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| RESEARCH ARTICLE

The Correlation of IL-6 Levels With the Degree of Rheumatoid Arthritis Disease Activity at Dr. Mohammad Hoesin Palembang

Triawan Adinata[1] ✉ Rodry Mikhael[2], Radiyati Umi Partan[3], Surya Darma[4], Muhammad Reagan[5] and Yulianto Kusnadi[6]

[123456]*Department of Internal Medicine, Faculty of Medicine, Universitas Sriwijaya/RSUP Dr. Moh. Hoesin Palembang, Indonesia*

Corresponding Author: Triawan Adinata, **E-mail**: triawan.adinata@gmail.com

| ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disease that requires careful management and regular evaluation of the degree of disease activity. AR is known for its pathophysiology and is strongly influenced by the increase of proinflammatory cytokines, especially IL-6. This study was conducted to determine the correlation of IL-6 levels with the degree of disease activity in AR patients at Dr. Mohammad Hoesin Palembang. A cross-sectional study was conducted on RA patients at the Rheumatology Polyclinic, Department of Internal Medicine, Dr. Moh Hoesin Palembang, who met the inclusion criteria consecutively in October 2021. The degree of RA disease activity was assessed using the Disease Activity Score (DAS 28). Statistical analysis was performed using SPSS version 24.0. A total of 34 subjects participated in the study, with most being women and a median age of 49.5 years. The majority of subjects had a moderate-high degree of RA activity. There is no significant correlation between IL-6 levels with DAS 28 CRP (r=0.256, p=0.072) and DAS 28 LED (r= 0.056, p=0.376). There was no significant correlation between serum IL-6 levels and disease activity in Rheumatoid Arthritis patients at Dr. Mohammad Hoesin Palembang.

| KEYWORDS

Interlukin 6, Rheumatoid Arthritis, DAS28

| ARTICLE INFORMATION

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1. Introduction

Rheumatoid arthritis (AR) is an autoimmune disease characterized by symmetrical erosive synovitis and extra-articular tissue involvement, which results in progressive joint destruction, disability, and even premature death. AR is characterized by the presence of *Rheumatoid Factor* (RF) autoantibodies or *Anti Citrullinated Peptide Antibodies* (ACPA) (Aletaha et al. 2010)

AR is an autoimmune-rheumatic disease that has high morbidity and causes a decrease in the quality of life of the sufferer. The prevalence of AR in America and some European regions is estimated at 1 %, while in Indonesia, it is 0.5-1% and is expected ~~to~~ continue to increase (Indonesian Rheumatology Association, 2021; Yen-Ju,2020).

The pathogenesis of AR is influenced by an increase in proinflammatory cytokines, especially Interleukin 6 (IL-6). IL-6 is a pleiotropic cytokine that is released by various immune cells, like cell epit e l, fibroblasts, monocytes, and T cells. IL-6 can contribute to the production of autoantibodies and act as a regulator of -cell differentiation T helper who will cause inflammation of joints and erosion bone patient AR. (Ishihara et al, 2002).

Management of AR should be carried out as early as possible, and evaluation of the degree of disease activity should be carried out routinely, intending to achieve remission or low disease activity. RA evaluation can be done by scoring the *Disease Activity Score on the 28 Joints* (DAS28) based on the number of joints experiencing inflammation, joint swelling, the ESR or *C-Reactive*

Protein (CRP) value, as well as a pain scale based on the *Visual Analog Scale* (VASE) (Eissa et al. 2017).
This study aims to assess the correlation of IL-6 levels with the activity of the disease degree of AR patients undergoing treatment at RSUP Dr. Mohammad Hoesin Palembang.

2. Method

2.1 Research Subject

This study used a cross-sectional design. The study was conducted at the Polyclinic of the Department of Internal Medicine, Dr. Moh Hoesin Hospital, Palembang. Data collection was carried out in October 2021. This study was approved by the Medical Research Ethics Committee, Faculty of Medicine, Sriwijaya University, Dr. Moh. Hoesin Hospital Palembang. Each subject signed *informed consent* before data collection. The inclusion criteria were AR patients diagnosed based on the *2010 American College of Rheumatology* classification criteria (Aletaha, 2010) and aged 18-60 years. Exclusion criteria were patients with autoimmune diseases other than AR, patients with comorbidities (chronic kidney failure, chronic heart failure, liver cirrhosis, diabetes mellitus), or currently suffering from other infectious and inflammatory diseases.

