Jurnal Ilmu Farmasi dan Farmasi Klinik
(Journal of Pharmaceutical Science and Clinical Pharmacy)
ISSN 1693-7899 (print) - 2716-3814 (online)
Volume 21 No 1 (2024): 1 – 10
DOI: 10.31942/jiffk.v21i1.9529

The Correlation of Age and Comorbid Diseases to the Risk of Renal Impairment in Tuberculosis Patients at the Prof. Dr. H. Aloei Saboe Regional General Hospital, Gorontalo City

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ABSTRACT: Tuberculosis (TB) is a major health problem in Indonesia, including Gorontalo City. Anti-tuberculosis drugs (OAT) are the primary therapy in TB treatment, but the use of OAT can trigger various side effects, such as kidney disorders. This study aims to analyze the side effects of renal impairment from OAT use and the relationship with age and comorbid diseases in TB patients at Prof. Dr. H. Aloei Saboe Hospital. The study employed an analytical observational approach with a retrospective design, utilizing medical record data collected from 2022 to 2024. Correlation analysis was conducted using the *chi-square* test . The results showed that the majority were male as many as 251 people (60.77%), the majority of the age group was 55-64 years old, as many as 98 people (23.73%) and most received OAT category 1 treatment for new cases as many as 398 people (96.37%). Diabetes mellitus (DM) comorbidity with 101 patients (24.45%), hypertension comorbidity with 55 patients (13.31%), and renal impairment side effects experienced by 45 patients (10.90%). The correlation between age and renal impairment was significant, at the age of 15-24 years (OR: 0.28; 95% CI: 0.08 - 0.94; p = 0.04), age 45-54 years (OR: 2.12; 95% CI: 1.08-4.16; p = 0.04), and age 35-44 years (OR: 0.13; 95% CI: 0.01-0.97; p = 0.03). The comorbid DM (OR: 2.54; 95% CI: 1.34-4.83; p = 0.00) and hypertension (OR: 2.58; 95% CI: 1.36-4.89; p = 0.00) with renal impairment was significant. In conclusion, age and comorbidities play an important role in determining the adverse effects of renal impairment in TB patients.

Keywords: Tuberculosis; OAT; Age; Comorbidities

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Submitted: 15-04-2025; Received in Revised Form: 06-09-2025; Accepted: 08-11-2025

INTRODUCTION

One disease that is still a major public health problem, especially in developing countries such as Indonesia, is tuberculosis (TB). TB is a communicable infectious disease caused by the *Mycobacterium tuberculosis* (Mtb) (Kemenkes, 2020). The prevalence of new TB cases in the world will reach 7.5 million in 2022 and more than 10 million people a year continue to fall ill with TB (WHO, 2022). According to the World Health Organisation (WHO), 10.6 million people will have TB in 2022, an increase from 2021 (10.3 million) and 2020 (10.0 million). In 2022, Indonesia has a percentage of 10%, more than in 2021 with 9.2% per 100,000 cases, so the number of TB cases in Indonesia increases from 969,000 (2021) to 1,060,000 (2022). This placed Indonesia in second place with the highest TB cases in the world (WHO, 2022). The number of TB cases in Gorontalo Province in 2022 was 3,340 cases (Dinas Kesehatan Provinsi Gorontalo, 2022). Gorontalo Province also ranked as the sixth highest contributor to DR-TB in Indonesia in 2022 with a percentage of 77% (Kemenkes, 2022).

Adverse events are a major factor in TB treatment that arise in patients due to the use of anti-tuberculosis drugs (OAT). OAT side effects experienced by patients become one of the causes of patients stopping TB treatment therapy or drug withdrawal which can also have an impact on failure in TB treatment therapy (Maelani & Cahyati, 2019). The old age factor is due to declining physical conditions so that the immune system in the body cannot fight germs, this decrease in immunity increases the risk of reactivation of latent TB infection (Sterling & Lin, 2020). The older age factor (≥ 45 years) in drug metabolism becomes less efficient so that it can increase the accumulation of toxic metabolites in the body and which can lead to an increased risk of drug toxicity (Konstandi & Johnson, 2023). One of the other factors that influence the occurrence of OAT side effects is the presence of comorbidities.

Comorbidities that often accompany TB will weaken the body's immune system (Saputra *et al.*, 2022). Based on the explanation above, this study was conducted to analyze risk factor variables that potentially affect the incidence of OAT side effects, namely age and comorbid diseases. Analyze the side effects of OAT consumed by patients and how the correlation between these variables and the incidence of OAT side effects in Tuberculosis patients at Prof. Dr. H. Aloei Saboe Hospital, Gorontalo City.

