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Age and Diabetes Mellitus Associated with Hematological Disorders and Peripheral Neuropathy in MDR-TB Patients Treated with the BPaL/M Regimen

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ABSTRACT

Introduction: Tuberculosis (TB) is a disease with a significant treatment burden. Current multidrug-resistant (MDR)-TB therapy uses the bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaL/M) combination. This combination is effective with a short treatment duration. Linezolid is one of the components of the BPaL/M regimen. However, despite its effectiveness, it has side effects that impact treatment management and success. This study aimed to find the association between characteristics and comorbidities with the incidence of linezolid side effects in patients with MDR-TB treated with the BPaL/M regimen.
Methods: This was a retrospective analytic study of MDR-TB patients receiving BPaL/M combination. Data were collected from medical records and analyzed using Fisher's exact test to analyze the association between patient characteristics and comorbidities with the incidence of linezolid side effects, namely hematological disorders, peripheral neuropathy, and visual disturbances.
Results: There was no significant association between overall patient characteristics and the incidence of linezolid adverse events. However, the results of bivariate analysis showed a significant association in age >50 years old with the incidence of hematological disorders, as well as in patients who have diabetes mellitus (DM) with the incidence of peripheral neuropathy as a side effect of linezolid.
Conclusion: Monitoring of MDR-TB patients aged >50 years old and those with DM to minimize the incidence of side effects during treatment is essential. This effort is expected to support the success of the national TB control and treatment program.

INTRODUCTION

Tuberculosis (TB) is a contagious infectious disease caused by *Mycobacterium tuberculosis* (MTB), primarily affecting the lungs. Globally, TB remains a serious health threat. According to the World Health Organization (WHO) Global Tuberculosis Report 2024, there were approximately 8.2 million new TB cases, and 1.25 million deaths from TB by 2023.[1] About 175,923 of these cases were multidrug-resistant (MDR)-TB.[1] This burden causes huge health and economic losses, especially in developing countries. In Indonesia, the burden of TB is also very high. Indonesia currently has the second-highest number of TB cases in the world after India.[1]

Managing MDR-TB is a medical challenge because it requires longer treatment, higher costs, and a greater risk of drug side effects than drug-sensitive TB.

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The burden of DR-TB in Indonesia is one of the highest in the world. In 2023, there were an estimated 24,637 cases of DR-TB in Indonesia.[2] Of these, MDR-TB cases are also increasing. They are one of the main focuses in the national TB elimination program by 2030.[2] Despite the national program, case finding remains challenging, with delayed diagnosis and treatment non-adherence often resulting from side effects. As of 2023, in Indonesia, a new treatment regimen, the bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaL/M), was available.[3]

The BPaL/M regimen is a revolutionary treatment in MDR-TB therapy, offering hope through shorter, simpler treatment and the oral administration of this combination, as well as promising therapeutic results. One of the main components of this regimen, linezolid, is an oxazolidinone-class antibiotic that is bacteriostatic against Gram-positive bacteria and also active against MTB.[4] Treatment with this combination is known to be highly effective. However, there are potential side effects that need attention, such as hematologic disorders, peripheral neuropathy, and visual disturbances, which can affect the continuity and success of treatment.[5]

One of the crucial factors that hinders the successful treatment and control of MDR-TB is the side effects of the drugs used in the therapy regimen, especially linezolid.[6] These side effects can cause significant clinical impairment and potentially decrease patient adherence to treatment, even leading to premature discontinuation of therapy.[7] Recent study also highlighted that linezolid-induced hematologic toxicity might be associated with its primary metabolite, PNU142586, which can interfere with deoxyribonucleic acid (DNA) topoisomerases (TOP2A and TOP2B), leading to mitochondrial dysfunction and cytotoxicity, even in the absence of renal impairment.[8] This mechanistic insight underscores the importance of clinical monitoring during prolonged linezolid use.