Each subject was assessed for the degree of AR disease activity using the *Disease Activity Score 28 (DAS28)* LED and DAS 28 CRP questionnaires based on clinical and laboratory data.(Fraenke,2021; Matsui, 2007) Each subject was taken a blood sample for examination of IL-6 levels, which was carried out in a separate laboratory accredited in Palembang.

2.2 Statistic Analysis

Data analysis was performed with SPSS 24.0 (SPSS Inc., Chicago, USA). Clinical and laboratory data are presented in the form of mean and standard deviation for normal distribution variables or median and range for abnormal distribution variables. The Shapiro-Wilk test was used to assess the normality of the data. Normally distributed data are presented in the mean ± SD, while the data are not normally distributed in the median (minimum-maximum). While the Pearson or Spearman correlation test was used to assess the correlation between Interleukin-6 levels and disease activity based on DAS 28 LED or DAS 28 CRP.

3. Results

The clinical characteristics of the subjects can be seen in table 1. In this study, most of the subjects were female (94.1%), with a median age of 49.5 years. Subjects' duration of illness varied from 2 to 288 months, with a median of 27 months. The majority of patients (85.3%) were treated with corticosteroids and were taking two types of immunosuppressants (70.6%).

Table 1. Clinical Characteristics of Rheumatoid Arthritis Patients at RSUP Dr. Mohammad Hoesin Palembang

Variable	Description (n=34)
Gender	
Female, n(%)	32 (94.1%)
Male, n(%)	2 (5.9%)
Age (years), median (min-max)	49.5 (19-58)
Body Mass Index (kg/m2), mean± SD	23.72±5.50
Disease duration (months), median (min-max)	27 (2-288)
IL-6 level (pg/ml), median (min-max)	10.88 (1.5-100.3)
Disease Activity	
DAS-28 LED, mean ±SD	4.88±0.97
DAS-28 CRP, mean± SD	4.00 ± 0.92
Treatment with steroids, n(%)	29 (85.3%)
Number of immunosuppressants	
1	5 (14.7%)
2	24 (70.6%)
3	5 (14.7%)

In table 2, it can be seen that from 34 research subjects, the number of AR patients with low disease activity and remission has the same number, each of 3 people (8.83%) with DAS28 CRP measurements. In the DAS28 ESR measurement, there were no patients with low disease activity, and only 1 person (2.94%) was in remission. In both DAS28 CRP and DAS28 LED, the highest number were patients with moderate disease activity (24 people on DAS28 CRP and 21 people on DAS28 LED).

Table 2. Disease activity of Rheumatoid Arthritis Patients at RSUP Dr. Mohammad Hoesin Palembang

DAS 28 CRP	**Amount**
High activity (> 5.1), n(%)	4 (11. 76 %)
Moderate activity (3.2-5.1), n(%)	24 (70.58 %) _
Low activity (2.6-3.2), n(%)	3 (8.8 3 %)
Remission (<2.6), n(%)	3 (8.83 %)
DAS 28 LED	
High activity (>5.1), n(%)	12 (35.3 %)
Moderate activity (3.2-5.1), n(%)	21 (61.76 %)
Low activity (2.6-3.2), n(%)	0 (0%)
Remission (<2.6), n(%)	1 (2.94 %)