METHODS

This study is a analytical observasional with a retrospective study design using patient primary data in the form of medical record data. This study was conducted at Prof. Dr. H. Aloei Saboe Hospital, Gorontalo City with the sampling method being a total sampling and conducted in the 2022-2024 period. Inclusion criteria were patients ≥ 18 years old on OAT therapy and patients with complete medical record data. Exclusion criteria in this study were patients in pregnant and breastfeeding conditions and patients with renal failure before TB diagnosis. Variables taken for this study included gender, age, OAT category, comorbid diseases, and side effects of renal impairment. Data were analyzed descriptively with univariate analysis to see frequencies and percentages. Bivariate analysis was performed using the *chi-square* test to determine the relationship between age and comorbidities with the occurrence of renal-impairment side effects. All analyses were conducted in google collab using the *python* programming language.

RESULT AND DISCUSSION

The results of patient characteristics in this study (Table 1), out of 413 patients showed that the majority were men as many as 251 people (60.77%), while there were 162 women (39.22%). The largest age group was 55-64 years old with 98 people (23.73%), and the least age group was 25-34 years old with 44 people (10.65%). Most TB patients received OAT category 1 treatment for new cases, 398 people (96.37%), while 15 patients (3.63%) underwent OAT category 2 treatment for drug-resistant TB cases (TB-RO). Comorbidities of diabetes mellitus were 101 patients (24.45%), comorbidities of hypertension were 55 patients (13.31%) and side effects of renal impairment were 45 patients (10.90%). Based on further analysis presented in Table 2, shows the correlation between age and comorbidity of diabetes mellitus (DM) and comorbidity of hypertension to renal impairment evaluated with bivariate analysis and using the chi-square test.

Table 1. The Characteristics of Tuberculosis (TB) Patiens

Variables		Frequency (n)	Percentage (%)
Gender	Male	251	60.77 %
	Female	162	39.23 %
Age	15-24 Years	77	18.65 %
	25-34 Years	44	10.65 %
	35-44 Years	55	13.32 %
	45-54 Years	85	20.58 %
	55-64 Years	98	23.73 %
	> 65 Years	54	13.07 %
OAT Category	Category 1	398	96.37 %
	Category 2	15	3.63 %
Comorbidities of Diabetes Mellitus	Yes	101	24.45 %
	No	312	75.55 %
Comorbidities of Hypertension	Yes	55	13.32 %
	No	358	86.68 %
Kidney Disorders	Yes	45	10.90 %
	No	368	89.10 %

In this study, the results of bivariate analysis showed that gender had no significant connection to the occurrence of renal impairment in tuberculosis (TB) patients, with a p-value = 0.09 and an odds ratio (OR) of 1.89 (95% CI: 0.94-3.78). Although there was a difference in proportion between males and females, there was no statistically significant difference. Other studies have also shown that although men have a higher prevalence of chronic kidney disease, this difference is not always statistically significant (Malinda *et al.*, 2022). Biologically, sex differences may affect kidney function through various mechanisms. The hormone estrogen in women is known to have a protective effect on the kidneys, while testosterone in men may increase the risk of kidney damage. However, within the scope of tuberculosis, these influences may not be strong enough to produce significant differences in the incidence of renal impairment between the sexes (Oktavia,

2022). Lifestyle factors also play a role in the difference in risk of renal impairment between the sexes. Men tend to have less healthy lifestyles, such as smoking and alcohol consumption, which may increase the risk of renal impairment. However, in this study, these factors may not be influential enough to produce a significant difference (Widiyanto *et al.*, 2020).

Table 2. The Correlations of Age and Comorbid Disease with Kidney Disorders

Variable	Kidney Disorders		
	P-value	OR	95% CI
Gender	0,09	1,89	0,94 - 3,78
15-24 Years	0,04	0,28	0,08 - 0,94
25-34 Years	0,24	0,36	0,08 - 1,54
35-44 Years	0,03	0,13	0,01 - 0,97
45-54 Years	0,04	2,12	1,08 - 4,16
55-64 Years	0,29	1,52	0,77 - 3,00
> 65 Years	0,09	2,10	0,97 - 4,54
OAT Category	1,0	1,27	0,27 - 5,81
Comorbidities of Diabetes Mellitus	0,00	2,54	1,34 - 4,83
Comorbidities of Hypertension	0,00	4,10	2,03 - 8,26

The age variable had a significant association with the incidence of renal impairment in TB patients. Bivariate analysis showed that those aged 15-24 years had an odds ratio (OR) of 0.28 (95% CI: 0.08 - 0.94; p = 0.04), those aged 35-44 years had an OR of 0.13 (95% CI: 0.01-0.97; p = 0.03) and those aged 45-54 years had an odds ratio (OR) of 2.12 (95% CI: 1.08-4.16; p = 0.04). This suggests that the risk of renal impairment increases with age, due to a physiological decline in kidney function, including a decrease in the number of nephrons and renal blood flow (Herman *et al.,* 2024). In healthy individuals, glomerular filtration rate (GFR) decreases with age, evidence indicates that aging is accompanied by declines in various physiological parameters, including renal blood flow, and with structural changes such as reduction in the number of nephrons, glomerulosclerosis, and tubulointerstitial fibrosis (Fenton *et al.,* 2018). In terms of pharmacokinetic implications, increasing age can affect drug activity in the body, body composition, drug absorption, drug distribution, protein binding, and drug clearance(Konstandi & Johnson, 2023). Thus, age is an important factor associated with the risk of renal impairment in TB patients through physiological mechanisms of decreased renal function.

