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Characteristic of SGOT and SGPT Elevation in Patient with Lung Tuberculosis within OAT Therapy:

From Lung Policlinic RSUP Dr. Hasan Sadikin Bandung within 2016

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***Abstract*—Lung Tuberculosis (TB) is still a disease-causing severe health problem globally, including Indonesia, based on morbidity yet mortality perspectives. Tuberculosis therapy having a side effect from its hepatotoxicity, causing hepatitis-caused anti-tuberculosis drugs (OAT). Many factors were to influence the incidence of age, gender, nutritional status, length of therapy, etc. This research was conducted to understand the characteristic of elevation of SGOT and SGPT in newly treated tuberculosis with OAT in RS Dustira from January to December 2016. This research design is descriptive, with a total sample of 99 patients. Based on the research, 26 patients were elevated (26,3%) and 73 patients with a regular limit value of SGOT and SPOT (73.7%). This research showed the 18 patients with 1st degree of hepatitis-caused OAT (69.2%), 2nd degree of hepatitis-caused OAT in 5 patients (19.3%), and 3rd degree of hepatitis-caused OAT. Overall, patient with TB in RS Dustira was to have an elevation of SGOT and SGPT were to be found within 40–49-year age of a group (34.5%), women (57,7%), underweight nutritional status (53.8%), and length of medication of 2 weeks (26,9%). In conclusion, most patients with newly diagnosed TB were to see an elevated SGOT and SGPT value after therapy.**

Keywords—tuberculosis, hetatitis-caused OAT, OAT, SGOT, SGPT

I. INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease that attacks almost all human body organs, especially the lungs. Tuberculosis is a serious threat to people around the world, both in terms of morbidity and mortality. Based on data from the World Health Organization (WHO), TB is one of the top 10 causes of death globally, with around 10.4 million patients and 1.8 million deaths. In 2015, Indonesia became the second country after India to have the highest TB disease globally, followed by China, Nigeria, Pakistan, and South Africa. The incidence of TB in Indonesia reaches 185 cases per 100,000 population. The number of TB incidence cases in Indonesia reached 82,799 new cases in 2016, reported from government hospitals and private hospitals in Indonesia, an increase from previously, which only amounted to 71,454 cases [1,2]. Referring to the high incidence rate, Indonesia is working with WHO to develop a TB control strategy, namely the directly observed treatment short-course (DOTS) strategy. One of the programs is implementing TB treatment with anti-tuberculosis drugs (OAT). TB treatment is divided into two phases: the intensive phase (2–3 months) and the advanced phase (4–7 months). The first-line drugs that are consumed, namely isoniazid, rifampin, pyrazinamide, streptomycin, and ethambutol [1,3,4]. TB treatment is given for 6 months with side effects that can be mild or severe. Severe and serious side effects can arise, especially when administering rifampin, isoniazid, and pyrazinamide are hepatotoxic events that can cause liver dysfunction. Clinical symptoms that appear can start from a mild to a severe increase in the liver function's value in the form of liver tissue necrosis [3-5]. An increase in the value of the high liver function or hepatotoxicity due to OAT can be indicated by an increase in the AST and ALT values. An increase in SGOT and SGPT will usually occur 1-2 months after consuming OAT. Each individual has a different susceptibility to the increased risk of SGOT and SGPT. This is what causes hepatotoxic side effects also vary in time.

The increase in AST and ALT values in administering OAT can also be influenced by several risk factors, including age, sex, and nutritional status. Based on previous research, there were several characteristics of TB patients at risk of hepatotoxicity, namely old age (more than 50 years), women, and poor nutritional status. Age can increase the risk of increasing AST and ALT after therapy because of decreased liver function. Besides, women are more susceptible to elevated AST and ALT because of the slower biotransformation of drugs than men. Malnutrition cases can also affect the increase in AST and ALT after OAT therapy. Malnutrition status will facilitate the occurrence of hepatocellular injury, thus increasing the risk of developing OAT-induced hepatitis. Another thing that affects the OAT itself is the risk factors, namely polypharmacy (combination of OAT) and the length of treatment [5-7].

