<0.00004$, respectively). The neutrophil-lymphocyte ratio (NLR), a key marker, was significantly higher in disease flare cases ($p<0.001$). Additionally, the mean Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was 9.14 in disease flare and 6.2 in infection cases, displaying a notable difference (p=0.02). Table IV visually depicts these comparisons, highlighting distinct biochemical profiles between disease flare and infectious conditions in SLE patients.

DISCUSSION:

In Rheumatological diseases, fever can arise from disease flares or infections. Our study revealed infections accounting for around 12% of admissions, predominantly in Rheumatoid Arthritis (RA) cases compared to Systemic Lupus Erythematosus (SLE). In RA, infections affected bones, joints, skin, soft tissues, and the respiratory tract, aligning with existing literature(2)(3). Similarly, in our study population, respiratory tract was the most common site for infections in RA patients. Joint infections were also not uncommon. However, SLE patients predominantly faced urinary tract infections, diverging from typical respiratory tract infection patterns. We also noted fever linked to complications like rituximab infusion reactions and various tropical infections mimicking rheumatological conditions.

Demographically, our findings mirrored previous reports in age and sex profiles. Increased disease activity in RA correlated with higher infection rates. It was reported that non adherence in SLE patients ranges from 3 to 76% in some recent studies(4)(5). Paralelling with previous studies, non-adherence to treatment emerged as a significant contributor to disease flares (47% in our study) and infections in SLE patinets, indicating persistent challenges associated with long-term therapies and socio-economic factors.

The rate of infections parallel the rate of increase in disease activity.

Each 0.6 unit increase in DAS28 score corresponded to a 4% increased rate of outpatient infections (IRR 1.04, p=0.01) and a 25% increased rate of infections requiring hospitalisation(6). Similarly, in our study most of the RA patients who presented with infection had moderate to high disease activity (54.8%).

Procalcitonin (PCT) and CRP have been the two most successfully studied biomarkers. Newer biomarkers including CD64, OAS and sTREM-1 have been studied in smaller cohorts of SLE patients. It is possible, however, that an isolated biomarker will not be sufficient to differentiate disease flare from infection in SLE patients. PCT has a higher diagnostic value in the detection of bacterial sepsis in patients with SLE, with a sensitivity of 75% and a specificity of 90%(7). CRP increases significantly in SLE patients with concomitant infection, but increases only slightly or not at all in patients with a lupus flare, unlike in other autoimmune diseases such as RA(8) . A similar observation was made in our study, PCT was significantly elevated in SLE patients with proven infection and CRP was elevated significantly in SLE patients with infections as compared to those with disease flare alone.
The neutrophil-lymphocyte ratio (NLR) emerged as a promising marker in recent studies (9). Correlating with the finding, in our study NLR paralelled disease flares and significantly increased in flare cases compared to infections in SLE. This highlights the importance of a comprehensive biomarker panel in differentiating disease activity from infections, aiding better clinical management and timely interventions in SLE patients.

CONCLUSION:

Fever is a common occurrence in Autoimmune Rheumatic Diseases (AIRDs), often stemming from infections and disease flares. It is imperative to meticulously evaluate the onset of fever in various AIRDs. A critical principle that must guide clinical practice is the thorough investigation of fever to rule out any underlying infections. This precaution is particularly crucial given that rheumatologists often utilize immunosuppressants, and administering these in the presence of an active infection can lead to catastrophic consequences. Notably, heightened disease activity and poor treatment adherence contribute significantly to the increased susceptibility to infections. Therefore, it is essential to prioritize comprehensive patient education regarding the nature of their disease and emphasize the crucial need for sustained adherence to long-term treatment regimens. Such measures serve to prevent disease flares and minimize the incidence of infectious complications in AIRD patients.

Conflict Of Interest: The authors declare no conflicts of interest.

REFERENCES:

1. Bleeker-Rovers CP, Vos FJ, de Kleijn EMHA, Mudde AH, Dofferhoff TSM, Richter C, et al. A prospective multicenter study on fever of unknown origin: The yield of a structured diagnostic protocol. Medicine [Internet]. 2007 Jan [cited 2022 Dec 25];86(1):26–38. Available from: https://journals.lww.com/md-journal/Fulltext/2007/01000/A_Prospective_Multicenter_Study_on_Fever_of.3.aspx
2. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: A population-based study. Arthritis Rheum [Internet]. 2002 Sep 1 [cited 2022 Dec 26];46(9):2287–93. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/art.10524
3. Irlapati R, Nagaprabu VN, Suresh K, Agrawal S, Gumdal N. Infections in rheumatology practice: an experience from NIMS, Hyderabad. Indian J Rheumatol [Internet]. 2022 [cited 2022 Dec 25];6(6):25. Available from: https://www.indianjrheumatol.com/article.asp?issn=0973-3698; year=2011; volume=6;issue=6;spage=25;epage= 30; aulast=Irlapati;type=0
4. Costedoat-Chalumeau N, Pouchot J, Guettrot-Imbert G, le Guern V, Leroux G, Marra D, et al. Adherence to treatment in systemic lupus erythematosus patients. Best Pract Res Clin Rheumatol [Internet]. 2013 [cited 2022 Dec 26];27(3):329–40. Available from: https://pubmed.ncbi.nlm.nih.gov/24238690/
5. Prados-Moreno S, Sabio JM, Pérez-Mármol JM, Navarrete-Navarrete N, Peralta-Ramírez MI. Adherence to treatment in patients with systemic lupus erythematosus. Med Clin (Barc) [Internet]. 2018 Jan 12 [cited 2022 Dec 26];150(1):8–15. Available from: https://pubmed.ncbi.nlm.nih.gov/28669516/
6. Au K, Reed G, Curtis JR, Kremer JM, Greenberg JD, Strand V, et al. High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. Ann Rheum Dis [Internet]. 2011 May [cited 2022 Dec 26];70(5):785–91. Available from: https://pubmed.ncbi.nlm.nih.gov/21288960/
7. Wu JY, Lee SH, Shen CJ, Hsieh YC, Yo PH, Cheng HY, et al. Use of serum procalcitonin to detect bacterial infection in patients with autoimmune diseases: A systematic review and meta-analysis. Arthritis Rheum [Internet]. 2012 Sep 1 [cited 2022 Dec 26];64(9):3034–42. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/art.34512
8. Firooz N, Albert DA, Wallace DJ, Ishimori M, Berel D, Weisman MH. High-sensitivity C-reactive protein and erythrocyte sedimentation rate in systemic lupus erythematosus. http://dx.doi.org/101177/0961203310393378 [Internet]. 2011 Mar 24 [cited 2022 Dec 26];20(6):588–97. Available from: https://journals.sagepub.com/doi/abs/10.1177/0961203310393378
9. Kim HA, Jung JY, Suh CH. Usefulness of neutrophil-to-lymphocyte ratio as a biomarker for diagnosing infections in patients with systemic lupus erythematosus. Clin Rheumatol [Internet]. 2017 Nov 1 [cited 2022 Dec 26];36(11):2479–85. Available from: https://pubmed.ncbi.nlm.nih.gov/28840341/