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CORRELATION BETWEEN C-REACTIVE PROTEIN CONCENTRATION WITH DISEASE SEVERITY IN NEW CASE PULMONARY TUBERCULOSIS WITH POSITIVE SMEAR PATIENTS IN MAKASSAR

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ABSTRACT Background: Tuberculosis is an infectious disease caused by various strains of mycobacteria, usually *Mycobacterium tuberculosis*. C-reactive protein is acute phase reactants that increase during inflammatory process occurs in the body. *Mycobacterium tuberculosis* enters the body, causes inflammation and releases various pro-inflammatory cytokines, mainly interleukin 8 and interleukin 6. Increased plasma concentration of interleukin 6 stimulates increased C-reactive protein synthesis by hepatocyte cells in the liver. Objective: Determined the correlation between C-reactive protein levels with Acid-Fast Bacilli smear positivity and extent of chest X-ray lesions in new Pulmonary Tuberculosis patients with positive Acid-Fast Bacilli smear. **Methods:** The study design was an analytical study with a prospective observational cohort. The subjects of the study were 50 subjects with new case pulmonary tuberculosis positive smear who were examined for AFB smear, chest X-ray, C-reactive protein levels before and after intensive phase treatment. **Results:** C-reactive protein levels were significantly higher ($p < 0,05$) in pulmonary tuberculosis subjects with advanced lesions (6,31+3,34) compared to minimal lesions (3,20+3,16). Based on Acid-Fast Bacilli smear positivity, the highest C-reactive protein levels were obtained in pulmonary tuberculosis samples with Acid-Fast Bacilli +2 (7,20+3,01). There was a significant reduction in C-reactive protein levels (69,6%) after two months of intensive phase treatment. **Conclusions:** C-reactive protein levels before treatment are significantly associated with the extent of chest X-Ray lesions, and Acid-Fast Bacilli smear positivity, so that can be used as a marker of severity of pulmonary tuberculosis disease. There is a significant reduction in C-reactive protein levels after intensive phase treatment.

KEYWORDS Pulmonary tuberculosis, Acid-Fast Bacilli smear, C-reactive Protein

12 Introduction

Pulmonary Tuberculosis (PTB) is an infectious disease caused by *Mycobacterium tuberculosis* (MTb) which mostly attacks the lungs, but also affects other organs such as skin, brain and bones. According to the WHO Global Tuberculosis Report 2017, in 2016, it is estimated that the incidence of TB is 10,4 million people, with a mortality rate of 1,3 million-plus 374.000 deaths in HIV-positive patients. Indonesia is currently 2nd ranked country with the highest TB burden in the world. The estimated incidence

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of TB in Indonesia in 2016 was 1.020.000 people (391/100.000 population) with the number of deaths from TB estimated at 110.000 deaths (42/100,000 population) per year.[1]

Apart from the availability of effective diagnostic, prevention and therapy facilities, TB remains one of the highest causes of death in adults by infectious diseases throughout the world. The most commonly used diagnostic tools currently are AFB smear examination and sputum MTb culture. However, these two biomarkers still have many limitations.[2] There is a need to obtain alternative markers that can predict severity so that it can help inpatient risk stratification for early intervention and better patient management. Markers that can be measured during TB treatment can help in identifying and preventing an increase in the incidence and mortality rates in TB patients.[3]

C-reactive protein (CRP) reported first in 1930 by Tillet and Francis is one of the most commonly used acute phase reactants as an indicator of inflammation. Mycobacterium tuberculosis enters the body and causes inflammation and releases various pro-inflammatory cytokines, mainly interleukin 8 (IL-8) and interleukin 6 (IL-6). [24] Increased CRP levels are caused by an increase in plasma concentrations of IL-6 which are mostly produced by macrophages, thereby stimulating increased CRP synthesis by hepatocyte cells in the liver.[4]

Several studies have evaluated the usefulness of CRP examination in TB. CRP usually shows a lower concentration in TB when compared to bacterial pneumonia. In several other studies, it was found that CRP levels were higher in patients with positive AFB smear compared to negative AFB smear and significantly increased with an increasing bacterial load on AFB smear examination.[5,6] Increased CRP levels are also related to the extent of lesions on chest X-Ray of PTB patients. High initial CRP levels are reported to correlate with slower sputum conversion after two months of treatment and treatment failure incidence.[7,8,9]

Methods

This study was an analytical study with observational prospective cohort design conducted at Wahidin Sudirohusodo Hospital in Makassar from November 2018 until January 2019. The ethical committee has approved it of Hasanuddin University Medicine Faculty with reference number: 1000 / H4.8.4.5.31 / PP36-KOMETIK / 2018.