Research on OAT treatment in TB patients with increased liver function values (SGOT and SGPT) is still small in number in Indonesia and has not been carried out for a long time. Therefore, research on the description of liver function after intensive OAT therapy needs to be done. Besides, Dustira Hospital is one of the referral hospitals in Cimahi, so the researchers decided to examine TB patients' characteristics with impaired liver function.

A. Tuberculosis Therapy

The TB treatment aims to cure patients, prevent death, prevent recurrence, and prevent MTB resistance to OAT. The bacteria that cause TB, MTB, are bacteria that can become dormant so that it is difficult to treat or can be killed but slowly. MTB also has properties rich in lipids and is not permeable to drugs so that the bacteria can form resistance. Therefore, TB patients need a combination of two or more drugs. This drug combination can overcome the possibility of resistance [4,8,9]. Based on the DOTS principle, OAT is not only given monotherapy but a combination. TB treatment is given in 2 stages, namely an intensive stage for 2 months and a follow-up stage for 4 months [4,10]. The pulmonary TB Eradication Program has been implemented with the DOTS strategy recommended by WHO to tackle TB disease in Indonesia. Based on DOTS, TB treatment is divided into 3 categories. The first category is 2HRZE / 4H3R3, the second category consumes 2HRZES / HRZE / 5H3R3E3, and the third category is 2HRZ / 4H3R3 and inserts (HRZE) [1,4].

The National Guidelines for TB Control in Indonesia and the Indonesian Association of Lung Doctors (PDPI) divide TB treatment categories into six categories. In the first category, namely TB new cases with positive smear results, it is recommended to use the 2RHZE / 4RH alloy. The second category, namely pulmonary TB cases with negative smear results, then pulmonary TB patients can use the 2RHZ / 4RH OAT alloy. The third category, namely TB with relapsing cases. In this category, patients can use the 3HRZE / 6RH alloy. The fourth category is TB with cases of treatment failure. This treatment category is the same as the fifth category (TB with chronic cases); that is, a resistance test is needed first. The last category, namely TB, with cases of neglect of treatment, then patients with this category must undergo a re-examination. The types, properties, and dosage of the first-line OAT can be seen in Table 1 [1].

TABLE I. TYPES, PROPERTIES AND DOSES OF FIRST-LINE ANTITUBERCULOSIS DRUGS

Kind of TB Therapy	**Characteristic**		**Dosage (mg/kg)**	
			Daily	***3x/Week***
Isoniazid (INH/H)	Bakterisid	Intra dan ekstraseluler	5 (4-6)	10 (8-12)
Rifampisin (R)	Bakterisid	Intra dan ekstraseluler	10 (8-12)	10 (8-12)
Pirazinamid (Z)	Bakterisid	Intraseluler	25 (20-30)	35 (30-40)
Etambutol (E)	Bakteriostati	Intra dan ekstraseluler	15 (15-20)	30 (20-35)
Strepto-micin (S)	Bakterisid	Ekstraseluler	15 (12-18)	15 (12-18)

B. Drug Metabolism in Liver

The liver has an important role in drug metabolism. The liver is an organ susceptible to exposure, both from drugs carried to the digestive tract through the portal vein and metabolite products produced by the liver itself. The goal of drug metabolism in the liver is to convert nonpolar (fat-soluble) drugs to water-soluble to be excreted through the kidneys [11-13].

In drug metabolism in liver cell microsomes, the drug will be processed through the liver so that the liver enzymes will make changes (biotransformation); then, the drug can be more soluble in the body and excreted through urine or bile. This hepatic biotransformation involves major oxidative pathways; the enzymes involved are cytochrome C-reductase and cytochrome P450. Therefore, the liver is susceptible to exposure to toxic chemicals that can cause liver damage [11-13].

Liver cells produce several enzymes such as lactate dehydrogenase (LD), alkaline phosphatase and y-glutamyl transferase (GGT), SGOT, and SGPT. SGOT and SGPT enzymes are often used to assess liver function, are found mainly in the cytosol, and will experience an increase in serum if there is damage to the hepatocytes that cause the enzyme to secrete excessively. Hepatocyte damage caused by drugs such as the first-line OAT can be started after 24 hours of drug consumption and has a maximum increase after 1–3 weeks of treatment. The increase in AST and ALT usually occurs 2 weeks after treatment [13].

