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CORRELATION BETWEEN LIVER TRANSAMINASE ENZYME AND LEUKOCYTE COUNT IN TUBERCULOSIS PATIENTS WHO RECEIVED ANTI-TUBERCULOSIS DRUG THERAPY

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ABSTRACT

Background: While effective in treating the disease, anti-tuberculosis drugs can also potentially harm the liver. Monitoring liver health using the transaminase enzyme and leukocyte counts can help in the early detection and prevention of such damage in tuberculosis patients. **Objectives:** The aim of the study was to determine the correlation between transaminase enzyme levels and the leukocyte count in patients with tuberculosis who took anti-tuberculosis drugs. **Methods:** This research was an observational analytical study with a cross-sectional approach. It used medical record data from TB patients who met the inclusion and exclusion criteria for anti-tuberculosis drug therapy at the medical records installation. **Results:** Forty-four samples were included in the research. The levels of aspartate transaminase (AST), alanine transaminase (ALT), and leukocyte count were 30 IU/L, 19.5 IU/L, and $9.35x10^3$/µL. The Spearman correlation test showed no correlation between AST and ALT levels and leukocyte counts, with p-values of 0.585 and 0.337. **Conclusion**: There was no correlation between AST and ALT levels and leukocyte counts in tuberculosis patients undergoing anti-tuberculosis drug therapy.

BACKGROUND

Tuberculosis (TB) is an infectious disease that causes the most deaths after COVID-19. According to the World Health Organization (WHO), an estimated 10 million people worldwide are affected by tuberculosis in 2021. In addition, tuberculosis is also the infectious disease that causes the most deaths in the world after the Coronavirus Disease 2019 (COVID-19). Indonesia is one of eight countries that account for half of the tuberculosis patients worldwide. In fact, in 2022, Indonesia is the country with the second-highest number of sufferers in the world after India, with an estimated number of cases of 969,000 cases. This figure is an increase of 17% from 2020, when there were 824,000 cases of tuberculosis.[1,2]

Tuberculosis is caused by infection with the bacteria Mycobacterium tuberculosis. The disease usually affects the lungs but can also attack other organs, such as the digestive system and the brain.[3] Rifampicin (RFP), isoniazid (INH), pyrazinamide (PZA), ethambutol (EMB), and streptomycin are the first-line drugs used to treat tuberculosis. These drugs are proven to be effective in curing tuberculosis; however, despite their benefits, they also have several side effects, one of which is on liver function. Hepatotoxic effects can certainly adversely affect the liver, which can also be called Anti Tuberculosis Drug Induced Liver Injury (ATDILI).[4-8]

Some of the first-line drugs used to treat tuberculosis can damage the liver. This is shown by higher levels of two types of transaminase enzymes in the blood: SGOT (Serum Glutamate Oxaloacetate Transaminase) or Aspartate Aminotransferase (AST) and SGPT (Serum Glutamate Pyruvate Transaminase) or Alanine Aminotransferase (ALT). Both of these enzymes regulate liver function. Inflammation or damage to the liver can cause increased release of ALT and AST.[9,10] This is supported by research by Sabiti and Sa'dyah. The study's findings showed that higher AST and ALT

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levels in people who were in the intensive treatment phase for tuberculosis were linked to side effects of antituberculosis drugs.[8,11,12]

Antituberculosis drug-induced liver damage may be mediated by the immune system. Tumor Necrosis Factor (TNF-α), Nitric Oxide (NO), and Interferon-gamma (IFN-γ) are some of the proinflammatory cytokines that will be released during this immune response. Inflammation can also cause liver damage if the inflammation is uncontrolled and can no longer be tolerated by the body.[13–15]

Based on research conducted by Chedid C et al. (2020) with a prospective cohort method, leukocyte counts significantly decreased in TB patients with antituberculosis drug therapy, indicating the success of therapy.[16] However, in the study of Zhao H et al. (2020) with a prospective cohort method, there was a significant increase in the number of leukocytes in patients with DILI due to antituberculosis drugs with a higher number of leukocytes according to the severity of DILI, where in DILI degrees 1-3 the number of leukocytes was 5.93 ± 3.10 x 10^9 U/L, while in DILI degrees 4-5 the number of leukocytes was 8.81 ± 4.22 x 10^9 U/L.[8] Leukocytes that increase due to DILI are different from leukocytes that increase when patients are infected with TB. This can be distinguished from the overall neutrophil and leukocyte counts, which should decrease after treatment, and lymphocytes, which increase after treatment.[5–7,16,17]

Based on the above description, leukocytes, AST, and ALT are released in the blood when there is inflammation in the liver that can be caused by antituberculosis drugs. Therefore, researchers are interested in knowing the correlation between AST and ALT levels with leukocyte counts in tuberculosis patients with antituberculosis drug therapy.

