



# Effects of The BPaL Regimen on Hematological Parameters in Patients with Multidrug-Resistant Tuberculosis



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## ABSTRACT

**Background:** BPaL is a new oral drug combination consisting of Bedaquiline (B), Pretomanid (Pa) and Linezolid (L) for multidrug-resistance tuberculosis. In Indonesia BPaL has been officially launched by the government as a therapeutic regimen for multidrug resistant tuberculosis patients since August 2023. One of the drugs in this regimen has the side effect of anemia. Until now, there are still no references explaining the effect of BPaL on the hematological profile.

**Objective:** To determine the differences in the hematological profile of multidrug resistance tuberculosis patients before receiving the multi drug resistance regimen BPaL anti-tuberculosis drug regimen and while receiving the multi drug resistance regimen BPaL anti-tuberculosis drug regimen.

**Methods:** : This research was a retrospective observational analytical study with a retrospective cohort design involving patients with multidrug-resistant tuberculosis in Dr Kariadi Hospital based on medical records. The difference test used the paired T-test and the Wilcoxon test.

**Results:** 40 subjects were recruited, there were significant differences in hemoglobin level ( $p=0.003$ ), hematocrit ( $p=0.002$ ), red blood cells count ( $p<0.001$ ), white blood cells count ( $p=0.004$ ), platelet count ( $p<0.001$ ) and RDW ( $p<0.001$ ) before therapy with the BPaL regimen and during therapy with the BPaL regimen.

**Conclusion:** There were significant differences in the hematological profiles of multidrug-resistant patients before treatment with the BPaL regimen and while receiving the BPaL regimen.

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## 1. Introduction

Tuberculosis is an infectious disease which affect almost all tissues and organs, primarily causing lung infections. Tuberculosis has been a major worldwide health problem. It was estimated that one-third of the global population was infected with tuberculosis from active TB patients.<sup>1</sup> Global targets and milestones for reducing TB incidence and mortality had been established as part of the Sustainable Development Goals (SDGs) and the End TB Strategy. By 2030, the TB plan sought a 90% drop in TB mortality and an 80% drop in TB incidence (new and relapse cases per 100,000 population annually) between 2015 and 2030. Indonesia had the second-highest TB burden in the world, following India, according to the Global TB Report 2022. WHO estimated that there were 969,000 TB cases in Indonesia, with a notification rate of 717,941 cases. The estimated TB incidence in Indonesia in 2021 was 969,000 cases, or 354 per 100,000 population. TB-HIV cases were estimated at 22,000 per year, or 8.1 per 100,000 population. The estimated number of MDR/RR TB cases in 2021 was 28,000, or 10 per 100,000, a 17% increase from the 24,000

cases in 2020. This represents a rate of 15% per 100,000 population. Drug-resistant cases of tuberculosis were detected in 12,531, resulting in a 51% coverage.<sup>2</sup>

Tuberculosis treatment involves the use of antibiotics to eradicate *Mycobacterium tuberculosis*. These antibiotics are collectively known as anti-tuberculosis drugs (ATDs). Because anti-tuberculosis therapy requires prolonged combination treatment, the emergence of drug resistance has become a major challenge.<sup>3</sup>

Tuberculosis could be cured with a 3–4 drug regimen for 6–9 months. Nevertheless, patients with *Mycobacterium tuberculosis* strains that were MDR-TB and XDR-TB had a limited number of treatment options. BPaL was a new oral drug combination consisting of bedaquiline (B), pretomanid (Pa), and linezolid (L). This regimen was approved by the FDA in August 2019. It had demonstrated a 90% cure rate in MDR-TB and XDR-TB patients in clinical trials. However, many patients experienced severe side effects related to long-term Linezolid administration.<sup>4-6</sup>