C. Drug-Related Hepatotoxicity

In the journal National England Journal of Medicine (NEJM) with the title Drug-Related Hepatotoxicity, hepatotoxicity is defined as injury to the liver associated with impaired hepatic function caused by exposure to certain drugs or other non-infectious agents. The difference between liver injury and function is very important because they are the most important when hepatic function is impaired followed by clinically significant symptoms and disease [13].

Based on the American College of Gastroenterology (AGA), liver injury reaction after taking the drug is divided into three, namely fast reaction, medium reaction, and slow reaction. This division is based on the time the liver injury occurs after taking the drug. Rapid reactions usually occur about 3 to 30 days after taking the drug, while intermediate reactions will occur about 30 to 90 days and slow reactions occur more than 90 days after taking the drug. An early marker of hepatotoxicity is an increase in transaminase enzymes, namely, an increase in SGOT secreted in parallel with ALT, a more specific marker for detecting liver damage [14,15].

Meanwhile, women whose mothers or sisters have endometriosis have a seven times greater risk of experiencing endometriosis. The incidence of endometriosis is 10-20% in women of reproductive age, rarely occurs at the age of premenars or menopause [16]. Women with short menstrual cycles can increase the risk of exposure to menstruation which will have an increased risk of retrograde menstruation/reflux, making it easier for endometriosis. This shortening of the menstrual cycle increases the hormone estrogen exposure compared to women who have long menstrual cycles [17].

The development and growth of endometriosis tissue depend on sex steroid hormones and local growth factors such as insulin-like growth factor 1 (IGF-1) or vascular endothelial growth factor (VEGF). Estrogen increases sharply in the short time before ovulation; estrogen itself has a synergistic effect with IGF-1 / VEGF and sometimes actually enhances the effect of IGF-1 / VEGF on the proliferation and mitosis of ectopic endometrial cells, which will result in the formation of endometriosis [18]. During the menstrual cycle of patients with endometriosis, cyclic bleeding can occur in the nasal cavity, which occurs due to the presence of estrogen receptors on the mucosal surface of the respiratory tract; this can occur due to an imbalance in the secretion of matrix metalloproteases (MMPs) and tissue inhibitor of metalloproteases (TIMPs) [19].

D. Hepatotoxicity Mechanisms of Antituberculosis Drugs

The liver is not the main target of drug reactions that can harm organs in the body. Only about 10%, drug reactions cause liver damage. However, the mortality rate in hepatotoxicity cases is often quite high, and many cases can lead to liver failure [1]. Hepatocyte death in drug-induced hepatotoxicity can occur through two processes, namely processes mediated by apoptosis or necrosis. In apoptosis, cell shrinkage and fragmentation occur into small pieces with the cell membrane intact. These fragments will be cleared through the process of phagocytosis and generally do not stimulate the host immune response. Conversely, necrosis causes loss of mitochondrial function and depletion of ATP, leading to cell swelling and lysis which stimulates the local inflammatory process.

The processes of apoptosis and necrosis can be triggered through various mechanisms. In most cases, DILI begins with the drug's bioactivation into reactive metabolites capable of interacting with cellular macromolecules, such as proteins, fats, and nucleic acids. This results in protein dysfunction, lipid peroxidation, DNA damage, and oxidative stress. These reactive metabolites can trigger disruption of the ionic gradient and intracellular calcium storage, leading to mitochondrial dysfunction and impaired energy production. This impaired cellular function can eventually lead to cell death and liver failure [13-15].

In INH administration, the frequency of liver dysfunction (in the form of hepatitis) ranges from 0.2–5%. This incidence will increase if INH is given together with rifampin. Meanwhile, the liver's toxic effect due to pyrazinamide occurs as much as 15% when the dose is given as much as 40-50 mg/kg/day.