METHODS

Study population and data collection

This study was an analytic observational study with a cross-sectional approach. The data were obtained from the medical records of patients diagnosed with tuberculosis at Dr. Kariadi Hospital with antituberculosis drug therapy who met the inclusion criteria. AST and ALT tests use the Modified IFCC (International Federation of Clinical Chemistry and Laboratory Medicine) principle using the Advia 8000 Chemistry System. Samples were taken by purposive sampling method. Data collection took place from June to July 2023. Inclusion criteria in this study were patients aged 30-75 years who underwent antituberculosis drug therapy for at least two weeks. People who had been diagnosed with liver diseases before taking antituberculosis drugs, fevers, hematological disorders (like leukemia or aplastic anemia), or cancer were not allowed to participate in this study.

Statistical analysis

The data obtained were analyze using the IBS SPSS Statistics 25.0 application. The analysis began with a normality test with Shapiro Wilk test. Bivariate analysis was performed to find the correlation between two ratio-scale variables. The type of correlation test performed was in accordance with the results of the normality test. The data were not normally distributed, so the correlation test used the Spearman test. The two variables were considered not to have a significant correlation because the p-value > 0.05 was obtained.

Ethical Approval

The research was conducted with ethical clearance from the Health Research Ethics Commission (KEPK) of the Faculty of Medicine, Universitas Diponegoro, number 261/EC/KEPK/FK-UNDIP/VI/2023.

RESULTS

Overview

This study involved 44 subjects that met the inclusion and exclusion criteria from digital medical records. In addition to testing the correlation between AST and ALT levels and leukocyte counts, researchers also gathered data on subject characteristics such as age, gender, hemoglobin level, administration of antituberculosis medications, and administration of vitamin B complex.

Based on the table 1, from a total of 44 tuberculosis patients with antituberculosis therapy, the average age was 50.89 years, with a median of 52 years. The sample population was also dominated by male gender at 59.1%. For hemoglobin levels, the mean was 34.29 mg/dL, the mean hematocrit was 34.29%, the mean number of erythrocytes was 4.21 x 106/µL, the mean MCH value was 26.18 pg, the mean MCV value was 81.50 fL, the mean MCHC value was

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32.08 gr/dL, the mean platelet count was 418.16 x 10^3/µL. Based on the table, the mean SGOT level was 38.80 IU/L, the mean SGPT level was 32.82 IU/L, and the mean leukocyte count in this population was 10.88 x 103 /µL.

Table 1. Characteristic of the subjects

Variable (n =44)	Mean ± SD	Median (min – max)	n (%)
Age (Years)	50.89 ± 11.53	52.00 (31-74)	
Gender			
Male			26 (59.1)
Female			18 (40.9)
Hemoglobin (mg/dL)	11.02 ± 1.96	10.80 (6-14.8)	
Hematocrit (%)	34.29 ± 5.57	33.65 (20.7-46.9)	
Erythrocytes (10^6/µL)	4.21 ± 0.57	4.24 (2.73-5.41)	
MCV (fl)	81.5 ± 7.6	82.2 (61.0-96.5)	
MCH (pg)	26.18 ± 3.08	26.70 (17.4-30.7)	
MCHC (gr/dL)	32.08 ± 2.04	32.30 (26.5-35.9)	
Platelets (10^3/µL)	418.16 ± 149.88	399.50 (127-842)	
AST (IU/L)	38.80 ± 32.38	30 (15-219)	
ALT (IU/L)	32.82 ± 31.10	19.5 (6-179)	
Leukocytes (10^3/µL)	10.88 ± 5.58	9.35 (3-29)	
Anti tuberculosis drugs administration			
First line			29 (65.9)
Second line			12 (27.3)
Mixture of first and second line			3 (6.8)
Vitamin B administration			
Not given			3 (6.8)
Vit B1			1 (2.3)
Vit B6			33 (75)
Vit B9			2 (4.5)
Vit B1 and B12			1 (2.3)
Vit B complex			4 (9.1)

Based on antituberculosis drug administration, it was found that the majority of TB patients in this study were given first-line antituberculosis drugs (65.9%) such as rifampicin, isoniazid, pyrazinamide, ethambutol, and streptomycin, either complete or in various combinations of these drugs. About 27.3% of the sample received second-line antituberculosis drug therapy, which included various combinations of drugs such as bedaquiline, cycloserine, linezolid, and others. The remaining 6.8% received a mixture of first- and second-line antituberculosis drugs.