A study by Kassa et al. showed that hemoglobin levels, hematocrit, and platelet count in tuberculosis patients

significantly decreased during the intensive phase of therapy. Significant variations in red distribution width (RDW) and platelet distribution width (PDW) were also observed between untreated patients and those who had completed the therapy programs. The most common hematological disorder among patients who underwent anti-tuberculosis treatment was anemia. All chronic infections, including tuberculosis, could cause anemia due to erythropoiesis suppression by inflammatory mediators. This type of anemia could be drug-induced, as anti-tuberculosis drugs could lead to hematological disorders affecting red blood cells, leukocytes/white blood cells, and platelets. Hemolytic anemia, methemoglobinemia, sideroblastic anemia, megaloblastic anemia, polycythemia, and aplastic anemia were among the drug-induced syndromes.<sup>1</sup>

## 2. Methods

This study was an observational analytic with a retrospective cohort design using medical record data. The research was conducted from May to June 2024 at Dr. Kariadi Hospital Semarang, and 40 subjects were recruited. The inclusion criteria included patients aged 18–70 years with MDR-TB detected through the molecular rapid assay Gene Xpert®, who had undergone at least 30 days of treatment with the MDR-TB BPaL regimen as a first-line treatment and had been receiving treatment at outpatient department at the MDR-TB Clinic. Routine clinical monitoring was actively performed within the critical first 6-8 weeks of therapy initiation. The exclusion criteria for this study were patients with HIV infection.

The laboratory data collected included hemoglobin levels, red blood cell count (RBC), white blood cells (WBC), platelet count, hematocrit, and RDW, from a complete blood count (CBC) examination using the Sysmex XN-1000 hematology analyzer with the impedance method. A paired t-test was used for comparative analysis, with statistical significance defined as  $p < 0.05$ . The Institutional Research Ethics Committee for Health and Medicine of Dr. Kariadi Hospital Semarang generated ethical clearance with number 1667/EC/KEPK-RSDK/2024.

## 3. Results

Forty subjects were recruited at the end of the study, consisting of 22 male and 18 female. (Table 1).

Table 1. Descriptive data characteristics of the subjects

| Variable                 | n (%)     | Mean ± SD     | Median (min-max) |
|--------------------------|-----------|---------------|------------------|
| Age (years)              |           | 45.88 ± 15.21 | 50 (18-70)       |
| Gender                   |           |               |                  |
| Male                     | 22 (55)   |               |                  |
| Female                   | 18 (45)   |               |                  |
| Weight (kg)              |           | 55.66 ± 11.43 | 55.5 (33.5-80)   |
| BMI (kg/m <sup>2</sup> ) |           | 21.4 ± 3.57   | 21.5 (14.3-30.1) |
| Underweight              | 9 (22.5)  |               |                  |
| Normoweight              | 17 (42.5) |               |                  |
| Overweight               | 8 (20.0)  |               |                  |
| Obesity                  | 6 (15.0)  |               |                  |
| Albumin (g/dL)           |           | 4.17 ± 0.52   | 4.2 (2.5-5.7)    |
| Hypo-albumin             | 3 (7.5)   |               |                  |
| Normal                   | 37 (92.5) |               |                  |
| Anemia                   | 18 (45)   |               |                  |
| Mild anemia              | 14 (35)   |               |                  |
| Moderate anemia          | 4 (10)    |               |                  |
| History of TB treatment  |           |               |                  |
| Yes                      | 15 (37.5) |               |                  |
| No                       | 25 (62.5) |               |                  |
| Other medication         |           |               |                  |
| Yes                      | 21 (52.5) |               |                  |
| No                       | 19 (47.5) |               |                  |
| Treatment outcome        |           |               |                  |
| Cured                    | 38 (95)   |               |                  |
| Fail                     | 2 (5)     |               |                  |
| Transfusion              |           |               |                  |
| Yes                      | 2 (5)     |               |                  |
| No                       | 38 (95)   |               |                  |