E. Risk Factors for Hepatitis Patients Induced by Antituberculosis Drugs

Age is an important factor affecting drug side effects, especially in the elderly and children (especially neonates and infants). In children, the body's ability to metabolize drugs is not yet fully developed, and this is why children are susceptible to drug side effects. In the elderly or older, the risk of drug side effects is influenced by several factors; drug combination; the ability of the liver to metabolize, and the ability of the kidneys to excrete drugs decreases, and due to decreased water content in the body and increased fat causes water-soluble drugs to reach high concentrations in the body. In contrast, fat-soluble drugs will accumulate in the body [16,17,20-22].

Nutritional status can play a role as a determinant of the outcome of clinical TB patients. Adequate nutritional needs are essential for the body, one of which is to produce a collection of amino acid tripeptides called glutathione. The glutathione reserves in the liver function as detoxifying toxins, which will later be converted into a form that can be excreted in the urine [23-27].

II. RESEARCH METHODS

The data were obtained from medical records at the Lung Polyclinic of Dustira Cimahi Hospital in 2016. When the study began in March 2017- February 2018. The sample is the research object that is part of the population that has met the inclusion criteria. The sampling method used was a total sampling technique. The researcher took all objects that met the inclusion criteria, which used a categorical descriptive formula with a minimum sample size of 90 samples. The variables in this study were age, parity, clinical features, and anatomical location. The variables measured in this study were the characteristics and risk factors for increased AST and ALT in pulmonary TB patients after therapy at Dustira Hospital in the 2016 period. Characteristics and risk factors for pulmonary TB patients to be studied were age, gender, nutritional status, and length of time treatment.

III. RESULTS AND DISCUSSION

A. Characteristics of Tuberculosis Patients in Lung Polyclinic of Dr. Hasan Sadikin Bandung within 2016

TABLE II. DISTRIBUTION OF TUBERCULOSIS PATIENTS AT DUSTIRA HOSPITAL BASED ON AGE

Group of Age (yr)	Frequency	Percentage
18-29	23	23.3
30-39	28	28.2
40-49	31	31.1
50-59	10	10.2
>59	7	7.2
Total	99	100

Based on medical record data at Dustira Hospital from January to December 2016 (table 2), the distribution of pulmonary TB patients based on age at Dustira Hospital can be

seen in Table 2. In this study, it was found that there were 23 patients (23.3%) of 18-29 years old TB patients (23.3%), 30--39 years old 28 patients (28.2%), 40-49 years old as many as 31 patients (31, 1%), 50–59 years as many as 10 patients (10.2%), and more than 59 years as many as 7 patients (7.2%). Based on the study results, it can be concluded that the age group of most TB patients at Dustira Hospital is the 40–49 years old group.

These results are consistent with Adriani et al. Regarding the distribution of socio-demographic characteristics of the sample based on the age of pulmonary TB patients hospitalized at the Arifin Achmad Hospital Pekanbaru in 2014. The results showed that the largest age group of pulmonary TB patients was 40–49 years of age, as many as 17 people (24.63%). The Govindan study stated that the most pulmonary TB patients were at the age of 41–60 years, as many as 27 patients (52.9%) of the 51 samples used. Freddy's study also stated that 35 patients with pulmonary TB were generally at the productive age of 18–59 years (77.8%).

Pulmonary TB is a disease that can attack all age categories. However, based on the Indonesian Health Profile, the largest percentage of pulmonary TB sufferers is aged 25-35 years (23.67%), followed by 35-44 years (20.46%), 15-24 years (18.08%), 45- 54 years (17.48%), 55–64 years (12.32%), more than 65 years (6.68%), and the lowest was 0–1 year (1.31%). This is presumably because the level of activity that is quite strenuous, the work environment, and the body's immune system decrease, allowing it to be easily infected by other pulmonary TB patients.

TABLE III. DISTRIBUTION OF TUBERCULOSIS PATIENTS BY GENDER

Gender	Frequency	Percentage
Male	43	43.4
Female	56	56.5
Total	99	100

The results showed 56 patients (56.6%) were women, and 43 patients (44.4%) were men. This result is different from the research conducted by Adriani et al. Based on this study, patients with pulmonary TB hospitalized at the Arifin Achmad Regional Hospital in 2014 were found to be 36 men (52.17%) and 33 women (47.82%). The distribution of respondents based on gender can be seen in Table 3.

