

Comparison of Ureum and Creatinine Levels Pulmonary Tuberculosis in Phase 0 and 6 Moths Treatment

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ABSTRACT

Pulmonary tuberculosis is a disease caused by Mycobacterium tuberculosis. Treatment for tuberculosis patients is given in the intensive and advanced stages. Anti-tuberculosis drugs can be nephrotoxic to cells in the kidneys. This research is an analytic observational study to know the comparison of urea and creatinine levels in pulmonary tuberculosis patients in the 0 and 6-month treatment phases at the Community Lung Health Center Purwokerto. The samples studied were 42 respondents who were taken by accidental sampling. This study was conducted from December 2021 to January 2022. Out of the 42 pulmonary tuberculosis patients who received treatment at 0 and 6 months, the majority of pulmonary tuberculosis patients were 28 patients (66.7%) had normal urea levels, and 38 patients (90.5 %) had normal creatinine levels. Urea levels in pulmonary tuberculosis patients during the 0-month treatment phase were 9 (2-24) mg/dL, while in the 6-month treatment phase, it was 8 (1-37) mg/dL. The creatinine level of pulmonary tuberculosis patients with 0-month treatment phase was 0.98 (0.64-1.62) mg/dL, while in the 6-month treatment phase it was 0.88 (0.62-1.92) mg/dL. There was no significant comparison of urea and creatinine levels in pulmonary tuberculosis patients with treatment phases 0 and 6 months ($p>0.05$).

Keywords: *pulmonary tuberculosis; urea; creatinine; treatment phase*

ABSTRAK

Tuberkulosis paru merupakan suatu penyakit yang disebabkan oleh Mycobacterium tuberculosis. Pengobatan bagi penderita tuberkulosis diberikan dengan tahap intensif dan tahap lanjutan. Obat Anti Tuberkulosis dapat bersifat nefrotoksik terhadap sel-sel pada ginjal. Penelitian ini bersifat observasional analitik dengan tujuan untuk mengetahui perbandingan kadar ureum dan kreatinin pada penderita tuberkulosis paru pada fase pengobatan 0 dan 6 bulan di Balai Kesehatan Paru Masyarakat Purwokerto. Sampel yang diteliti sebanyak 42 pasien tuberkulosis paru kategori 1 yang diambil secara accidental sampling. Penelitian ini dilakukan pada bulan Desember 2021 sampai Januari 2022. Dari 42 pasien tuberkulosis paru (kategori 1) yang mendapat pengobatan fase 0 dan 6 bulan, pasien tuberkulosis paru

mayoritas 28 pasien (66,7%) memiliki ureum normal dan 38 pasien (90,5%) memiliki kadar kreatinin normal. Kadar ureum pasien tuberkulosis paru dengan fase pengobatan 0 bulan adalah 9 (2-24) mg/dL, sedangkan pada fase pengobatan 6 bulan adalah 8 (1-37) mg/dL. Kadar kreatinin pasien tuberkulosis paru dengan fase pengobatan 0 bulan adalah 0.98 (0.64-1.62) mg/dL, sedangkan pada fase pengobatan 6 bulan adalah 0.88 (0.62-1.92) mg/dL. Tidak terdapat perbandingan signifikan pada kadar ureum dan kreatinin pasien tuberkulosis paru dengan fase pengobatan 0 dan 6 bulan ($p>0.05$).

Kata Kunci: tuberkulosis paru; ureum; kreatinin; fase pengobatan

INTRODUCTION

Tuberculosis (TB) is an infectious disease and is one of the causes of poor health status worldwide. TB is the leading cause of death from a single infectious agent other than HIV/AIDS (WHO, 2022). Tuberculosis is caused by the bacterium *Mycobacterium tuberculosis*. *Mycobacterium tuberculosis* infection can attack various organs of the body, especially the lungs. Pulmonary TB is contagious through the intermediary of sputum or droplets of sufferers and transmits to others through the respiratory system. Pulmonary TB sufferers can emit about 3000 phlegm splashes every time they cough or sneeze into the air so that they can infect other people who breathe the air (Widyanti, et.al., 2021). Globally in 2020, there are 1.7 billion people infected with the bacterium *Mycobacterium tuberculosis* (Yao et al., 2020). The five countries with the highest case incidence are India, Indonesia, China, the Philippines, and Pakistan. WHO defines high-burden countries (HBC) for TB based on three indicators, namely TB, TB/HIV,

and MDR-TB. Indonesia along with 13 other countries, is included in the HBC list for these three indicators, so it can be interpreted that Indonesia has big problems in dealing with pulmonary TB disease (Kemenkes, 2018).