Table 4. Comparison Test Results of Paired Hematological Profiles

| Variable                       | Pre BPaL       | During BPaL    | Effect Size (Cohen's d/r) | p                     |
|--------------------------------|----------------|----------------|---------------------------|-----------------------|
| Hb (g/dL)                      | 12.65 ±1.92    | 11.94 ±1.68    | 0.45 (Moderate)           | 0.003 <sup>†</sup> *  |
| Hct (%)                        | 39.64 ±5.33    | 37.42 ±5.15    | 0.46 (Moderate)           | 0.002 <sup>†</sup> *  |
| RBC (10 <sup>6</sup> /μL)      | 4.76 ±0.62     | 4.34 ±0.62     | 0.83 (Large)              | <0.001 <sup>†</sup> * |
| WBC (10 <sup>3</sup> /μL)      | 9.84 ±3.70     | 8.03 ±3.56     | 0.49 (Moderate)           | 0.004 <sup>†</sup> *  |
| Platelet (10 <sup>3</sup> /μL) | 399.38 ±111.10 | 301.72 ±126.20 | 0.85 (Large)              | <0.001 <sup>†</sup> * |
| RDW (%)                        | 14.50 ±1.72    | 15.87 ±2.18    | 0.71 (Large)              | <0.001 <sup>†</sup> * |

\* < 0.05; † Wilcoxon; ‡ Paired-T test

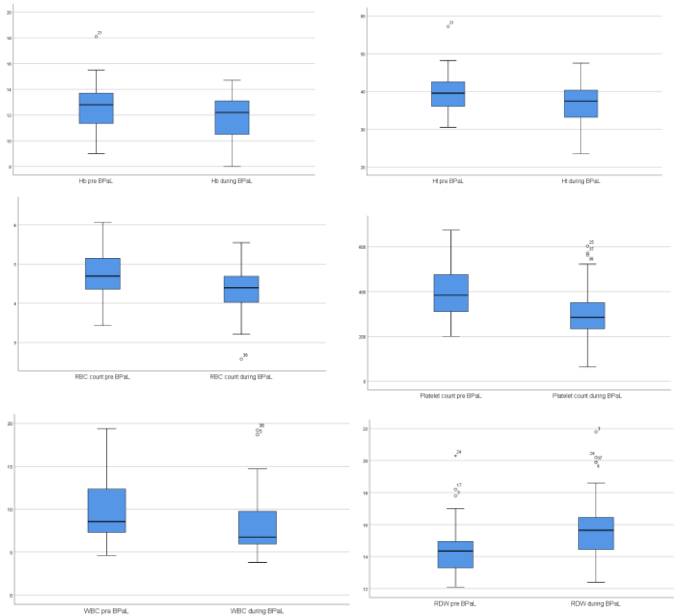


Fig.1 Boxplot diagram Hematological profile Pre and During BPaL

## 4. Discussion

Multidrug-resistant tuberculosis is a specific form of tuberculosis that is caused by *M. tuberculosis complex* strains that are resistant to isoniazid and rifampicin. There are other classifications that describe different levels of tuberculosis resistance, such as pre-extensively drug-resistant tuberculosis (pre-XDR TB) and rifampicin-resistant tuberculosis (RR-TB).<sup>7</sup> Pre-XDR TB refers to tuberculosis caused by *M. tuberculosis complex* strains that are resistant to rifampicin, isoniazid, and fluoroquinolones (either levofloxacin or moxifloxacin). Meanwhile, RR-TB is tuberculosis caused by *M. tuberculosis complex* strains resistant to rifampicin, which may also exhibit resistance to isoniazid or other first- and second-line anti-tuberculosis drugs.<sup>8,9</sup>

Affecting both blood cells and plasma components, tuberculosis has been linked with a broad spectrum of hematological abnormalities. Apart from causing different blood cell abnormalities, antituberculosis treatment itself shows a spectrum of hematologic toxicity. This study compared the hematological profiles MDR-TB patients before initiating treatment with the BPAL regimen and after at least one month of therapy. The findings showed significant differences in hemoglobin levels, hematocrit values, erythrocyte count, leukocyte count, platelet count, and RDW before and during BPAL therapy.<sup>10</sup>

The BPAL regimen represents a major advancement in the treatment of multidrug-resistant tuberculosis (MDR-TB). Developed by the TB Alliance, this all-oral regimen combines bedaquiline, pretomanid, and linezolid and shortens the treatment duration to six to nine months, replacing the previously recommended 18- to 24-month regimen that included injectable agents.<sup>11</sup>