TABLE IV. DISTRIBUTION OF PULMONARY TB PATIENTS BASED ON NUTRITIONAL STATUS

Nutritional status	Frequency	Percentage
Underweight	23	23.3
Normal	65	65.5
Obesity	11	11.1
Total	99	100

The results of the study of TB patients based on nutritional status showed that 23 TB patients (23.2%) had underweight nutritional status, 65 patients (65.6%) had normal nutritional status, and 11 patients (11.1%) had normal nutritional status. obesity nutritional status. The distribution of respondents based on nutritional status can be seen in Table 4. This is following previous research conducted by Pramastuti. This study found that 56 out of 130 patients (43%) with pulmonary tuberculosis had normal nutritional status.

B. Distribution of SGOT and SGPT Values in Pulmonary Tuberculosis Patients

TABLE V. DISTRIBUTION OF SGOT AND SGPT VALUES IN PULMONARY TUBERCULOSIS PATIENTS

Status of Nutrition	Mean	Median	Min-Max	SD
SGOT	53.53	29	18-342	27.97
SGPT	29.90	25	13-189	13.93
Total	99	100		

Based on table 5, the mean value of AST levels after giving OAT is 53.53. The mean (mean) level of SGPT after giving OAT was 29.90. The standard deviation (SD) value of AST levels after giving OAT was 27.97. The SD value of SGPT levels after giving OAT was 13.93. The minimum value of AST levels after giving OAT is 18. The minimum value of AST levels after giving OAT is 13. The maximum value of AST levels after giving OAT is 342. The maximum value of SGPT levels after giving OAT is 189.

C. Distribution of Antituberculosis Drug-induced Hepatitis Patients

Based on Table 6, it was found that as many as 73 patients (73.7%) had normal liver function values after OAT therapy at the intensive stage. As many as 26 patients (26.3%) experienced an increase in liver function values, namely the SGOT and SGPT values were above normal. Patients who experienced pulmonary TB and had SGOT and SGPT values within normal limits after OAT therapy at Dustira Hospital in 2016 were found to be 73 patients (73.7%) and 26 patients (26.3%) who experienced an increase in SGOT and ALT.

TABLE VI. DISTRIBUTION OF PATIENTS WITH PULMONARY TUBERCULOSIS AND ANTI-TUBERCULOSIS DRUG-INDUCED HEPATITIS

Hepatitis-induced OAT	Frequency	Percentage
Normal	73	73.3
Hepatitis-induced OAT	26	26.3
Total	99	100

Another study conducted by Inez Clarasanti on the description of the transaminase enzyme in pulmonary tuberculosis patients being treated with anti-tuberculosis drugs at Prof. Dr. R. D. Kandou Manado also showed that 48 out of 186 pulmonary TB patients had liver function values, namely high SGOT and SGPT [20].

Based on the degree of severity, OAT-induced hepatitis was divided into 4. Based on the study, it was found that 18 patients (69.2%) experienced an increase of 1.25-2.5 times from normal (grade 1 OAT-induced hepatitis) of 18 patients (18.2%). %), 5 patients (19.3%) experienced an increase of

2.6–5 times from normal (Hepatitis induced by OAT level 2), 3 patients (11.5%) experienced an increase of 5.1-10 times from normal (hepatitis effect of OAT grade 3). There were no patients who increased more than 10 times than normal (Hepatitis induced by OAT grade 4). The distribution of OAT-induced hepatitis patients based on the degree of severity can be seen in Table 7.