It is essential to determine whether specific patient characteristics, such as age, gender, nutritional status, education, or the presence of comorbidities like diabetes mellitus (DM) and human immunodeficiency virus (HIV), are associated with linezolid side effects. This study analyzed the association between the characteristics and comorbidities of MDR-TB patients receiving BPaL/M treatment and the incidence of linezolid side effects, providing a scientific basis for more targeted monitoring, prevention, and management of side effects, and supporting the success of the national TB control program.

METHODS

This was a retrospective analytical study with a cross-sectional design that aimed to analyze the association between the characteristics and comorbidities of MDR-TB patients with the incidence of linezolid side effects in patients receiving BPaL/M regimen therapy at Haji Adam Malik General Hospital, Medan, in 2024.

The study population was all MDR-TB patients undergoing BPaL/M therapy who met the inclusion criteria. Samples were taken by total sampling based on the inclusion criteria, namely, MDR-TB patients who were routinely controlled every month until they were declared cured. This study utilized medical records as secondary data from MDR-TB patients receiving BPaL/M therapy regimens at the MDR-TB polyclinic, which were recorded in the hospital's electronic medical record system, during the period from January to December 2024.

The dependent variable was the incidence of linezolid side effects, including hematologic disorders, which are conditions of abnormality in one or more parameters of complete blood count examination that occur during treatment, as evidenced by laboratory tests. These hematological disorders include anemia, leukopenia, or thrombocytopenia. Another side effect is peripheral neuropathy, a condition characterized by impaired peripheral nerve function, which manifests as complaints such as tingling, pain, burning, numbness, or weakness in the extremities during therapy. The diagnosis was based on the patient's history of symptoms and assessment using the Toronto Clinical Neuropathy Scoring System.

Examinations were performed by medical personnel and recorded in the medical record. In addition to hematologic disorders and peripheral neuritis, visual impairment was also examined in this study. Visual disturbance is a condition characterized by subjective patient complaints such as blurred vision, decreased visual acuity, double vision, or impaired color vision that appear during treatment. The independent variables included age, gender, education, nutritional status, measured in this study based on the patient's body mass index (BMI), as well as the patient’s comorbidities, namely DM and HIV infection. Data were collected from medical records, including the type of adverse event, the time of occurrence, and the treatment administered.

Data were analyzed bivariately using Fisher’s exact test. A p-value of <0.05 was considered to indicate

a statistically significant association. This study received approval from the Health Research Ethics Committee of Universitas Sumatera Utara, Medan (No. 177/KEPK/USU/2025) on 10 March 2025.

RESULTS

In this study, 105 subjects were obtained. One hundred three subjects met the inclusion criteria, while two subjects did not meet the inclusion criteria because they passed away during treatment.

Table 1. Characteristics and comorbidities of study subjects

Characteristics and Comorbidities	n	%
Age (years old)		
≤17	2	1.9
18-39	40	38.8
40-49	17	16.5
50-59	21	20.4
60-69	19	18.4
≥70	4	4
Gender		
Female	27	26.2
Male	76	73.8
Education		
Elementary school	5	4.9
Junior high school	8	7.8
High school	79	76.7
Diploma	2	1.9
Undergraduate	9	8.7
Magister	0	0
Body Mass Index		
Underweight	46	44.7
Normoweight	43	41.7
Overweight	14	13.6
Obesity	0	0
Diabetes Mellitus		
Yes	40	38.8
No	63	61.2
Human Immunodeficiency Virus		
Yes	0	0
No	103	100

Of the 103 study subjects, the majority were patients aged 18-39 years old, comprising 40 patients (38.8%), and most subjects were male, specifically 76 patients (73.8%). The majority of the research subjects' education was at the high school level, accounting for 76.7%. The nutritional status of patients, measured using BMI according to WHO standards, found that most subjects had an underweight BMI, namely 46 patients (44.7%), followed by normal weight (43, 41.7%), and overweight (14, 13.6%). No obese patients were found in this study. Of the 103 study subjects, 40 patients (38.8%) had DM, whereas 63 patients (61.2%) did not have DM. During the period January to December 2024, there were no HIV patients who received BPaL/M regimen (Table 1).

