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Prognostic Factors and Predictors of Disease Flare in Patients with Rheumatoid Arthritis

Protocol of thesis submitted for partial fulfillment of Ph.D degree in Rheumatology & Rehabilitation Medicine

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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammatory synovitis, progressive joint destruction, and potentially extra-articular involvement **(Chauhan et al., 2025)**.

RA treatment failure can lead to increased incidence of disease complications and severe functional disability**(Wang et al., 2021)**. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have endorsed the treat-to-target strategy, aiming that the treatment of RA should target remission or low disease activity (LDA) in every patient, which has yielded superior treatment outcomes in comparison to standard care **(Smolen et al., 2016, 2020)**. If remission or LDA is reached, this state should be maintained. However, up to 30% of patients with RA experience flares **(Bykerk et al., 2014).**

Although the concept of RA flare is yet to have a solid definition, it can be described as enhanced joint pain, joint swelling, and elevated levels of acute phase reactants **(Oh et al., 2020).** Flares are often reported to be associated with impaired physical function, increased fatigue, and reduced quality of life, as well as serious long-term sequelae, including incremental joint damage **(Markusse et al., 2015)**. Despite their importance, RA flare patterns and predictors remain poorly understood and are challenging to investigate because of their sporadic and unpredictable nature. The ability to predict flares when patients reach remission or LDA could facilitate decisions regarding treatment maintenance or reduction **(Rayner et al., 2024).**

On the other hand, emerging novel inflammatory biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and, more recently, pan-immune-inflammation value (PIV), have emerged as important indicators of systemic inflammation. Their role in disease flare prediction remains an area of recent research **(SATIS, 2021; Tutan & Doğan, 2023).**

Aims of the Work

1. To identify clinical, serological, radiographic, and treatment-related predictors of disease flare in RA patients who have achieved persistent clinical remission or LDA.
2. Evaluation of blood-cell-derived inflammatory indices: Neutrophil/lymphocyte ratio (NLR), Platelet/neutrophil ratio (PNR), Platelet/lymphocyte (PLR), Lymphocyte/monocyte ratio (MLR), Systemic Inflammatory Response Index (SIRI), Systemic Immune-inflammation index (SII), and Pan Immune Inflammation Value (PIV), in relation to disease flares in RA.

Patients and Methods

Study approval:

- This research will be revised by the Scientific Ethical Committee of the Faculty of Medicine-Sohag University.
- Written informed consent will be obtained from all participants in the study.
- Privacy and confidentiality of the patients' data will be assured.

Study design:

- Prospective, observational cohort study

Place of the study:

- Rheumatology department, Sohag University Hospitals

Inclusion criteria:

- Age: patients >18 years old.
- Patients with Rheumatoid arthritis diagnosed according to the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology Classification Criteria for RA **(Kay & Upchurch, 2012).**
- Clinical remission or low disease activity according to the disease activity score in 28 joints (DAS28)**(Fleishman et al., 2008).**

Exclusion criteria:

- Age < 18 years.
- Any autoimmune disease other than Rheumatoid arthritis.
- Severe infection, pregnancy, and malignancy.

Study methodology:

- This study will include all patients presenting to the Rheumatology department, Sohag University Hospitals, from February 1st, 2026, till June 30th, 2027, and who were diagnosed with Rheumatoid Arthritis according to the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology Classification Criteria for RA **(Aletaha et al., 2010)**.

The following data will be reviewed for each patient:

1. Demographic data (e.g., age, gender, residence, marital status, socioeconomic status, etc.)
2. Medical history and physical examination.
3. Thorough rheumatological examination.
4. Disease characteristics (disease duration, time to diagnosis, time to remission, time to starting DMARDs, radiographic disease state, and extra-articular manifestations).
5. Medication data will be collected.
6. Follow up every 3 months for assessment of disease flare through the assessment of:
    a. Assessment of Tender Joints Count (TJC) and Swollen Joints Count (SJC).
    b. Assessment of Visual Analogue Scale (VAS).
    c. Patient and evaluator global assessments (PGA and EGA).
    d. Assessment of disease activity by DAS28, and SDAI scores**(Aletaha & Smolen, 2007, 2009)**.
    e. ACR 20, ACR50, and ACR70 response: American College of Rheumatology criteria measuring treatment response 20%, 50% and 70% of improvement (respectively)**(Felson et al., 1998).**
    f. Assessment of functional status by modified health assessment questionnaire (HAQ) **(Anderson et al., 2010)**.
    g. Assessment of treatment adherence.
    h. Laboratory assessment of acute phase reactants (ESR and CRP) in addition to RF, ACPA, CBC, ALT, AST, serum creatinine, and blood urea nitrogen.