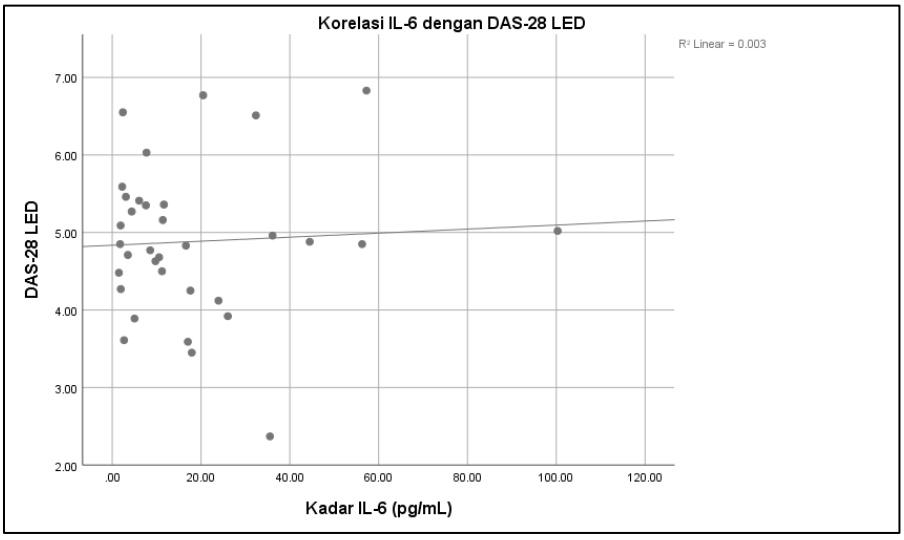
The correlation between Interleukin-6 levels and AR disease activity can be seen in Table 3 and Figure 1. In this study, there was no significant correlation between IL-6 levels based on DAS-28 ESR (figure 1a) and DAS-28 CRP (figure 1b).

Table 3. Correlation of Interleukin-6 Levels with Disease Activity of Rheumatoid Arthritis Patients at Dr. Mohammad Hoesin Palembang

		Disease Activity	
		DAS 28 CRP	DAS 28 LED
IL-6 . levels	r	0.256	0.056
	p	0.072	0.376
	n	34	34

Note: Pearson Correlation Test. If p > 0.05, there is no significant correlation between the levels of Interleukin-6 with DAS 28 CRP and DAS 28 LED.
The value of r < 0.2 indicates a very weak correlation, r = 0.2-0.4 indicates a weak correlation, r = 0.4-0.6 indicates a moderate correlation, r = 0.6-0.8 is a strong correlation, and r> 0.8 is a very strong correlation.

(a)



(b)

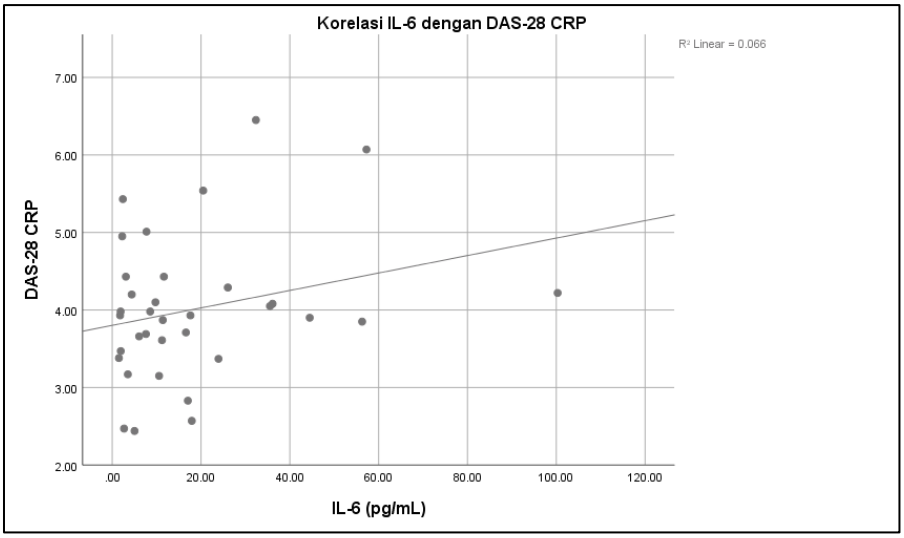


Figure 1 . Spread Diagram of the Correlation of Interleukin-6 Levels with Disease Activity of Rheumatoid Arthritis Patients at Dr. Mohammad Hoesin Hospital Palembang based on (a) DAS-28 LED and (b) DAS-28 CRP