Table 2. Incidence of linezolid side effects

Linezolid Side Effects	n	%
Hematologic Disorders		
Yes	55	53.4
None	48	46.6
Peripheral Neuropathy		
Yes	22	21.4
None	81	78.6
Visual Impairment		
Yes	5	4.9
None	98	95.1

The incidence of linezolid side effects, namely hematological disorders, occurred in 55 patients (53.4%). Another side effect was peripheral neuropathy, accounting for as many as 21.4% of the patients. The last side effect was visual impairment, which occurred in 4.9% of the patients (Table 2).

Figure 1 illustrates further analysis, showing that side effects in patients can occur singly or

simultaneously. There were 43% of MDR-TB patients who only experienced hematological disorders, 9% experienced peripheral neuropathy along with hematological disorders, 7% only experienced peripheral neuropathy, 4% experienced visual disturbances and peripheral neuropathy, and 1% experienced all three side effects. Other patients (36%) did not experience any side effects. These data suggest that linezolid has the potential to cause hematologic and neurologic disorders singly or in combination. Hence, regular monitoring during therapy is necessary.

Based on data before and during treatment, there are indications that linezolid has a role in changes in the hematological condition of MDR-TB patients, especially in the form of increasing the degree of anemia, thrombocytopenia, and the emergence of cases of leukopenia. The side effects of hematological disorders showed the most common manifestation as being mild to moderate anemia. Additionally, there was an increase in thrombocytopenia cases, from 2.9% to 7.8%, during treatment, indicating a possible side effect of linezolid on the bone marrow. Meanwhile, most patients experienced improved leukocyte and platelet values during BPaL/M alloy treatment, despite not having leukopenia before treatment. One case of leukopenia developed during treatment. Thus, hematologic disorders remain a prominent side effect and need to be monitored regularly.

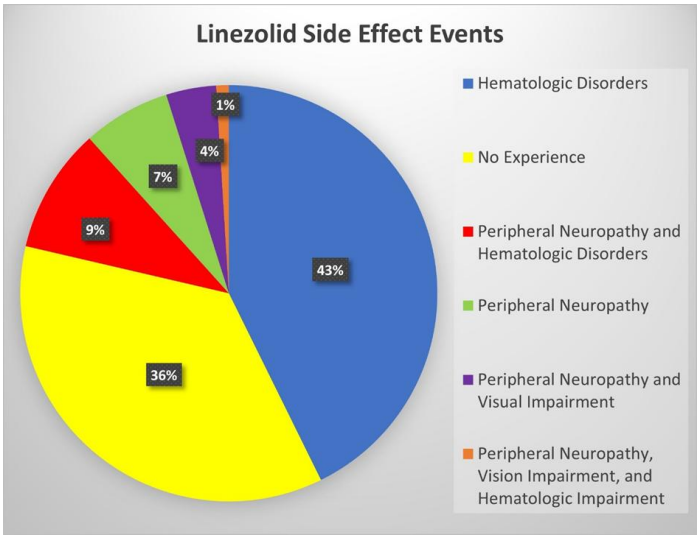

Figure 1. Linezolid side effect incidence diagram

From the analysis of 103 MDR-TB patients receiving linezolid therapy, there was no statistically significant association between patient characteristics and comorbidities with the incidence of side effects such as peripheral neuropathy, visual disturbances, and hematologic disorders. Age (p=0.062), gender (p=0.642), BMI (p=0.151), and education (p=1) showed no significant association. Comorbidities such as DM and HIV also showed no significant association (p=0.092). Overall, none of the patient characteristics and comorbidities were significantly associated with linezolid side effects (Table 3).

In one of the adverse events of linezolid patients, namely hematological disorders, only age showed a statistically significant association with the incidence of hematologic disorders in MDR-TB patients (p=0.01). Gender, education, BMI, DM, and HIV were not significantly associated with the incidence of hematologic disorders in this study (Table 4).