i. Blood-cell-derived inflammatory indices will be calculated for each patient at every follow-up visit:
   - Neutrophil/lymphocyte ratio (neutrophil count /lymphocyte count),
   - Platelet/neutrophil ratio (platelet count/neutrophil count).
   - Platelet/lymphocyte ratio (platelet count/lymphocyte count)
   - Lymphocyte/monocyte ratio (lymphocyte count/monocyte count)
   - Systemic Immune Inflammation index (neutrophil count x platelet count/lymphocyte count)
   - Systemic Inflammatory Response index: (neutrophil x monocytes/lymphocyte counts)
   - Pan-immune inflammatory response (monocytes x platelets x neutrophils/lymphocytes).

j. Clinical evaluation of any newly emerging symptoms or signs suggesting any form of increased disease activity or extraarticular manifestations.
k. Duration and frequency of disease flares for each patient
l. Radiographic progression of disease as measured by the modified Sharp scoring system **(van der Heijde et al., 1989)**.

Flare was defined as an increase in DAS28 compared with baseline of >1.2 or >0.6 if concurrent DAS28 ≥3.2 **(van der Maas et al., 2013).**

Statistical analysis:

Statistical analysis will be performed using SPSS software (version 26.0 or later, IBM Corp., Armonk, NY, USA). Continuous variables will be expressed as mean ± standard deviation, and categorical variables as frequencies and percentages. Independent samples t-test or Mann-Whitney U test will be used to compare continuous variables between groups, while chi-square test or Fisher's exact test will be used for categorical variables. Pearson's or Spearman's correlation coefficient will be used to assess correlations between continuous variables. (p-value considered significant if < 0.05). Other statistical analyses will be done if needed.

References:

Aletaha, D., Neogi, T., Silman, A. J., Funovits, J., Felson, D. T., Bingham, C. O., Birnbaum, N. S., Burmester, G. R., Bykerk, V. P., Cohen, M. D., Combe, B., Costenbader, K. H., Dougados, M., Emery, P., Ferraccioli, G., Hazes, J. M., Hobbs, K., Huizinga, T. W., Kavanaugh, A., … Hawker, G. (2010). 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Annals of the Rheumatic Diseases*, *69*(9), 1580–1588. https://doi.org/10.1136/ard.2010.138461

Aletaha, D., & Smolen, J. S. (2007). The Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) to monitor patients in standard clinical care. *Best Practice & Research. Clinical Rheumatology*, *21*(4), 663–675. https://doi.org/10.1016/j.berh.2007.02.004

Aletaha, D., & Smolen, J. S. (2009). The Simplified Disease Activity Index and Clinical Disease Activity Index to monitor patients in standard clinical care. *Rheumatic Diseases Clinics of North America*, *35*(4), 759–772, viii. https://doi.org/10.1016/j.rdc.2009.10.006

Anderson, J., Sayles, H., Curtis, J. R., Wolfe, F., & Michaud, K. (2010). Converting modified health assessment questionnaire (HAQ),

multidimensional HAQ, and HAQII scores into original HAQ scores using models developed with a large cohort of rheumatoid arthritis patients. *Arthritis Care & Research*, *62*(10), 1481–1488. https://doi.org/10.1002/acr.20265

Bykerk, V. P., Shadick, N., Frits, M., Bingham, C. O., Jeffery, I., Iannaccone, C., Weinblatt, M., & Solomon, D. H. (2014). Flares in rheumatoid arthritis: Frequency and management. A report from the BRASS registry. *The Journal of Rheumatology*, *41*(2), 227–234. https://doi.org/10.3899/jrheum.121521

Chauhan, K., Jandu, J. S., Brent, L. H., & Al-Dhahir, M. A. (2025). Rheumatoid Arthritis. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK441999/

Felson, D. T., Anderson, J. J., Lange, M. L., Wells, G., & LaValley, M. P. (1998). Should improvement in rheumatoid arthritis clinical trials be defined as fifty percent or seventy percent improvement in core set measures, rather than twenty percent? *Arthritis and Rheumatism*, *41*(9), 1564–1570. https://doi.org/10.1002/1529-0131(199809)41:9%253C1564::AID-ART6%253E3.0.CO;2-M

Fleishman, Ye. V., Sokova, O. I., Kirichenko, O. P., Konstantinova, L. N., Metelkova, N. F., Popa, A. V., & Shneider, M. M. (2008). Complex karyotype abnormalities in pediatric acute myeloid leukemia. *Vestnik Rossiiskoi Akademii Meditsinskikh Nauk*, 3–7.