The main symptoms shown by pulmonary TB patients include coughing up phlegm for 2 weeks or more. Cough followed by additional symptoms, namely phlegm mixed with blood, coughing up blood, shortness of breath, weakness, decreased appetite, weight loss, malaise, night sweats without physical activity, and fever for more than one month. In HIV-positive patients, cough is not a typical symptom of pulmonary TB (Kemenkes, 2018). Treatment for tuberculosis patients is given in 2 stages. The first stage is called the initial stage or what is often referred to as the intensive stage while the second stage is called the advanced stage. Tuberculosis control in Indonesia is carried out nationally with the Directly Observed Treatment Shortcourse (DOTS) strategy or direct supervision that is

integrated with basic health services by consuming drugs for approximately 6 months continuously without breaking. Drugs consumed during treatment are anti-tuberculosis drugs consisting of Isoniazid, Rifampicin, Pyrazinamide, Ethambutol, and Streptomycin (Pratiwi, 2015).

Anti-tuberculosis drugs that are consumed for a long time can be toxic to the body it will affect the performance of the liver and kidneys. Damage to the kidney organs can cause kidney failure where the organ cannot function properly (Widyanti, et.al., 2021). The use of category 1 anti-tuberculosis drugs can cause side effects on the liver and kidneys. Anti-tuberculosis drugs that have side effects include Isoniazid (INH) which can cause anorexia, nausea, vomiting, and icterus; Pyrazinamide has side effects of gastrointestinal disorders, impaired hematopoiesis, liver damage, and increased uric acid; ethambutol can cause gastrointestinal disturbances, allergic reactions, and eye nerve disease; while rifampin has side effects Cholestatic jaundice (rare), fever, thrombocytopenia and kidney failure; and streptomycin can cause renal tubular damage, vestibular damage and ototoxicity (Harison, 2019). One of the important prognostic factors to evaluate the effect of Anti Tuberculosis

drugs is by observing kidney function with laboratory indicators such as urea and creatinine tests. (Widyanti et.al., 2021).

Urea is the end product of protein and amino acid catabolism produced by the liver, which is then channeled through the intracellular and extracellular fluids into the blood, which will be filtered by the glomerulus in the kidneys. Creatinine is an endogenous metabolism that is very useful for assessing glomerular function. Creatinine is generally derived from muscle metabolism in large amounts. Under normal circumstances (kidney function, diet regulation, muscle mass, and normal metabolism), creatinine is produced in equal amounts and excreted in the urine every day (Denrison P and Erdiana G, 2019). Damage to kidney function can be detected by increasing levels of urea and creatinine. The normal value of urea at the age of 18-60 years is 6-20 mg/dL (2.1-7.1 mmol/L), while the age of 60-90 years is 8-23 mg/dL (2.9-8.2 mmol/L). The normal value for creatinine is 0.6-1.3 mg/dL (53-115 mmol/L) (Kemenkes, 2018).

Based on literature studies from Widyanti et al. (2021) of 5 journals of TB patients who took anti-tuberculosis drugs, it can be seen that from 167 respondents, 55

respondents had increased urea values and 112 respondents had normal urea levels, while research from (Wahdaniah, et.al., 2017). The comparison between cystatin C and creatinine in detecting impaired kidney function in TB patients with anti-tuberculosis drugs therapy stated that there was an increase in the average creatinine level in the first month of 1.18 mg/l (95% CI: 0.39 – 1.96) while the mean Creatinine levels in the second month were 0.714 mg/dl (95% CI: 0.44-0.98). This study was conducted to determine the comparison of urea and creatinine levels in patients with pulmonary tuberculosis in the 0 and 6-month treatment phases at the Purwokerto Community Lung Health Center.