TABLE VII. DISTRIBUTION OF ANTITUBERCULOSIS DRUG-INDUCED HEPATITIS PATIENTS BY DEGREE OF SEVERITY

Hepatitis Induced OAT	Frequency	Percentage
1st Degree	18	69.2
2nd Degree	5	19.2
3rd Degree	3	11.5
4th Degree	0	0
Total	26	100

This is following research conducted by Govindan that 39 Pulmonary TB patients (76.5%) at a normal AST value and found 9 patients (17.6%) had mild drug-induced hepatitis and as many as 3 patients (5.9%) had moderate OAT-induced hepatitis. Meanwhile, based on the SGPT value, it was found that as many as 40 patients (78.4%) had normal AST, 7 patients (13.7%) had mild OAT-induced hepatitis, and 4 patients (7.8%) had OAT-induced hepatitis moderate [22].

D. Hepatitis Induced by Antituberculosis Drugs by Gender

The distribution of TB patients with OAT-induced hepatitis by sex can be seen in Table 8. Based on Table 8, the results showed that the proportion of patients who experienced OAT-induced hepatitis grade 1 was 8 patients (30.8%), 2 patients had OAT-induced hepatitis grade 2 (7.7%), Hepatitis induced by OAT grade 3 was 1 people (3.8%). None of the patients had grade 4 OAT-induced hepatitis. In comparison, 10 patients (38.5%) had OAT-induced hepatitis, grade 2 OAT-induced hepatitis (11,5%), 2 patients (7.7%) of OAT-induced hepatitis, and no patient had grade 4 OAT-induced hepatitis.

This is consistent with previous research conducted by Shakya Rajani regarding evaluating risk factors for OAT-induced hepatitis in Nepal which stated that women tend to be more susceptible to developing OAT-induced hepatitis. This is because the biotransformation of drugs in women is slower than in men. Besides, acetylators in women are slower. If the acetylation is slow, it will cause the slow change of the drug into inactive metabolites [20].

TABLE VIII. DISTRIBUTION OF ANTITUBERCULOSIS DRUG-INDUCED HEPATITIS BY GENDER

Hepatitis Induced OAT	Gender				*N*	Total (%)
	Male		Female			
	N	*Percentage (%)*	*N*	*Percentage (%)*		
1st degree	8	30.8	10	38.5	18	69.3
2nd degree	2	7.7	3	11.5	5	19.2
3rd degree	1	3.8	2	7.7	3	11.5
4th degree	0	0	0	0	0	0
Total	11	42.3	15	57.7	26	100

Based on Ayu's research regarding the increase in SGOT / SGPT in pulmonary TB patients, it was found that the most sex-based distribution was female, with an increase in AST and ALT levels by 45% and a decrease in AST and ALT levels by 10% [17]. This is in line with the research conducted by Ike Pramastuti on 27 patients, and it was found that the number of male patients was 11 people, namely 40.74% and 16 women, namely 59.26%. The increase in AST for male patients was 63.64% and 81.25% for women, while the increase in SGPT for male patients was 81.82% and 81.25% for female patients.

E. Hepatitis Induced by Antituberculosis Drugs by Age

The distribution of TB patients with OAT-induced hepatitis by age can be seen in Table 9. Based on Table 4.8, the results showed that there were 2 patients in the 18–29-year group (7.70%) who had grade 1 OAT-induced hepatitis, 1 patient (3 ,8%) had OAT-induced hepatitis grade 2, and no patient had grade 3 OAT-induced hepatitis. Patients in the 30–39-year age group were found to have 5 patients (19.2%) with OAT-induced hepatitis grade 1 and 1 patient (3.8%) with OAT-induced hepatitis grade 2. Patients in the 40-49 year age group were found to have 7 patients (26.9%) who had grade 1 OAT-induced hepatitis, and 1 patient (3.8%) each had hepatitis grades 2 and 3. Patients with the age group more than 59 years old were found to be 1 patient (3.8%) each who experienced OAT-induced hepatitis grades 1, 2, and 3. Overall, pulmonary TB patients who had The most common OAT i in the age group 40-49 years as many as 9 patients.