In the OAT category variable, the p-value = 1.0 and the odds ratio (OR) was 1.27 (95% CI: 0.27-5.81). This indicates that the use of OAT category 1 or OAT category 2 does not significantly increase the risk of renal impairment in TB patients (Dasuki, 2020). Anti-tuberculosis drugs (OAT) such as rifampicin and pyrazinamide have nephrotoxic potential. Rifampicin can trigger acute immunological interstitial nephritis, this occurs because the drug is an inverse hypersensitivity reaction to an increasing number of drugs (Risma, R., & Rahman, A, 2022). Metabolism of pyrazinamide occurs in the liver by amidases that convert pyrazinamide to pyrazinoic acid (PA). PA is then further oxidized by xanthine oxidase (XO) and 5-hydroxy-pyrazines acid (5-OHPA) is formed. Furthermore, PA is conjugated with

glycine to form pyrazinuric acid, and most of its metabolites are excreted by the kidneys *(*Rahman M.M. *et al.,* 2023) In clinical practice, appropriate dose adjustment and regular renal function monitoring can prevent significant renal impairment in TB patients receiving OAT.

In this study, comorbid diabetes mellitus (DM) showed a significant association with the risk of renal impairment in TB patients, with a p-value = 0.00 and an odds ratio (OR) of 2.54 (95% CI: 1.34-4.83). Hyperglycemia that occurs in DM can trigger kidney damage through mechanisms such as hemodynamic changes, endothelial dysfunction, activation of inflammatory cells, and changes in the expression of vascular factors (Suherman *et al.*, 2023). Biologically, chronic hyperglycemia in DM causes oxidative stress and inflammation that damage renal structures, including the glomerulus and tubules. In addition, DM can cause microangiopathy that worsens renal perfusion, increasing the risk of diabetic nephropathy (Rumondang *et al.,* 2022). Hyperglycemia creates a favorable environment for bacterial growth that enhances the development of TB in patients with DM, by affecting the immune response and producing advanced glycation end products (AGEs) and chronic inflammation (Ferlita *et al.*, 2019). Impaired immune response and reduced intracellular bacterial killing in patients with DM, potentially increase bacteria and chronic inflammation (redox imbalance stress), which exacerbates lung damage, thereby creating a favorable environment for bacterial growth and worsening TB disease severity *(Boadu et al.,* 2024). Thus, comorbid DM contributes significantly to the increased risk of renal impairment in TB patients.

Likewise, the comorbidity of hypertension with the risk of renal impairment showed a significant association with a p-value = 0.00 and an odds ratio (OR) of 2.58 (95% CI: 1.36-4.89). Uncontrolled hypertension can cause damage to the renal blood vessels. High creatinine levels are eight times more common in hypertensive patients than in other individuals with normal blood pressure (Suryawan D.G.A *et al*, 2016). Uncontrolled high blood pressure in patients with hypertension can damage blood vessels in the kidneys, inhibit blood flow, and cause damage to the organ (Handini & Hunaifi, 2021). Sustained high blood pressure can damage small blood vessels in the kidney, reduce blood flow, and cause renal ischemia. In addition, activation of the renin-angiotensin-aldosterone system (RAAS) due to hypertension can increase glomerular pressure and cause structural damage to the kidneys (Fatah *et al.*, 2025.). Thus, the combination of these two comorbid diseases can accelerate the deterioration of renal function through mutually reinforcing mechanisms. When these two conditions occur together in TB patients, the nephrotoxic effects become more significant, increasing the risk of renal impairment substantially, and requiring special attention in the management and monitoring of renal function in TB patients.

CONCLUSION

The age groups of 15–24, 35–44, and 45–54 years, as well as comorbidities such as diabetes mellitus and hypertension, may increase the risk of renal impairment in tuberculosis (TB) patients undergoing anti-tuberculosis drug therapy. Therefore, caution and close monitoring of renal function are essential in patients with these risk factors.

ACKNOWLEDGMENT
The Directorate of Research, Technology, and Community Service, Ministry of Education, Culture, Research, and Technology, Indonesia, provided funding for this work under grant No.107/ES/PG.02.00.PL/2024,069.12/LL5.INT/AL.04/2024,115/PTM/LPPM.UAD/VI/2024, 15 June 2024. Additionally, the author would like to thank the Prof. Dr. H. Aloei Saboe Hospital in Gorontalo City for their help with this research support.

AUTHOR CONTRIBUTION
AFH: Concepts; methodology; data analysis; manuscript preparation; literature search.
MHW: Manuscript editing; literature search.
SNA: Manuscript editing; literature search.
ED: Manuscript editing; manuscript review.
SS: Manuscript review.

ETHICS APPROVAL
The research study was approved by the Ethics Committe of Ahmad Dahlan University with approval number 012405106.

CONFLICT OF INTEREST
No conflicts of interest

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