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### Correlation of IL-17 Serum Levels with Carotid Intima-Media Thickness and Degree of Disease Activity in Rheumatoid Arthritis Patients at Dr. Mohammad Hoesin General Hospital Palembang, Indonesia

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#### ABSTRACT

**Background:** Rheumatoid arthritis (AR) is an autoimmune disease characterized by chronic and progressive systemic inflammation, in which the joints are the main target. AR has long been associated with increased cardiovascular risk. Vascular inflammation plays an important role in atherosclerosis. In AR, there is an increase in IL-17, which accelerate the formation of atherosclerosis. In Indonesia alone, there is no data that publishes the correlation between IL-17 levels with carotid IMT and the severity of AR. **Methods:** This type of research is a descriptive observational study with a correlation test approach. A total of 31 subjects participated in this study who were AR patients and calculated a DAS score of 28. Carotid IMT was measured by high-resolution carotid Doppler ultrasound B-mode ultrasound machine (PHILIPS, iE33) equipped with an 11 MHz linear array transducer. IL-17 was measured by the ELISA method. Data analysis was performed with a correlation test with SPSS software version 25. **Results:** There was a strong positive correlation between IL-17 and the degree of disease activity in AR (DAS28 score) with  $r = 0.657$ ;  $p = 0.0001$ ;  $n=31$ . There was no significant correlation between carotid IMT and IL-17 levels ( $r= 0,207$ ;  $p=0,264$ ;  $n=31$ ). **Conclusion:** There is a strong positive correlation between IL-17 and the degree of AR disease activity. There was no significant correlation between carotid IMT and IL-17 levels.

#### 1. Introduction

Rheumatoid arthritis (AR) is a chronic systemic autoimmune disease that affects all ethnic groups worldwide, where the incidence in women is 2.5 times higher than in men. The classic clinical manifestation of AR is symmetric polyarthritis, mainly affecting the small joints of the hands and feet. In addition to the synovial lining of the joints, AR can also affect organs outside the joints, such as the skin, heart, lungs, and

eyes. Mortality increases due to cardiovascular complications, infection, kidney disease, malignancy, and comorbidities. Making the diagnosis and starting therapy as early as possible can reduce the progression of the disease.<sup>1</sup>

AR has long been associated with increased cardiovascular risk. The worldwide incidence of death in AR patients due to cardiovascular disease is around

40%, and despite improvements in disease management, mortality remains high. Atherosclerosis is more common in AR than in the general population, and atherosclerotic lesions develop more rapidly and are easier to rupture, which has clinical implications. Cells and cytokines involved in the pathogenesis of AR are also involved in the development and progression of atherosclerosis, which is generally known as an inflammatory condition.<sup>2</sup> In A meta-analysis study conducted by van Sijl et al. in 2011 in the Netherlands, of 22 studies, there were 1,384 AR patients and 1,147 controls. There was a significant increase in carotid IMT in AR patients compared to control patients ( $p = 0.001$ ).<sup>2</sup>

A number of similarities are found in the pathological processes of both rheumatoid synovitis and atherosclerosis. This process can occur simultaneously in both the joint and the vessel wall in AR, or the mediators produced in the synovium can have further secondary effects on the arteries.<sup>3</sup> AR is the most common autoimmune disease, which is influenced by effector T cells, especially Th17 cells, which have pro-inflammatory activity through the production of a potent pro-inflammatory molecule, namely IL-17.<sup>4</sup> In AR patients, there is an increase in IL-17 and accelerated atherosclerosis formation.<sup>5</sup> This study aims to determine the correlation between levels of IL-17 with carotid intima-media thickness and degree of disease activity in rheumatoid arthritis patients at Dr. Mohammad Hoesin General Hospital Palembang, Indonesia.

## 2. Methods

This study is a descriptive observational study with a correlation test approach. This study was conducted at the Internal Medicine Polyclinic, Rheumatology

Division, Dr. Moh Hoesin General Hospital Palembang from January - December 2020. A total of 31 research subjects participated in this study, where the research subjects met the inclusion criteria in the form of patients who had been diagnosed with AR aged 18-60 and agreed to participate in this study which was marked by the signing of the informed consent. This study has been approved by the medical and health research ethics committee of Dr. Mohammad Hoesin General Hospital Palembang, Indonesia.

This study further evaluated the clinical improvement of AR using DAS 28. Carotid intima-media thickness was measured by high-resolution carotid Doppler ultrasound B-mode ultrasound machine (PHILIPS, iE33®) equipped with an 11 MHz linear array transducer. IL-17 was measured by the ELISA method, according to the manufacturer's protocol (Cloud Clone®). Data analysis was processed using SPSS for Windows version 25. data is presented in the form of tables and graphs. The data is tested to whether the distribution is normal or not. If the distribution is normal, then the Pearson correlation test is carried out. If the distribution data is not normal, the Spearman test is used. The level of significance used is  $p < 0.05$ .