The BPAL regimen can cause adverse effects both during and after therapy. Bedaquiline exhibits bactericidal properties by inhibiting mycobacterial ATP synthase. The recommended dosage is 400 mg daily for two weeks, followed by 200 mg three times per week. However, bedaquiline has been associated with increased mortality and QT prolongation. Pretomanid acts by inhibiting mycolic acid biosynthesis, thereby disrupting the bacterial cell wall. Mycolic acid is a vital component that enables *M. tuberculosis* to survive. The prescribed dose of pretomanid is 200 mg daily, but its use has been associated to hepatotoxicity. Linezolid, administered 600 mg daily, has been reported to cause adverse effects such as blurred vision, altered color perception, difficulty recognizing details, restricted visual fields, and severe diarrhea with blood and mucus, which can be life-threatening. Additionally, linezolid is associated with peripheral neuropathy and anemia. A study conducted by Marjorie et al. found that severe anemia was more prevalent among patients receiving 1200 mg of linezolid compared to those receiving 600 mg.<sup>11-12</sup>

This study showed significant difference in hemoglobin levels before and during BPAL therapy. Additionally, there was statistically significant decrease in erythrocyte count and hematocrit, along with significant

increase in RDW. These findings indicate the presence of anemia, as hemoglobin, erythrocyte count, and hematocrit levels declined during BPAL therapy compared to pre-treatment levels. This effect may be attributed to the linezolid component in the BPAL regimen, as the administered dose of linezolid was 600 mg, which was uniformly documented across all 40 subjects without protocol-driven dose adjustments during the observed phase. Linezolid acts at two primary sites: the bacterial ribosome and the mitochondrial ribosome in humans. In bacterial ribosomes, linezolid inhibits bacterial protein synthesis, thereby suppressing bacterial growth and reducing its ability to infect host cells. Furthermore, linezolid disrupts mitochondrial protein synthesis by targeting mitochondrial ribosomes, resulting in mitochondrial dysfunction. Consequently, the production of ATP in bone marrow precursor cells decreases, leading to bone marrow suppression, which is characterized by anemia, neutropenia, and thrombocytopenia. Hematological monitoring should be conducted during the first 6–8 weeks of treatment to adjust the dosage or interval of linezolid administration.<sup>13-16</sup> The findings in this study was in contrast to Putra et al., who reported increase in hemoglobin, erythrocyte count, and hematocrit. This discrepancy is highly likely driven by differences in the drug regimens and timing of measurement; while Putra et al., evaluated standard regimens that successfully eradicated systemic infection over a long period thereby resolving the anemia of chronic disease our study captures the acute, direct mitochondrial toxicity of linezolid during the active phase of the BPAL regimen. However, that study did not specify the type of treatment regimen used.<sup>10</sup>

Furthermore, while linezolid is the primary driver of myelosuppression, the potential indirect hematological impacts of other BPAL components must be considered. Bedaquiline is well-known for its potential to cause QT prolongation, which induces cardiovascular safety risks but is not heavily linked to direct bone marrow suppression. On the other hand, pretomanid is associated with hepatotoxicity. Severe liver dysfunction can secondarily affect hematological parameters by disrupting the synthesis of coagulation factors or altering erythropoietin regulatory pathways. Although severe hepatotoxicity was not explicitly logged as a cause of systemic anemia in this cohort, the synergistic metabolic stress of the combination regimen on the liver and bone marrow requires careful clinical monitoring.<sup>17,18</sup>

Regarding WBC profiles, this study found significant decrease in WBC count before and during BPAL therapy. This reduction may be caused by granulopoiesis suppression by activated T cells, folate and vitamin B12 deficiency, bone marrow fibrosis or dysfunction due to disease localization, or splenic sequestration. Linezolid has been noted to lead to pancytopenia, which means a decrease in blood cells, including erythrocyte, leukocyte, hemoglobin, and platelets, after taking it for 30 days.<sup>14</sup> The platelet count also showed significant decrease, which may be related to the effect of linezolid on the phosphorylation

process of myosin light chain 2 in megakaryocytes. This disruption affects the binding of glycoprotein IIb/IIIa on the platelet membrane, then impairing platelet formation.<sup>19,20</sup>

This study demonstrated significant difference in the hematological profile of MDR-TB patients before and during treatment with the BPaL regimen. However, limitation of this study is that it did not account for other potential causes of anemia, underlying comorbidities, or concurrent illnesses.