The sample population was also given vitamin B complex, where the majority of the sample (75%) received vitamin B6 (pyridoxine) as therapy. The rest received vitamin B1 (2.3%), vitamin B9 (4.5%), a combination of vitamin B1 and B12 (2.3%), vitamin B complex (9.1%), and no vitamin B at all (6.8%).

Increase in AST, ALT and leukocyte levels

Based on the data obtained, there was an increase in AST levels in 43.18% of the subjects, there was an increase in ALT levels in 11.36% of the subjects, and there were also 11.36% of subjects who experienced an increase in AST and ALT together. For leukocyte counts, 34.09% of the subjects experienced an increase in leukocyte counts, and 9.09% of the subjects experienced an increase in AST, ALT, and leukocyte counts simultaneously.

Table 2. Increase in AST Level, ALT Level, and Leukocyte Count in Subjects

Parameter	Status	n (%)
ALT levels	Normal	25 (56.82)
	Increase	19 (43.18)
AST levels	Normal	39 (88.37)
	Increased	5 (11.36)
Leukocyte count	Normal	29 (65.91)
	Increased	15 (34.09)

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Correlation between AST and ALT levels with leukocyte count

Based on the results of the Spearman correlation test, it was found that AST levels were not significantly correlated with the number of leukocytes in tuberculosis patients receiving anti-tuberculosis drug therapy (p=0.585, r=0.085). In addition, an insignificant correlation was also found between ALT and the number of leukocytes (p=0.337, r=0.148). (Fig.1)

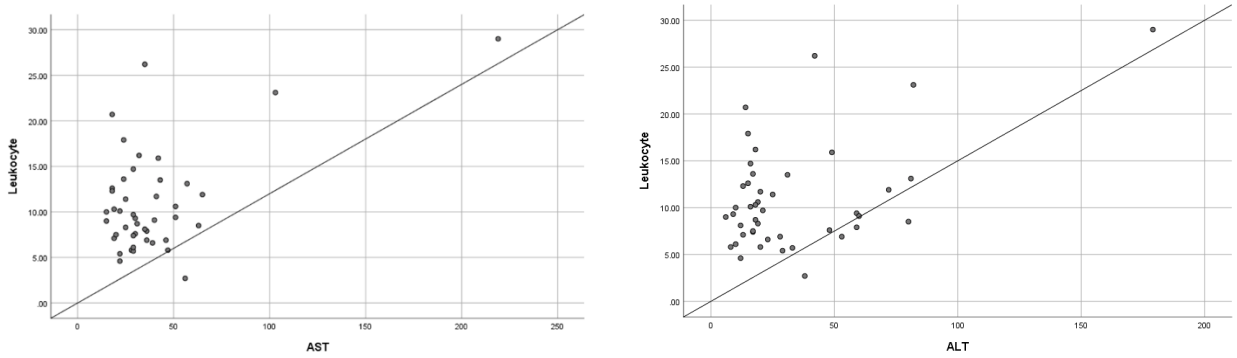

Fig 1. Correlation between AST and ALT levels with leukocyte count

DISCUSSION

This study was conducted on 44 tuberculosis patients taking antituberculosis drugs at Dr. Kariadi General Hospital Semarang. The average age of the patients was 50.98 years, which is in line with the literature review by Pramono J (2021), which states that the highest age of tuberculosis incidence is in the young, pre-elderly, and elderly age groups. This result is also in line with the research by Soedarsono et al. (2018) on the increasing incidence of ATDILI, which is influenced by advancing age, where in this study, the average age was in the pre-elderly group.[18,19]

The gender of the sample in this study was dominated by men, who comprised as much as 59.1% of the sample population. These results may affect the results of the study, which are not significant because Soedarsono et al (2018) stated that female gender is a risk factor for ATDILI.[19] Based on statistical tests that have been carried out, it is found that the relationship between AST levels and the number of leukocytes in tuberculosis patients undergoing antituberculosis drug therapy is not significant, with a value of p=0.585 (p>0.05).