## 3. Results

The general characteristics of the research subjects included age, gender, education, occupation, body mass index, systolic and diastolic blood pressure, dyslipidemia, degree of AR, duration of AR, a daily dose of methylprednisolone (MP), DMARD, rheumatoid factor, and smoking habits. Table 1 shows the median age of the study subjects, 48 (19-59) years. There were 27 female subjects (87.1%) and 4 male subjects (12.9%).

Table 1. General characteristics of research subjects.

Characteristics	N (%)	Mean + SD	Median
Age (years)			48 (19-59)
19-29	3 (9.7)		
30-39	4 (12.9)		
40-49	13 (41.9)		
≥50	11 (35.5)		
Gender			
Male	4 (12.9)		
Female	27 (87.1)		
BMI		24.4 ± 5.6	
Less	3 (9.7)		
Normal	13 (41.9)		
More	5 (16.1)		
Obese	10 (32.3)		
Education			
Elementary	3 (9.7)		
Junior	3 (9.7)		
High School	12 (38.7)		
Diploma/Bachelor	13 (41.9)		
Occupation			
Housewives	15 (48.4)		
Civil Servant	2 (6.5)		
Private	13 (41.9)		
College Students	1 (3.2)		
AR Duration (months)			24(2-96)
1-12	10 (32.3)		
13-24	12 (38.7)		
>24	9 (29.0)		
DAS 28 Score		5.1 ± 1.4	
Degree of AR Severity			
Remission	1 (3.2)		
Mild	1 (3.2)		
Moderate	15 (48.4)		
Severe	14 (45.2)		
Daily MP Dose (mg)			4(4-24)
Mild (≤ 6)	27 (87.1)		
Moderate (7-24)	4 (12.9)		
Number of other immunosuppressants			
1	30 (96.8)		
≥2	1 (3.2)		
TDS/TDD			120 (110-150)/ 70(60-80)
Rheumatoid factor			
Non-reactive	8 (25.8)		
Reactive	23 (74.2)		
Smoking			
Yes	2 (6.5)		
No	29 (93.6)		
Dyslipidemia			
Yes	10 (32.3)		
No	21 (67.7)		
Heart disease			
Yes	0 (0.0)		
No	31 (100.0)		

Table 2 shows the correlation test between test variables. The thickness of the carotid intima has a weak but not significant correlation with IL-17 levels. At the same time, the correlation test between DAS 28

and IL-17 levels showed a moderate and significant correlation. The higher the DAS 28 score will be followed by an increase in IL-17 levels and vice versa.

Table 2. Correlation between test

Variables		IL-17
Carotid Intima-Media Thickness	R	0.207
	p	0.264
DAS 28	R	0.657
	P	0.001

\*Spearman correlation, p=0.05

#### 4. Discussion

IL-17 is part of the course of AR itself. The properties of IL-17 are known as markers of inflammation. AR disease, as well as autoimmune disease, causes inflammation in various degrees depending on the severity of AR disease itself. The level of IL-17 itself depends on the production of T cells, which will eventually continue in the course of autoimmune diseases. It was explained that IL-17 acts on many receptors, including in the case of AR. IL-17 locally acts on synoviocytes and osteoblasts where which will cause synovitis and joint disorders as the main complaints that arise in AR patients.<sup>6-10</sup> IL-17 is a potent pro-inflammatory cytokine.<sup>11-13</sup> In this study, it was found that the correlation of serum IL-17 levels has a strong correlation with the DAS 28 score, which is a description of the severity of the disease. This is consistent with the course of the autoimmune and chronic inflammatory disease described in theory. The level of IL-17 itself depends on the production of T cells, which will eventually continue in the course of autoimmune diseases. It was explained that IL-17A acts on many receptors, including in the case of AR. IL-17A locally acts on synoviocytes and osteoblasts where which will cause synovitis and joint disorders as the main complaints that arise in AR patients. These complaints increased with the severity of the disease as measured by the DAS 28 score. Therefore, the results of this study which stated that serum IL-17 levels were in line with the DAS 28 score, were in accordance with the theory. The relevance of IL-17 to atherosclerosis in humans is still under debate due to conflicting results from animal studies. Where several studies state that IL-17 has a proatherogenic role and an atheroprotective role in the atherosclerosis process.<sup>14-16</sup>

#### 5. Conclusion

There was no correlation between serum IL-17 levels and carotid tunica intima-media (IMT) wall thickness in AR patients. There is a strong positive correlation between serum IL-17 levels and the degree of AR disease activity using a DAS 28 score.

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