A key limitation of this study is its single-arm retrospective design without a parallel control group, such as MDR-TB patients receiving alternative injection-based regimens. Consequently, absolute causal attribution must be interpreted with caution. Additionally, due to the retrospective nature of medical record data, statistical adjustments for potential baseline confounders including baseline tuberculosis severity, detailed nutritional markers (e.g., micronutrient status), and exact dosing consistency throughout the entire treatment course could not be performed. However, utilizing patients as their own historical controls through paired statistical analysis partially mitigates inter-individual biological confounding.

## 5. Conclusion

There was difference in the hematological profiles of multidrug-resistant tuberculosis patients before and during treatment with the BPaL drug regimen. Further research is needed to consider other potential causes of anemia and patients underlying comorbidity. Future studies should also expand the hematological parameters evaluated, specifically incorporating peripheral blood smear interpretations to closely observe the qualitative and morphological changes that accompany these hematological shifts. Additionally, conducting comparative studies to contrast the hematological profiles of patients on the BPaL regimen against those on alternative drug regimens will provide a stronger clinical foundation for optimizing multi-drug resistant TB management in Indonesia.

## Ethical Approval

Conceptualization, D.R.; methodology, S.A.; investigation, S.A, D.R.; data curation, S.A, V.S.; formal analysis, A.J.; writing original draft preparation, S.A, D.R.; writing review and editing, D.R, A.J; project administration, V.S. All authors have read and agreed to the published version of the manuscript

## Conflicts of Interest

The authors declare no conflict of interest.

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## Author Contributions

Conceptualization, D.R.; methodology, S.A.; investigation, S.A, D.R.; data curation, S.A, V.S.; formal analysis, A.J.; writing original draft preparation, S.A, D.R.;

writing review and editing, D.R, A.J; project administration, V.S. All authors have read and agreed to the published version of the manuscript.

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## References

1. Kassa E, Enawgaw B, Gelaw A, Gelaw B. Effect of anti-tuberculosis drugs on hematological profiles of tuberculosis patients attending at University of Gondar Hospital, Northwest Ethiopia. *BMC Hematol.* 2016;16:1.
2. P2P Kemenkes RI. Laporan Program Penanggulangan Tuberkulosis Tahun 2022. Jakarta: Kementerian Kesehatan RI; 2022. 156 p.
3. Putra P. Effect of Anti-Tuberculosis Multi Drug Resistance Regimen on Hematological Lung Tuberculosis Patients Profile with Multi Drug Resistance. *Berk Kedokt.* 2018 Mar 1;14:59.
4. Network TT& H investigative. Programmatic Introduction of the BPaL Regimen: A Practical Implementation Guide. THINK International; 2021. 95 p.
5. Pratt M, McNicol M, Hunter M, Dedicoat M. First use of Bedaquiline, Linezolid, and Pretomanid (BPaL) in a family cluster of multi-drug resistant (MDR) TB infection. *Ulster Med J.* 2024 Dec;93(2):55-57. Epub 2024 Dec 11. PMID: 39669953; PMCID: PMC11633317.
6. Haley CA, Schechter MC, Ashkin D, et al. Implementation of Bedaquiline, Pretomanid, and Linezolid in the United States: Experience Using a Novel All-Oral Treatment Regimen for Treatment of Rifampin-Resistant or Rifampin-Intolerant Tuberculosis Disease. *Clin Infect Dis.* 2023;77(7):1053-1062. doi:10.1093/cid/ciad312
7. van de Berg SEJ, Pelzer PT, van der Land AJ, Abdrakhmanova E, Ozi AM, Arias M, et al. Acceptability, feasibility, and likelihood of stakeholders implementing the novel BPaL regimen to treat extensively drug-resistant tuberculosis patients. *BMC Public Health.* 2021 Jul;21(1):1404.
8. Departement of Health Republic of South Africa. Introduction of BPaL-L, a 6-month RR-TB regimen. Knowledgehub; 2022. 1–10 p.
9. NHS England. BPaLM / BPaL for patients aged  $\geq 14$  years with suspected , functional or confirmed rifampicin resistant ( RR ) tuberculosis ( TB ), multidrug-resistant ( MDR ) TB or pre-extensively drug resistant ( pre-XDR ) TB [ URN : 2310 ] Plain language summary. NHS England; 2024.
10. Putra O, Faizah A, D.N N. Six Months of Bedaquiline-Pretomanid-Linezolid (BPaL) Regimen in Patients with Drug-Resistant Tuberculosis: A Narrative Review. *J Endocrinol Trop Med Infect Dis.* 2023 Jul