TABLE IX. DISTRIBUTION OF PATIENTS WITH ANTITUBERCULOSIS DRUG-INDUCED HEPATITIS BY AGE

Hepatitis Induced OAT	Group of Age										Total	
	18-29		30-39		40-49		50-59		>=60			
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
1st	2	7.7	5	19.2	7	26.9	3	11.5	1	3.8	18	69.2
2nd	1	3.8	1	3.8	1	3.8	1	3.8	1	3.8	5	19.2
3rd	0	0	0	0	1	3.8	1	3.8	1	2.8	3	11.5
4th	0	0	0	0	0	0	0	0	0	0	0	0
Total	3	11.5	6	23	8	34.5	5	19.1	3	11.4	26	100

These results are consistent with Inez Clarasanti regarding the increase in the transaminase enzyme after administering OAT at the RSUP. Prof. DR. R. D. Kandou Manado [20]. Based on this study, the largest age group that showed improvement was the 41-50 years age group with 16 patients (33%) of 48 patients. This study is in line with the research conducted by Adriani; it was found that the most pulmonary TB patients who experienced hepatotoxicity based on AST

were in the 40–49-year age group; namely, 4 people and the highest hepatotoxicity based on SGPT was in the 18–29-year age group, namely 3 people. Another study stated that hepatitis OAT-induced hepatitis was most prevalent in the age group of 40-60 years with 7 patients. Research conducted by Ike Pramastuti also stated that patients in the 40–59-year age category most often experienced an increase in liver function values. Another study by Govindan also stated that there were 12 pulmonary TB patients aged 41-60 years who suffered from OAT-induced hepatitis and the cause was due to an increase in age [17,20,23-25,28,29].

OAT-induced hepatitis in older patients is caused by decreased liver function so that physiological function will decrease. The increasing age, the higher the risk of drug-induced hepatitis because hepatic function decreases with increasing age. Another study also states that OAT-induced hepatitis in pulmonary tuberculosis patients is influenced by increasing age due to decreased clearance of drugs metabolized by the CYP-450 enzyme and changes in hepatic blood flow and liver changes size with increasing age [22].

F. Hepatitis Caused by Antituberculosis Drugs Based on Nutritional Status

The distribution of TB patients with OAT-induced hepatitis based on nutritional status can be seen in Table 4.9. Based on Table 4.9, the results showed that the proportion of respondents with underweight nutritional status who experienced OAT-induced hepatitis level 1 were 10 patients (38.5%), 2 patients (7.7%) had level 2 OAT-induced hepatitis. As many as 2 patients (7.7%) had grade 3-induced hepatitis. While the proportion of patients with normal nutritional status who experienced grade 1 OAT-induced hepatitis was found to be 7 patients (30.8%), as many as 3 patients (11.5%) had induced hepatitis. Grade 2 OAT and only 1 patient (3.8%) had grade 3 OAT-induced hepatitis. In pulmonary TB patients with obese nutritional status, only 1 patient (3.8%) had grade 1 OAT-induced hepatitis.

This study's results are consistent with previous research conducted by Rajani Shakya in the city of Nepal, where the most TB patients with liver dysfunction were in the group with underweight nutritional status. Inez Clarasanti's research results also stated that around 15 patients out of 48 patients, who had OAT-induced hepatitis, had underweight nutritional status [21].

TABLE X. DISTRIBUTION OF ANTI-TUBERCULOSIS DRUG-INDUCED HEPATITIS BASED ON NUTRITIONAL STATUS

Hepatitis-induced OAT	Nutritional Status						Total	
	Under		Normal		Obese			
	N	(%)	N	(%)	N	(%)	N	(%)
1st degree	10	38.5	7	30.8	1	3.8	18	69.3
2nd degree	2	7.7	3	11.5	0	0	5	19.2
3rd Degree	2	7.7	1	3.8	0	0	3	11.5
4th degree	0	0	0	0	0	0	0	0
Total	14	53.8	11	42.3	1	3.8	26	100

The same thing was also found in a previous study by Nurazminah (table 10) regarding the prevalence of pulmonary TB with OAT-induced hepatitis and the associated risk factors at the Friendship Hospital Jakarta and RSPG Cisarua in 2012, which found that nutritional status influenced the incidence of OAT-induced hepatitis. The same result is shown by Pratomo (2012) that nutritional status plays a role in determining the outcome of TB patients. In individuals with underweight nutritional status, the glutathione reserves in the liver are generally also low to reduce the function of glutathione as detoxification of toxins. Glutathione is a protein naturally produced by the body, which plays an important role in the immune system and cell regeneration and acts as an antioxidant and antitoxin. Without adequate amounts of glutathione, it is susceptible to oxidative injury. Besides, patients with underweight nutritional status had slower drug metabolism than patients with normal nutritional status [21].