An increase in AST levels in 43.18% of the sample population was found in this study. This shows that an increase in AST levels occurred in the sample, but not significantly. This result is not in line with the results of research by Sabiti F and Sa'dyah N (2022), which states that there is a significant relationship between the relationship between the side effects of antituberculosis drugs use and AST levels in tuberculosis patients in the intensive treatment phase. Patients who experienced mild side effects had normal AST levels, while patients who experienced severe side effects had abnormal ALT levels.11 In addition, the results of this study are also not in line with the research of Mirlohi MS et al. (2016), which states that there is a significant decrease in AST levels after undergoing antituberculosis therapy.[6] This difference in results may occur for several reasons. In addition to taking antituberculosis drugs, almost all TB patients are also given B vitamins during antituberculosis drug therapy, especially in the form of vitamin B6 (pyridoxine) and vitamin B complex.

Vitamin B6 has hepatoprotective properties because it is an antioxidant. The antioxidant properties of vitamin B6 can reduce the effects of toxic properties possessed by antituberculosis drugs metabolic products in the liver, where these antituberculosis drugs metabolic products can cause damage and inflammation in the liver. This is supported by research by Giustina A. et al. in 2019. In the study, rats that experienced sepsis were given vitamin B6 supplements. As a result, mice given vitamin B6 showed a decrease in oxidative stress formation activity. This means that vitamin B6 reduces the acute inflammatory response caused by neutrophils in these sepsis mice.[20,21]

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In addition to vitamin B6, some patients also take vitamin B complex consisting of B1 (thiamine), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine), B7 (biotin), B9 (folic acid), and B12 (cobalamin). Vitamin B complex has antioxidant and hepatoprotective properties that can reduce the incidence of inflammation in the liver. Of course, this also means that vitamin B complex can reduce blood levels of AST and ALT and prevent ATDILI. This is supported by a study by Amazon K et al. in 2017, which stated that the administration of methionine and B- complex vitamins in patients taking antituberculosis drugs showed a significant decrease ($p < 0.001$) in AST and ALT levels at the end of the intensive treatment phase compared to patients who only took antituberculosis drugs. This means that the administration of vitamin B complex can reduce the incidence of DILI in patients taking antituberculosis drugs.[21,22]

In this study, AST levels were not significantly associated with the number of leukocytes in tuberculosis patients undergoing antituberculosis therapy. These results align with the research conducted by Arfian F et al. (2018) on the relationship between AST levels and leukocyte counts in NSTEMI patients in the ICCU. The study stated that the insignificant results were due to the unknown number of standard leukocytes in NSTEMI patients in the ICCU.[23]

Based on statistical tests that have been carried out, it is found that the relationship between ALT levels and the number of leukocytes in tuberculosis patients undergoing antituberculosis drug therapy is not significant, with a value of $p=0.337$ ($p>0.05$). An increase in ALT occurred in 11.36% of the sample population found in this study. This shows that AST levels increased in the sample but not significantly. This is not in line with the research of Sabiti F and Sa'dyah N (2022), which states that there is a significant relationship between the relationship between side effects of antituberculosis drug use and ALT levels in tuberculosis patients in the intensive treatment phase. Patients who experienced mild side effects had normal ALT levels, while patients who experienced severe side effects had abnormal ALT levels.[11] In addition, the results of this study are also not in line with the research of Mirlohi MS et al (2016), which states that there is a significant decrease in ALT levels after undergoing antituberculosis therapy.[6]

The increase in ALT occurs less than the increase in AST. This may be due to the more hepatic-specific nature of the ALT test compared to the AST test, where ALT is mostly found in the liver, while AST is also found in skeletal muscle, heart, and kidney.[9,10]

The insignificant increase in ALT may also be caused by the administration of vitamin B complex, especially vitamin B6 (pyridoxine) in tuberculosis patients undergoing antituberculosis drug therapy. Vitamin B6 has antioxidant properties that can protect the liver from inflammation caused by the metabolic products of hepatotoxic antituberculosis drugs. In addition, other components in the vitamin B complex, such as vitamins B1, B9, and B12, also have antioxidant and hepatoprotective properties.[21-23]

The limitation of this study is that there is no research on the length of therapy using antituberculosis drugs. Antituberculosis Drug Induced Liver Injury (ATDILI) is a reaction that occurs acutely and mostly occurs within 2 weeks after the use of antituberculosis drugs. Therefore, the duration of drug use can be further investigated as it may affect the significance of the study results.[13]

CONCLUSIONS

Based on the research that has been done, it can be concluded that there is no significant correlation between AST and ALT levels with the number of leukocytes in tuberculosis patients undergoing antituberculosis drugs therapy.

CONFLICT OF INTEREST

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

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