METHOD

This type of research is an analytic observational study with a cross-sectional research design. The sampling of this research was carried out at the Community Lung Health Center Purwokerto, while the sample examination was carried out at the D4 Medical Laboratory Technology Laboratory, Faculty of Health Sciences, Muhammadiyah University, Purwokerto. The research was carried out from December 2021 to January 2022. This research was carried out after obtaining permission from the Faculty of Medicine,

General Soedirman Purwokerto University, with Ref: 200/KEPK/IX/2021.

The research sample was taken by accidental sampling technique, as many as 42 patients who underwent treatment with anti-tuberculosis Drug category 1 (patients who confirmed pulmonary TB and took anti-tuberculosis drugs in the intensive phase) with treatment phases of 0 and 6 months, with inclusion criteria including being willing to sign an informed consent, aged 20-70 years, TB patients with treatment phases 0 and 6 months, and do not suffer from HIV, hypertension and diabetes mellitus based on history and laboratory examination results; while the exclusion criteria included TB patients with autoimmune disorders, metabolic syndrome, hematological disorders, thyroid disorders, urinary disorders, liver disorders and heart disease based on anamnesis and laboratory results, extrapulmonary TB patients,

The tools used in this study were a photometer, centrifuge, block incubator, micropipette, micropipette tip, serological tube, tourniquet, syringe, serum cup, and timer. The materials used were serum samples, urea, creatinine reagent kits, aqua dest, alcohol cotton, plasters, gloves, and

masks. Blood Sampling; blood samples were taken from a vein, then centrifuged at

4000 rpm for 15 minutes, then the serum sample was put in the serum cup. Examination of urea; the method used for the examination of urea is Glutamate Dehydrogenase (GLDH). The working reagent and standard solution were left at room temperature, 1000 l of working reagent and 10 l of the sample were taken, homogenized, then read the results on a photometer with a wavelength of 340 nm after 30 seconds, then recorded the results (Biolab Medika Evogen). The method of

checking creatinine is Jaffe. The working reagent and standard solution were left at room temperature, 1000 l of working reagent and 25 l of the sample were taken, homogenized, then read the results on a photometer with a wavelength of 510 nm after 120 seconds, then recorded the results. The data obtained were analyzed by the Mann-Whitney U test using Jeffreys' Amazing Statistics Program (JASP) version 0.16.0.0 software.

RESULTS AND DISCUSSION

Table 1. Product Eligibility Criteria

Characteristics	Frequency (n)	Percentage (%)	Average \pm SD	median (Min-Max)
Gender				
Man	25	59.5	-	-
Woman	17	40.5		
Age	-	-	41 \pm 15,437	44 (20-70)
Treatment phase				
0 Months	21	50		-
6 months	21	50	1.50 \pm 0.506	
Urea Level (mg/dL)				
Low	11	26.2		
Normal	28	66.7	10.24 \pm 7.509	8.50 (1-37)
Tall	3	7.1		
Creatinine Level (mg/dL)				
Low	0	0		
Normal	38	90.5	0.9698 \pm	0.9200
Tall	4	9.5	0.270966	(0.62-1.92)

Based on Table 1, it can be seen that the majority of male respondents (59.5%) are more at risk of developing Mycobacterium tuberculosis compared to women (40.5%). This is in line with

research from (Wahdaniah, et.al., 2017) that more patients with pulmonary TB are male because of their lifestyle, namely smoking and consuming alcohol, because cigarettes contain proteins that are

harmful to the kidneys while consuming excessive alcohol can cause changes in kidney function. Pulmonary TB patients in this study were $41 \pm 15,437$ years old on average. This is in line with research (Harison, 2019) which states that the incidence of pulmonary tuberculosis of 70% occurs in productive age because at productive age, bacterial tuberculosis infection can occur due to fatigue, lack of or late eating, and stress. Untreated stress in a person with TB disease will stimulate the hypothalamus to secrete corticotropin-releasing factor (CRF) so that the pituitary gland secretes adrenocorticotropin releasing hormone (ACTH), which stimulates the adrenal cortex to secrete cortisol. Increased excessive cortisol secretion in pulmonary TB patients can cause complications, decreased immune system, and excessive metabolism (Nihayati *et al.*, 2019)