G. Hepatitis Caused by Antituberculosis Drugs Based on Duration of Treatment

The distribution of patients who have high liver function values based on OAT administration duration can be seen in Table 11. Table 11 shows that there were 5 patients (19.2%) who experienced an increase in function values in the first week, 7 patients (26.9%) in the second week, 6 patients (23%) in the third week, 3 patients in the fourth week. (11.5%), the fifth and sixth weeks of each patient were 2 (7.7%), and the eighth week only 1 patient (3.8%). Overall, it was found that patients had the most elevated liver function scores at the second week. These results are consistent with Inez Clarasanti regarding the increase in the transaminase enzyme after administering OAT at the RSUP. Prof. DR. R. D. Kandou Manado stated that the increase in liver function values mostly occurred from the first week to the third week. This result is different from the results of the previous study by Praditya, which found that 17 people (43%) of pulmonary tuberculosis patients experienced the highest increase in transaminase enzymes in the fourth to the sixth week after administering OAT at Siti Hajar Hospital Medan, North Sumatra [16].

TABLE XI. DISTRIBUTION OF PATIENTS WHO HAVE HIGH LIVER FUNCTION VALUES BASED ON THE DURATION OF OAT ADMINISTRATION

Weeks	Frequency	Percentage
1st Weeks	5	19.2
2nd Weeks	7	26.9
3rd Weeks	6	23
4th Weeks	3	11.5
5th Weeks	2	7.7
6th Weeks	2	7.7
7th Weeks	0	0
8th Weeks	1	3.8
Total	26	100

Hepatotoxicity is the most serious side effect of antituberculosis therapy, so the America Thoracic Society (ATS) recommends initial assessment of liver function values, namely AST and ALT, before starting OAT therapy, during therapy, and after OAT therapy. Besides, regular follow-up of

AST and ALT is recommended in patients who have risk factors for developing OAT-induced hepatitis. OAT-induced hepatitis OAT induced by OAT can cause mortality and morbidity, which reduces the effectiveness of therapy.

Asymptomatic elevated AST and ALT values are common during OAT therapy. However, hepatotoxicity can be fatal if not recognized early and if therapy is not stopped at the right time.9 OAT-induced hepatitis is generally more common in weeks to months than days to weeks as it occurs in a hypersensitivity reaction. From clinical symptoms, hepatic reactions usually appear in the first two months of treatment but can also appear at any time during the therapy period. Clinical signs and symptoms are not specific enough to confirm liver disorders; therefore, laboratory confirmation to assess liver function is needed. Complaints due to drug-induced hepatitis can largely disappear if therapy is stopped [30].

IV. Conclusion

Based on the results of research on the increase in AST and ALT in pulmonary TB patients after OAT therapy at the Lung Polyclinic of the Dustira Cimahi Hospital for the period 2016, it can be concluded: (1) Age 40-49 years (31.1%), female (56.6%)). Normal nutritional status (65.6%) had the most TB. (2) A total of 26 patients (26.3%) experienced an increase in AST and ALT after OAT therapy. (3) Age 40–49 years (34.5%) is the largest age group that increases AST and ALT after OAT therapy. (4) Women (57.7%) experienced the most increase in AST and ALT after OAT therapy. (5) TB patients with poor nutritional status experienced the most increase in AST and ALT, as many as 14 patients (53.8%). (6) Pulmonary tuberculosis patients experienced the most increase in AST and ALT after therapy, namely in the second week (26.9%).

For further research, it is also advisable for further research in examining AST levels that are carried out periodically, both before, during, and after the first-line OAT administration in TB patients with or without indication, for more effective treatment and reducing complications and OAT administration.

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