A. Population

The population of this study were all inpatients and outpatients with new positive smear PTB at Wahidin Sudirohusodo Hospital in Makassar and Hospital network in Makassar. The inclusion criteria were patients diagnosed with new smear-positive tuberculosis, aged > 18 years and willing to take part in the study and sign a research approval letter. Exclusion criteria were patients who had a history of received anti-tuberculosis medication, patients who did not complete intensive phase treatment for two months, patients with 1 or more comorbidities were as follows: Multi-Drug Resistant TB, HIV, Type 2 Diabetes Mellitus, cancer, heart disease, systemic lupus erythematosus, rheumatoid arthritis and acute infection.

1 Methods and data collection

Sampling was done by consecutive sampling; patients who met the inclusion criteria were included in this study until the number of samples was fulfilled. Based on the positivity level of AFB smear, patients were grouped into three categories, AFB

+1, AFB +2 and AFB +3. Patients are grouped into two categories based on chest X-ray examination; minimal lesions and advanced lesions that assessed by radiologist. Patients received intensive phase treatment for two months with drugs regimen, i.e. rifampicin, isoniazid, pyrazinamide and ethambutol. CRP examination is carried out in a laboratory using the immunoturbidimetry method before treatment is started, and after the intensive phase, treatment is complete.

C. Statistical Analysis

Datas were analyzed using the Statistical Package for Social Science (SPSS) program version 22. The statistical analysis performed was the calculation of descriptive statistics and frequency distribution as well as the Paired-t, Independent-t and Chi Square test. The test results are significant if the value is $p < 0.05$.

Results

During the study period, 50 research subjects met the inclusion criteria. Table 1 shows that the majority of the subjects studied were male (54.0%), aged 30-49 years (44.0%) with underweight nutritional status (72.0%).

Table 2 shows the subject age range is between 18-65 years, with a mean of 38,02 years. Based on the Body Mass Index (BMI), it was obtained between 12,1-23,0 with a mean of 17,15, which indicates that most subjects had a malnutrition status. CRP levels before treatment were found in the subjects between 0,05-17,45 with an average of 5,69 + 3,50 and after the intensive phase treatment between 0,08-10,47 with a mean of 1,73 + 2,43.

Table 3 shows the relationship between CRP levels before treatment with the extent of chest X-ray lesions and positivity of AFB smear before treatment. CRP levels before treatment were higher in advanced lesions than minimal lesions, which were 6,31 compared to 3,20 ($p < 0.05$). CRP levels before treatment were highest in subjects with AFB +2 (7,20+3,01) and lowest in subjects with AFB +1 (4,41+2,98) ($p < 0.05$). This shows a positive correlation between CRP levels with the extent of chest X-ray lesions and positivity of AFB smear. [23]

Table 4 shows a reduction between CRP levels before and after treatment. There was a significant reduction in CRP levels after treatment, from 5,69+3,50 to 1,73+2,43 or 69.6% reduction ($p < 0.001$).

3 Discussion

C-reactive protein is one of the acute phases reactants that increase significantly during the inflammatory process that occurs in the body. Mycobacterium tuberculosis enters the body, causes inflammation and releases various pro-inflammatory cytokines, mainly IL-8 and IL-6. From a study conducted by Grace Lui et al., there was an increase in proinflammatory cytokines in patients with PTB who also correlated with the extent of lesions on chest radiographs, bacterial load and length of hospitalization. IL-6 is the main transcript of CRP synthesis in the liver.[10]

Based on the IUATLD (International Union Against Tuberculosis and Lung Disease) scale, researchers divided the positivity of AFB smear into three groups; AFB +1, AFB +2 and AFB +3 which described the number of TB bacterial load. While based on the extent of chest X-ray lesions, our sample was divided into two groups; minimal lesions and advanced lesions.[2]

There is a positive correlation between the extent of chest X-ray lesions with CRP levels which found higher CRP levels in

Table 1 Demographic Profile of PTB Subjects (n=50).