Kay, J., & Upchurch, K. S. (2012). ACR/EULAR 2010 rheumatoid arthritis classification criteria. *Rheumatology (Oxford, England)*, *51 Suppl 6*, vi5-9. https://doi.org/10.1093/rheumatology/kes279

Markusse, I. M., Dirven, L., Gerards, A. H., van Groenendael, J. H. L. M., Ronday, H. K., Kerstens, P. J. S. M., Lems, W. F., Huizinga, T. W. J., & Allaart, C. F. (2015). Disease flares in rheumatoid arthritis are associated with joint damage progression and disability: 10-year results from the BeSt study. *Arthritis Research & Therapy*, *17*(1), 232. https://doi.org/10.1186/s13075-015-0730-2

Oh, Y.-J., Moon, K. W., Oh, Y.-J., & Moon, K. W. (2020). Predictors of Flares in Patients with Rheumatoid Arthritis Who Exhibit Low Disease Activity: A Nationwide Cohort Study. *Journal of Clinical Medicine*, *9*(10). https://doi.org/10.3390/jcm9103219

Rayner, F., Hiu, S., Melville, A., Bigirumurame, T., Anderson, A. E., Kerrigan, S., Mcgucken, A., Dyke, B., Prichard, J., Shahrokhabadi, M. S., Hilkens, C., Innes, I. B. M., Ng, W. F., Goodyear, C. S., Teare, D., Filer, A., Siebert, S., Raza, K., Pratt, A., … Isaacs, J. (2024). Pos0068 Flare and Drug-Free Remission in Rheumatoid Arthritis—Clinical Predictors from the Bio-Flare Study. *Annals of the Rheumatic Diseases*, *83*(Suppl 1), 455–456. https://doi.org/10.1136/annrheumdis-2024-eular.2043

SATIS, S. (2021). New Inflammatory Marker Associated with Disease Activity in Rheumatoid Arthritis: The Systemic Immune-Inflammation Index.

Current Health Sciences Journal, *47*(4), 553–557. https://doi.org/10.12865/CHSJ.47.04.11

Smolen, J. S., Breedveld, F. C., Burmester, G. R., Bykerk, V., Dougados, M., Emery, P., Kvien, T. K., Navarro-Compán, M. V., Oliver, S., Schoels, M., Scholte-Voshaar, M., Stamm, T., Stoffer, M., Takeuchi, T., Aletaha, D., Andreu, J. L., Aringer, M., Bergman, M., Betteridge, N., … van der Heijde, D. (2016). Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Annals of the Rheumatic Diseases*, *75*(1), 3–15. https://doi.org/10.1136/annrheumdis-2015-207524

Smolen, J. S., Landewé, R. B. M., Bijlsma, J. W. J., Burmester, G. R., Dougados, M., Kerschbaumer, A., McInnes, I. B., Sepriano, A., Vollenhoven, R. F. van, Wit, M. de, Aletaha, D., Aringer, M., Askling, J., Balsa, A., Boers, M., Broeder, A. A. den, Buch, M. H., Buttgereit, F., Caporali, R., … Heijde, D. van der. (2020). EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Annals of the Rheumatic Diseases*, *79*(6), 685–699. https://doi.org/10.1136/annrheumdis-2019-216655

Tutan, D., & Doğan, A. G. (2023). Pan-Immune-Inflammation Index as a Biomarker for Rheumatoid Arthritis Progression and Diagnosis. *Cureus*, *15*(10), e46609. https://doi.org/10.7759/cureus.46609

van der Heijde, D. M., van Riel, P. L., Nuver-Zwart, I. H., Gribnau, F. W., & vad de Putte, L. B. (1989). Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. *Lancet (London, England)*, *1*(8646), 1036–1038. https://doi.org/10.1016/s0140-6736(89)92442-2

van der Maas, A., Lie, E., Christensen, R., Choy, E., de Man, Y. A., van Riel, P., Woodworth, T., & den Broeder, A. A. (2013). Construct and criterion validity of several proposed DAS28-based rheumatoid arthritis flare criteria: An OMERACT cohort validation study. *Annals of the Rheumatic Diseases*, *72*(11), 1800–1805. https://doi.org/10.1136/annrheumdis-2012-202281

Wang, Z., Huang, J., Xie, D., He, D., Lu, A., & Liang, C. (2021). Toward Overcoming Treatment Failure in Rheumatoid Arthritis. *Frontiers in Immunology*, *12*, 755844. https://doi.org/10.3389/fimmu.2021.755844