In one of the other linezolid side effects, peripheral neuropathy, only DM showed a statistically significant association with the incidence of peripheral neuropathy in MDR-TB patients (p=0.047). Age, gender, education, BMI, and HIV were not significantly associated with the side effect of peripheral neuropathy in this study (Table 5).

In another linezolid side effect, visual impairment, no factors showed a statistically significant association with the incidence of visual impairment in MDR-TB patients (Table 6).

Table 3. Factors associated with adverse events

Variable	Linezolid Side Effects				Total		p-value
	Yes		None				
	n	%	n	%	n	%	
Age (years old)							
<50	33	55.9	26	44.1	59	100	0.062
≥50	33	75	11	25	44	100	
Gender							
Female	16	59.3	11	40.7	27	100	0.642
Male	50	65.8	26	34.2	76	100	
Education							
Low	8	61.5	5	38.5	13	100	1
High	58	64.4	32	35.6	90	100	
Body Mass Index							
Abnormal	42	70	18	30	60	100	0.151
Normal	24	55.8	19	44.2	43	100	
Diabetes Mellitus							
Yes	30	75	10	25	40	100	0.092
No	36	57.1	27	42.9	63	100	
Human Immunodeficiency Virus							
Yes	0	0	0	0	00	0	-
No	66	64.1	37	35.9	103	100	

*Fisher's exact test. The p-value >0.05 was not statistically significant.

Table 4. Factors associated with hematologic disorders

Variable	Hematologic Disorders				Total		p-value
	Yes		None				
	n	%	n	%	n	%	
Age (years old)							
<50	25	42.4	34	57.6	59	100	0.01
≥50	30	68.2	14	31.8	44	100	
Gender							
Female	12	44.4	15	55.6	27	100	0.370
Male	43	56.6	33	43.4	76	100	
Education							
Low	7	53.8	6	46.2	13	100	1
High	48	53.5	42	46.7	90	100	
Body Mass Index							
Abnormal	35	58.3	25	41.7	60	100	0.317
Normal	20	46.5	23	53.5	43	100	
Diabetes Mellitus							
Yes	25	62.5	15	37.5	40	100	0.160
No	30	47.6	33	52.4	63	100	
Human Immunodeficiency Virus							
Yes	0	0	0	0	00	0	-
No	55	53.4	48	46.6	103	100	

*Fisher's exact test. The p-value >0.05 was not statistically significant.

Table 5. Factors associated with peripheral neuropathy

Variable	Peripheral Neuropathy				Total		p-value
	Yes		None				
	n	%	n	%	n	%	
Age (years old)							
<50	10	20	49	83.1	59	100	0.232
≥50	12	27.3	32	72.7	44	100	
Gender							
Female	9	33.3	18	66.7	27	100	0.101
Male	13	17.1	63	82.9	76	100	
Education							
Low	3	23.1	10	76.9	13	100	1
High	19	21.1	71	78.9	90	100	
Body Mass Index							
Abnormal	14	23.3	46	76.7	60	100	0.632
Normal	8	18.6	35	81.4	43	100	
Diabetes Mellitus							
Yes	13	32.5	27	67.5	40	100	0.047
No	9	14.3	54	85.7	63	100	
Human Immunodeficiency Virus							
Yes	0	0	0	0	00	0	-
No	22	21.4	81	78.6	103	100	

*Fisher's exact test. The p-value >0.05 was not statistically significant.

Table 6. Factors associated with visual impairment

Variable	Visual Impairment				Total		p-value
	Yes		None				
	n	%	n	%	n	%	
Age (years old)							
<50	2	3.4	57	96.6	59	100	0.649
≥50	3	6.8	41	93.2	44	100	
Gender							
Female	1	3.7	26	96.3	27	100	1
Male	4	5.3	72	94.7	76	100	
Education							
Low	1	7.7	12	92.3	13	100	0.498
High	4	4.4	86	95.6	90	100	
Body Mass Index							
Abnormal	3	5	57	95	60	100	1
Normal	2	4.7	41	95.3	43	100	
Diabetes Mellitus							
Yes	3	7.5	37	92.5	40	100	0.374
No	2	3.2	61	96.8	63	100	
Human Immunodeficiency Virus							
Yes	0	0	0	0	00	0	-
No	5	4.9	98	95.1	103	100	

*Fisher's exact test. The p-value >0.05 was not statistically significant.