An older age person is closely related to the decline in organ function. This is due to changes in body anatomy and function of the kidneys. Increasing age causes the number of nephrons in the kidneys to decrease and causes kidney function to decline (Djasang & Saturiski, 2019). In this study, the treatment phase of

category one was observed, namely treatment carried out for 0-6 months. Research result (Harison, 2019) stated that 61% of kidney damage in patients receiving anti-tuberculosis drug therapy occurred two months after treatment (intensive phase). In the majority of pulmonary TB patients, as many as 28 patients (66.7%) had normal urea levels. The results of this study are in line with previous research from (Djasang & Saturiski, 2019), namely from 30 respondents as many as 25 (83.33%) respondents had normal urea levels and there was no significant comparison between urea levels with 0 and 6 months of treatment phase in pulmonary TB patients.

The results of the test on creatinine levels showed that 38 (90.5%) respondents had normal creatinine levels, and 4 (9.5%) respondents had increased creatinine levels. This research is in line with research from (Denrison P & Erdiana G, 2019) 20 respondents of 17 (85%) respondents did not experience an increase in creatinine levels and there was no significant comparison between creatinine levels with 0 and 6 months of treatment phase in pulmonary TB patients.

Table 2. Comparison of Ureum Levels against Respondents' Treatment Phase.

Treatment phase	Frequency (n)	Urea Level (mg/dL) (Min-Max)	<i>p Value</i>
0 Months	21	9 (2-24)	0.781
6 months	21	8 (1-37)	

Based on Table 2, it can be seen that the urea level of TB patients in the 0-month treatment phase was 9 (2-24) mg/dL. The urea level in pulmonary TB patients with the lowest 0-month treatment phase was 2 mg/dL, while the highest was 24 mg/dL. The urea levels in pulmonary TB patients with a 6-month treatment phase were 8 (1-37) mg/dL. Urea levels in pulmonary TB patients with the lowest 6-month treatment phase were 1 mg/dL, while the highest was 37 mg/dL, with a mean ranking of 10,571. There was no significant comparison between urea levels and treatment phase 0 and 6 months in patients with pulmonary TB ($p > 0.05$).

Increased levels of urea indicate that urea as a screening test for examination of renal excretory function illustrates that there is no effect of anti-tuberculosis drugs on renal excretory function. This is because the administration of anti-tuberculosis drugs to patients considers the suitability of indications, namely the use of drugs according to clinical needs, and the suitability of the type of anti-tuberculosis drugs based on the patient's

weight. On the aspect of the appropriateness of the dose of anti-tuberculosis drug use, adherence during anti-tuberculosis drugs treatment, and a history of diseases other than pulmonary TB to prevent contraindications (Indrasari 2015).

There are several factors that trigger an increase in urea, including eating too many foods that contain high protein and age. The first factor is eating high-protein foods, high-protein food intake will cause high levels of urea and creatinine. (Indrasari, 2015) explained that several types of drugs can affect the increase in urea, such as nephrotoxic drugs; diuretics (hydrochlorothiazide, ethacrynic acid, furosemide, triamterene); antibiotics (bacitracin, cephaloridine (large dose), gentamicin, kanamycin, chloramphenicol, methicillin, neomycin, vancomycin); antihypertensive drugs (methyldopa, guanethidine); sulfonamides; propranolol, morphine; lithium carbonate; salicylates, while drugs that can reduce urea levels such as phenothiazines. High levels of urea in the blood that are not excreted due

to decreased kidney function can become toxic substances in the body, because urea is a residual substance of protein metabolism through protein exchange,

namely the breakdown and resistance of all cell proteins that take place continuously (Djasang & Saturiski, 2019).