Variable		n	%
Gender	Male	27	54,0
	Female	23	46,0
Age	<30 yo	16	32,0
	30-49 yo	22	44,0
	> 50 yo	12	24,0
Nutritional Status	Underweight	36	72,0
	Normoweight	14	28,0
Lesion extent	Advanced	40	80,0
	Minimal	10	20,0
AFB smear before treatment	+1	26	52,0
	+2	16	32,0
	+3	8	16,0
AFB smear after treatment	Negative	34	68,0
	+1	13	26,0
	+2	3	6,0

Table 2 Descriptive Statistics of Research Variables (n=50).

Variable	Min	Max	Mean	SD
Age	18	65	38,02	15,6
BMI	12,1	23,0	17,15	2,4
CRP before treatment	0,05	17,45	5,69	3,50
CRP after treatment	0,08	10,47	1,73	2,43

Table 3 CRP Levels According to the Extent of Chest X-Ray and Positivity of AFB Smear

		n	Mean	SD	P
Lesion extent	Advanced	40	6,31	3,34	0,01
	Minimal	10	3,20	3,16	
AFB smear	+1	26	4,41	2,98	0,23
	+2	16	7,20	3,01	
	+3	8	6,82	4,69	

Table 4 Comparison of CRP levels before and after treatment.

Variable	n	Mean	SD	% Decrease	P
CRP before treatment	50	5,69	3,50	69,6	0,000
CRP after treatment	50	1,73	2,43		

chest X-ray with advanced lesions compared to minimal lesions with an average of 6,31+3,34 compared to 3,20+3,16 ($p < 0,05$). These results are in line with the research conducted by Sharma et al., which found a positive correlation between CRP values and the extent of chest X-ray lesions. The MTb causes this fact in lungs of PTB patients associated with the inflammation process of lung tissue, which correlates with changes in CRP levels.[3]

Several previous studies have revealed that the positivity of AFB smear has a positive correlation with serum CRP levels. This means that patients with AFB +3 sputum had higher CRP levels than patients with AFB +2 and AFB +1 sputum.[6,7] The results our study were not consistent with previous studies. We obtained a higher CRP level in subjects with AFB +2 compared to AFB +3 with an average of 7,20+3,01 compared to 6,82+4,69 ($p < 0,05$). However, these results are consistent with studies by Teixeira and Soedarsono, which showed that CRP levels did not increase significantly with higher AFB smear positivity, but CRP values increased significantly based on disease severity according to the extent of chest X-ray lesions. Increased serum CRP is more affected by damage to lung tissue than MTb bacterial load.[3,11,12]

In this study there is significant decrease in CRP levels from a mean of 5,69+3,50 before treatment to 1,73+2,43 (69,9% decrease) after 2 months intensive phase treatment ($p < 0,000$). CRP has been reported in various studies to increase significantly in inactive PTB patients and will decrease after treatment and correlate with the patient's clinical response. High CRP levels are associated with the severity of TB disease, poor prognosis and successful rate of treatment. Mycobacterium tuberculosis and its components are known to stimulate mononuclear phagocytes in vitro to release IL-6, which is an inflammatory mediator. IL-6 then induces acute phase reactants in the liver, namely CRP. Some previous studies also found a correlation between IL-6 and CRP. The study by Bekker et al. said the reduction in CRP levels in pulmonary TB patients undergoing treatment was positively correlated with a reduction in IL-6 levels so that the reduction in serum CRP concentrations during treatment also correlated with a reduction in lung tissue inflammation in PTB patients.[12,13,14]

Conclusion

CRP levels before treatment are significantly associated with the extent of chest X-ray lesions and positivity of AFB smear, so that it can be used as a marker of severity of pulmonary TB disease. There was also a significant reduction in CRP levels after two months of intensive phase treatment in PTB subjects.

Competing Interests

The authors declare that there is no conflict of interest in this study.

Ethics committee approval

The ethical committee has approved it of Hasanuddin University Faculty of Medicine with reference number: 1000 / H4.8.4.5.31 / PP36-KOMETIK / 2018.

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