DISCUSSION

This study found a significant association between age and hematological disorders (p=0.01), and between DM with peripheral neuropathy (p=0.047). This aligns with the study by Azimi, *et al*. (2022), which stated that age could affect the risk of side effects.[9] The study reinforced that age was associated with the incidence of hematologic disorders.[9] Another study by Qin, *et al*. (2021) also found that age ≥60 years old was an independent risk factor for linezolid-induced anemia.[7] Another study by Rupani, *et al*. (2020) also showed that advanced age with longer treatment duration, and the presence of decreased renal function were significantly correlated with linezolid-induced hematologic toxicity.[10] Several theories explain the relationship between age and the risk of hematological side effects associated with the use of linezolid. Linezolid is primarily metabolized non-enzymatically in the liver. The excretion of its metabolites still depends on kidney function. Therefore, in the elderly, drug levels in plasma may persist longer and reach potentially toxic levels.

From a pharmacodynamic perspective, aging leads to a decrease in hematopoietic reserves and increased susceptibility of bone marrow progenitor cells to drug toxicity. Linezolid is known to inhibit mitochondrial protein synthesis. In older adults, mitochondria tend to have reduced functional capacity and self-repair mechanisms, making them more susceptible to damage. As a result, the process of blood cell formation and maturation is disrupted, leading to anemia, thrombocytopenia, or leukopenia.[11]

Additionally, elderly patients often have chronic comorbidities such as kidney disease, liver disease, or DM, and frequently undergo polypharmacy, which can slow drug elimination and increase the risk of myelosuppressive drug interactions.

Patients with DM are more prone to develop this disorder due to pre-existing nerve damage, aggravated by the neurotoxic effect of linezolid on mitochondria.[9] Chronic hyperglycemia in DM leads to oxidative stress, accumulation of advanced glycation end products (AGEs), and impaired microvascular blood flow to peripheral nerve tissues.[12–15] These processes cause axonal damage and myelin dysfunction, thus increasing the risk of neuropathy. This condition will worsen if blood sugar control is not optimal, either due to poor adherence to antidiabetic treatment or due to drug interactions between antidiabetics and anti-TB drugs (ATD) that have the potential to increase toxicity or reduce the effectiveness of therapy.[12–15] These findings are similar to the studies of Jaspard, *et al*. (2020) and Jones, *et al*. (2020), which showed that patients with DM have a higher tendency to experience neuropathy during TB treatment.[16,17]

Based on the results of this study, neither gender nor nutritional status was found to have a significant association with the incidence of linezolid side effects. A previous study also found no association of gender with the incidence of adverse events.[18] Hence, gender is not influential enough to be the primary predictor factor. Therefore, both males and females have a similar risk of experiencing side effects from linezolid therapy.

Although education level was not statistically associated with the incidence of linezolid side effects in this study, education still plays an indirect role in patient adherence to MDR-TB treatment. A higher level of education may influence the patient's level of knowledge about the disease, the treatment received, including awareness of drug side effects, which may affect treatment adherence.[19,20] Therefore, efforts to improve health education and effective communication between health workers and patients remain essential to ensure proper understanding, minimize stigma, and support therapeutic success, especially in the use of regimens containing linezolid.