11. WHO. Module 4: Drug-resistant tuberculosis treatment. In: WHO consolidated guidelines on tuberculosis. WHO Press; 2022. p. 98.
12. Wijasa WN, Suyatno D, Barliana MI, Pradipta IS. Efikasi, Keamanan, Efisiensi Biaya Penggunaan Regimen Bedaquilin, Pretomanid, dan Linezolid (BPaL) dalam Pengobatan Tuberkulosis REsisten Obat Ganda. *Maj Farm dan Farmakol*. 2023;27(3):76–81.
13. Conradie F, Bagdasaryan TR, Borisov S, Howell P, Mikiashvili L, Ngubane N, et al. Bedaquiline-Pretomanid-Linezolid Regimens for Drug-Resistant Tuberculosis. *N Engl J Med*. 2022 Sep;387(9):810–23.
14. Oehadian A, Santoso P, Menzies D, Ruslami R. Hematologic Toxicity of Linezolid in Multidrug Resistant and Extensively Drug Resistant Tuberculosis (MDR/XDR-TB): the role of mitochondria. *Tuberc Respir Dis (Seoul)*. 2022 Jan 20;85.
15. CDC. Updates to Provisional Guidance for the Use of Pretomanid as Part of a Regimen [Bedaquiline, Pretomanid, and Linezolid (BPaL)] to Treat Drug-Resistant Tuberculosis Disease. 2022.
16. Imperial MZ, Nedelman JR, Conradie F, Savic RM. Proposed Linezolid Dosing Strategies to Minimize Adverse Events for Treatment of Extensively Drug-Resistant Tuberculosis. *Clin Infect Dis*. 2022 May 30;74(10):1736-1747. doi: 10.1093/cid/ciab699. PMID: 34604901; PMCID: PMC9155613.
17. Hasan T, Medcalf E, Nyang'wa BT, Egizi E, Berry C, Dodd M, et al. The safety and tolerability of linezolid in novel short-course regimens containing bedaquiline, pretomanid, and linezolid to treat rifampicin-resistant tuberculosis: an individual patient data meta-analysis. *Clin Infect Dis*. 2024;78(3):730-741. doi:10.1093/cid/ciad653.
18. Ahmad HA. P-1386. Real-world safety profile of pretomanid: an analysis of FAERS data. *Open Forum Infect Dis*. 2026;13(Suppl 1):ofaf695.1573. doi:10.1093/ofid/ofaf695.1573.
19. Shah AR, Desai KN, Maru AM. Evaluation of hematological parameters in pulmonary tuberculosis patients. *J Fam Med Prim care*. 2022 Aug;11(8):4424–8.
20. Lange C, Abubakar I, Alffenaar J-WC, Bothamley G, Caminero JA, Carvalho ACC, et al. Management of patients with multidrug-resistant/extensively drug-resistant tuberculosis in Europe: a TBNET consensus statement. Vol. 44, *The European respiratory journal*. England; 2014. p. 23–63.