4. Discussion

The median age of AR patients in this study was 46.54 years, with the majority being female. The predisposition of the female sex to AR is related to the role of the sex hormone estrogen as an immunomodulatory hormonal regulator. Estrogen has a role in the activity of B cells and T-helper cells and maintains autoreactive T cells. Meanwhile, the decrease in postmenopausal estrogen will cause an increase in proinflammatory cytokines such as TNF-, IL-1β, and especially IL-6, which will cause clinical symptoms in AR (Alpízar-Rodríguez, 2017).

Joint swelling and pain increased ESR and CRP in AR patients are initiated by environmental factors, exposure to dust, microbes, or foreign substances in the respiratory tract, gastrointestinal microbiome, oral and dental mucosa, and genetic susceptibility. These factors lead to increased production of proinflammatory cytokines such as IL-6, TNF-, MMP, and prostaglandins. These cytokines will activate osteoclasts, causing bone erosion. This inflammation will cause the finger joints, especially the PIP, MCP, CMC, wrist, shoulder, elbow, and other joints, to *become* swollen and painful. To assess how much pain the study subjects felt with the VAS. Inflammatory effects can have a systemic effect which is characterized by an increased CRP or ESR. The magnitude of the disease activity of AR subjects can be assessed by the high activity value of the DAS28 LED or DAS28 CRP scores. (Chen et al., 2019).

In table 3, it can be seen in this study that most of the subjects had moderate and high disease activity. This is to the studies of Ruksakul (202 2) and Kabul (2020) but different from the study of Batko et al. (2017), which found that the proportion of patients with high disease activity was more common (Chen et al. 2022). This is because the samples taken in this study were more likely to have been diagnosed with AR with a longer duration than other studies and had undergone treatment with immunosuppressant drugs as standard therapy before.

In this study, the median value of IL-6 levels was 10.88 (1.5-100.3). This is to the research of Somaiya Mateen et al. (2017) and Helal et al. (2012), who found increased levels of IL-6 in their research subjects (Abdel Moneim, 2012).

Based on the correlation test, in this study, there was no significant correlation between IL-6 levels based on DAS-28 LED (figure 1a) and DAS-28 CRP (figure 1b). This is not to the research of Yogita Sharma et al. (2016), who in their research found a strong correlation between serum IL-6 levels and disease activity in AR patients. (Abdel Moneim, 2021). But the results of this study are by the research of Soo Jin Chung et al. (2011), who found no significant correlation between levels of IL-6 and DAS28 cytokine families. The difference in the results of this study is due to the different involvement of the IL-6 cytokine in local and systemic reactions. In AR, IL-6 concentrations can be measured in either the patient's serum or synovial membrane, and IL-6 is primarily involved in local reactions (Chung, 2011).

IL- 6 is a cytokine pleiotropic which has a wide range of biological effects. *IL-6 is* produced by both lymphoid and non-lymphoid cells, including T cells, B cells, monocytes, fibroblasts, keratinocytes, endothelial cells, cells mesangial cells, and some tumor cells,

which means that these cytokines are not disease-specific certain. In patients which is AR, there is infiltration of cells and inflammatory cells such as monocytes and lymphocytes in synovial tissue that are thought to be the source of *the IL-6. soluble receptor* (sIL-6R), which will increase disease activity, is characterized by several clinical changes, such as surrounding soft tissue swelling joints due to inflammatory cell infiltration, which results in levels of IL-6 is also increased. However, apart from IL-6, several proinflammatory cytokines also play a role in the pathogenesis of AR, such as TNFa and IL-17. These cytokines are also thought to play a role in increasing AR disease activity in addition to IL-6. (Fraenkel, 2021; Yap, 2018).

This study has several limitations. First, the number of samples in this study is limited, so future research with a larger number of samples is needed. Second, the type of drug in this patient was not assessed, so the possibility of assessing the effect of therapy on disease activity and IL-6 levels could not be known. Third, this study did not analyze the effect of long-suffering from AR, so it can be biased in assessing the effect of cytokine levels on AR disease activity.