In this study, nutritional status, as measured by BMI, also showed no significant association with adverse events ($p = 0.151$). This study did not reveal a significant association between nutritional status and the occurrence of linezolid side effects in MDR-TB patients, which differs from the findings of some previous studies. This difference is likely due to several factors, such as the relatively small sample size. Haji Adam Malik General Hospital, Medan, is a tertiary referral hospital where patients from referral hospitals have complex clinical conditions and multiple diagnoses that may obscure the influence of nutritional status, nutritional assessment methods that may be less sensitive in detecting micronutrient deficiencies, and the presence of rapid nutritional interventions at referral facilities, thereby reducing the potential for adverse effects. However, biologically, nutritional status, especially poor nutrition, can affect the body's tolerance to drugs, interfere with drug metabolism and distribution, and increase the risk of more serious side effects due to weakened organ and immune system function.[21,22]

Poor nutritional status, particularly protein-energy malnutrition, significantly affects drug metabolism by reducing clearance and altering distribution and excretion, leading to an increased risk of drug accumulation and toxicity.[23] In addition, malnutrition weakens the immune system through hematopoietic dysfunction, including a decrease in the number of neutrophils and monocytes, as well as impaired cellular response, which increases susceptibility to infection even after nutritional rehabilitation.[24] The combination of impaired drug metabolism and immune function makes patients with malnutrition more susceptible to drug side effects, necessitating dose adjustments, stricter monitoring, and integrated nutritional support as part of the treatment plan.

The WHO has recommended the effectiveness of linezolid in BPaL/M regimen therapy, but there is a risk of side effects. A global observational study by Jones, *et al*. (2020) in 518 patients from 26 countries showed that 40.3% of patients experienced at least one side effect, and 13.1% of these were directly related to linezolid.[17] Frequently reported non-hematological side effects included peripheral neuropathy and optic neuritis, while hematological effects included anemia, thrombocytopenia, and leucopenia.[17] About 22% of patients even had to discontinue at least one drug due to side effects.[17]

Another study by Pratama, *et al*. (2021) of 93 patients showed that anemia was the most common hematological side effect, followed by leucopenia and thrombocytopenia.[25] The risk increased in patients with body weight <54 kg or those who received doses >11 mg/kgBB/day.[25] Therefore, regular monitoring of hemoglobin, leukocytes, and platelets is strongly recommended, especially in patients with low body weight. These findings support the importance of thorough risk evaluation before and during therapy, especially in patients with complex clinical conditions. Thus, although some patient characteristics and comorbidities showed no statistically significant association with linezolid side effects, clinical factors such as DM and HIV should still be seriously

considered. Careful monitoring of hematological, neurological, and organ function parameters is key to maximizing the effectiveness of therapy while minimizing the risk of complications. This study emphasizes the importance of an individualized approach in managing BPaL/M regimen therapy, particularly in patients at high risk of linezolid side effects.

CONCLUSION

Further analysis indicated that DM often coincided with peripheral neuropathy, while advanced age was more commonly associated with hematological disorders. The results of this study can be used as a consideration in the treatment and monitoring of side effects in MDR-TB patients using linezolid, especially in patients with DM and older age.

LIMITATIONS OF THE STUDY

The limitations of this study include its retrospective design and potential information bias due to reliance on secondary data from electronic medical records, inability to control for key confounding variables such as renal/hepatic function, linezolid dose and duration, and concomitant medications, as well as the risk of misclassification due to the use of subjective assessment without confirmatory diagnostic tests for peripheral neuropathy or visual impairment.

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Conflict of Interest
The authors declared there is no conflict of interest.

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Authors' Contributions
Conceived and designed the study, conducted the research, collected and analyzed the data, manuscript writing and preparation: FWT. Provided academic guidance, critical feedback, conceptual supervision throughout the research process, and assisted in the development of the theoretical framework: BYMS. Offered methodological guidance, oversight during the research implementation, and contributed to the refinement of the research objectives and structure: JH. Provided revisions and suggestions to improve the overall quality of the study: RSD. Supported the dissemination of the study: YLS. Offered critical insights and recommendations for revision and ensuring accuracy and academic integrity: JS. Reviewed the manuscript: FWT, BYMS, JH, RSD, JS, YLS. All authors contributed and approved the final version of the manuscript.

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