Table 3. Comparison of Creatinine Levels to Respondents' Treatment Phase

Treatment phase	Frequency (n)	Creatinine Level (mg/dL) (Min-Max)	p Value
0 Months	21	0.98 (0.64-1.62)	0.940
6 months	21	0.88 (0.62-1.92)	

Based on table 3, it is known that the creatinine level of pulmonary TB patients with a 0-month treatment phase is 0.98 (0.64-1.62) mg/dL. The creatinine level of pulmonary TB patients with the lowest 0-month treatment phase was 0.64 mg/dL, while the highest creatinine level was 1.62 mg/dL. The creatinine level of pulmonary TB patients during the 6-month treatment phase was 0.88 (0.62-1.92) mg/dL. The lowest creatinine level in pulmonary TB patients with a 6-month treatment phase was the lowest 0.62 mg/dL, while the highest creatinine level was 1.92 mg/dL. There was no significant comparison between creatinine levels with 0 and 6-month treatment phases in pulmonary TB patients ($p > 0,05$). Elevated creatinine levels can be caused by medications, dehydration, changes in muscle mass and a diet rich in meat.

According to (Rampa et al., 2019) There are several causes of increased levels of creatinine in the blood, namely

dehydration, excessive fatigue, use of drugs that are toxic to the kidneys, kidney dysfunction with infection, uncontrolled hypertension and kidney disease. A doubling of the serum creatinine level indicates a decrease in renal function 50% and a mild increase in the normal upper range is an indication of subclinical changes in renal function in persons with normal serum creatinine level (Rampa et al., 2019) On the other hand, creatinine levels can be lower than normal people because they are vegetarian or malnourished.(Priyanto et al., 2018).

According (Denrison P and Erdiana G, 2019), the kidney is an essential organ in the body and functions to get rid of metabolic waste and body toxins in the form of urine, which is removed from the body. Concomitant drug therapy may also affect renal excretion of the active drug. Damage to kidney function can cause nephron damage caused by drugs, so that

laboratory tests can show an increase in blood creatinine levels (Dennison P & Erdiana G, 2019)

Reducing the dose of anti-tuberculosis drugs can reduce the risk of nephrotoxicity, where giving doses of drugs that are not carried out every day will reduce the risk of nephrotoxicity because the body is not exposed to drugs continuously. Referring to research (Perdina et al. 2017) that anti-tuberculosis drugs can cause impaired kidney function (acute renal failure), which will occur during two months of anti-tuberculosis treatment. In the first two months of rifampin treatment will cause damage to the renal tubules. The damage caused by anti-tuberculosis is reversible which will return to normal in 3-4 months of treatment. Another study stated that an increase in blood creatinine would occur after undergoing five days of aminoglycoside treatment. The use of aminoglycosides which have a nephrotoxic effect, will be reversible, but when used, creatinine levels in plasma must always be monitored to see side effects during the treatment period.(Perdina *et al.*, 2017).

According to (Suryawan et al., 2016). To assess kidney function, requests for serum

urea and creatinine tests are always combined to determine the ratio of the two tests. The serum urea/creatinine ratio is a good index to differentiate between the various possible causes of uremia. The urea/creatinine ratio is usually in the 12-20 range. If the urea level is elevated but the creatinine level is normal, pre-renal uremia is likely. If both are increased there is a possibility of damage to the kidneys where the increase in urea is faster than creatinine. A low urea/creatinine ratio (<12) to normal creatinine is found in pre-renal uremia, a high protein diet, gastrointestinal bleeding, and a catabolic state. A high urea/creatinine ratio (>20) to high creatinine is seen in pre-renal azotemia with renal disease, renal failure, and post-renal azotemia (Ariffriana. et al, 2016).

CONCLUSION

There is no significant comparison of urea and creatinine levels in pulmonary TB patients with treatment phases 0 and 6 months in pulmonary tuberculosis patients with the p value of urea levels being 0.781 and the p value of creatinine was 0.940 ($p > 0.05$). Further research is needed on the relationship between urea and creatinine levels on urea and creatinine levels in pulmonary tuberculosis patients.

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