5. Conclusion

Rheumatoid arthritis (RA) is an autoimmune disease that requires careful management and regular evaluation of the degree of disease activity. AR is known for its pathophysiology and is strongly influenced by the increase of proinflammatory cytokines, especially IL-6. This study was conducted to determine the correlation of IL-6 levels with the degree of disease activity in AR patients at Dr. Mohammad Hoesin Palembang. From this study, it was found that there was no significant correlation between IL-6 and AR disease activity. So serum IL-6 levels cannot be used as an indicator of the severity of disease activity in AR patients. Further research on the role of IL-6, as well as other cytokines, in the pathogenesis of AR disease activity, remains to be done.

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References

[1] Aletaha D, and Smolen JS. (2018) Diagnosis and Management of Rheumatoid Arthritis: A Review. JAMA - *Journal of the American Medical Association; 320* (13):1360–72.
[2] Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, and Bingham CO. (2010) Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Rheumatoid Arthritis.;62(9):2569–81.
[3] Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, and Bingham CO. (2010) Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis and Rheumatism; 62*(9):2569–81.
[4] Alpízar-Rodríguez D, Pluchino N, Canny G, Gabay C and Finckh A (2017). The role of female hormonal factors in the development of rheumatoid arthritis. Rheumatology. Aug 1:56(8):1254–63
[5] Alpízar-Rodríguez D, Pluchino N, Canny G, Gabay C and Finckh A. (2017). The role of female hormonal factors in the development of rheumatoid arthritis. Rheumatology. 1:56(8):1254–63.
[6] Abdel Moneim H. Helala, Enas M. Shahinea, Marwa M. Hassana, Doaa I. Hashadb, and Riham A. (2012). Fatigue in rheumatoid arthritis and its relation to interleukin-6 serum levels. The Egyptian Rheumatologist; 34(4):153-157
[7] Batko B, Stajszczyk M, wierkot J, Urbański K, Raciborski F, Jędrzejewski M. (2019). Prevalence and clinical characteristics of rheumatoid arthritis in Poland: A nationwide study. *Archives of Medical Science.;15*(1):134–40.
[8] Chung SJ, Kwon YJ, Park MC, Park YB, Lee SK.(2011). The Correlation between Increased Serum Concentrations of Interleukin-6 Family Cytokines and Disease Activity in Rheumatoid Arthritis Patients. *Yonsei Med J.;52*(1)113-20
[9] Chen Z, Bozec A, Ramming A, Schett G, (2019). Anti-inflammatory and immune-regulatory cytokines in rheumatoid arthritis. Nature Reviews Rheumatology.15 (1):9–17.
[10] Eissa M, El Shafey A, Hammad M. (2017) Comparison between different disease activity scores in rheumatoid arthritis: an Egyptian multicenter study. *Clinical Rheumatology; 36*(10):2217–24.
[11] Fleischmann R, Van Der Heijde D, Koenig AS, Pedersen R, Szumski A, Marshall L. (2015) How much does Disease Activity Score in 28 joints ESR and CRP calculations underestimate disease activity compared with the Simplified Disease Activity Index? *Annals of the Rheumatic Diseases; 74*(6):1132–7.
[12] Fraenkel L, Bathon JM, England BR, St.Clair EW, Arayssi T, Carandang K. (2021) American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care and Research;73* (7):924–39
[13] Fraenkel L, Bathon JM, England BR, St. Clair EW, Arayssi T, Carandang K. (2021) American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care Res (Hoboken);73*(7):924–39.
[14] Goh FG, Midwood KS. (2012) Intrinsic danger: Activation of Toll-like receptors in rheumatoid arthritis. Rheumatology; 51(1):7–23.
[15] Guo Q, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. (2018) Rheumatoid arthritis: Pathological mechanisms and modern pharmacologic therapies. Bone Research [Internet];6(1):1–14. Available from: http://dx.doi.org/10.1038/s41413-018-0016-9
[16] Gopal K, Thevarajah M, Ng CM, Raja J. (2019) Effects of vitamin D on disease activity and serum interleukin-6 in rheumatoid arthritis. *International Journal of Rheumatic Diseases. 1*:22(5):834–41.

[17] Gary S F (2017). Etiology and Pathogenesis of Rheumatoid Arthritis. In: Firestein GS, Budd RC, Gabriel SE, Mcinnes IB, O'Dell J, editors. *Kelley and Firestein Textbook of Rheumatology 10th ed. 10th ed. Phi: Elsevier*. 1115–66.
[18] Ishihara K, Hirano T. (2002) IL-6 in autoimmune disease and chronic inflammatory, proliferative disease. *13, Cytokines & Growth Factor Reviews*.
[19] Indonesian Rheumatology Association (2021). Diagnosis and Management of Rheumatoid Arthritis.. 1–52.
[20] Kim H, Baek S, Hong SM, Lee J, Jung SM, Lee J. (2020) 1,25-dihydroxy Vitamin D3, and Interleukin-6 Blockade Synergistically Regulate Rheumatoid Arthritis by Suppressing Interleukin-17 Production and Osteoclastogenesis. Journal of Korean Medical Science. 17:35(6).
[21] Matsui T, Kuga Y, Kaneko A, Nishino J, Eto Y, Chiba N, et al(2007). Disease Activity Score 28 (DAS28) using C-reactive protein underestimates disease activity and overestimates EULAR response criteria compared with DAS28 using erythrocyte sedimentation rate in a large observational cohort of rheumatoid arthritis patients. Annals of the Rheumatic Diseases.;66(9:1221–6.
[22] Nygaard G, Firestein GS (2020). Restoring synovial homeostasis in rheumatoid arthritis by targeting fibroblast-like synoviocytes. Nature Reviews Rheumatology;16(6):316–33.
[23] Oky P, Tania A, Simamora D, Dyah Parmasari W, Rahmawati F, Biomedicine B. (2014) Interleukin 6 (IL-6) levels as an indicator of the progression of rheumatoid arthritis (ra). Medical Science ;3.
[24] Paulson A, Abraham FA, Davis F, Ranji NM, Panayappan KKL (2021). Assessment of Disease Severity in Rheumatoid Arthritis Patients Using Das28, Cdai, Raad Score and Rapid-3 – A Review. *International Journal of Multidisciplinary and Current Educational Research; 3(*2):146–8.
[25] Ruksasakul R. (2022) Factors Associated with Disease Severity in Rheumatoid Arthritis Patients at Phra Nakhon Si Ayutthaya Hospital. *Journal of the Association of Preventive Medicine of Thailand;12*(1):132–45.
[26] Son KM, Kim SY, Lee SH, Yang CM, Seo Y Il, Kim HA. (2016). Comparison of the disease activity score using the erythrocyte sedimentation rate and C-reactive protein levels in Koreans with rheumatoid arthritis. *International Journal of Rheumatic Diseases;19(*12):1278–83.
[27] Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, et al.(2018) Rheumatoid arthritis. Nature Reviews Disease Primers.8;4.
[28] Sharma Y, Kumar N and Thakur D. (2021) Interleukin 6 in Patients with Rheumatoid Arthritis. Interleukins-*The Immune and Non-Immune Systems' Related Cytokines: IntechOpen .1-8.*
[29] Yap HY, Tee S, Wong M, Chow SK, Peh SC, and Teow SY (2018).Pathogenic Role of Immune Cells in Rheumatoid Arthritis: Implications in Clinical Treatment and Biomarker Development. Cells;7(10):161.
[30] Yen-Ju L, and Martina-Anzaghe SS. (2020) Update on the Pathomechanism, Diagnosis, and Treatment Options for Rheumatoid Arthritis. Cells;880(9):1–43.
[31] Yap HY, Tee S, Wong M, Chow SK, Peh SC, and Teow SY (2018). Pathogenic Role of Immune Cells in Rheumatoid Arthritis: Implications in Clinical Treatment and Biomarker Development. *Cells; 7*(10):161.